Allergy

INTERNATIONAL TEXTBOOK OF ALLERGY

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Edited by

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DEDICATED TO
THE FRIENDSHIP AND COOPERATION
OF ALL THOSE
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PREFACE

Due to the fact that the allergic phenomenon can take place in every human organ and tissue, each practicing physician, whatever his branch of medicine, will be confronted with allergic problems. Although allergy is a definite entity, its manifestations, however, may assume a different character according to the organ concerned and the problems which arise may vary widely.

Because of the extensiveness of the field, it has become extremely difficult, if not impossible, for one physician to write with sufficient competence on such varied phases as allergy of the respiratory tract, skin, eyes, digestive system, vascular and collagen tissue, as well as on the physiologic, immunologic, and even botanic aspect; to discuss at the same time the morbid manifestations of the disease and the way to combat them and introduce the reader to the many *terra incognita* of Experimental Medicine. Herefrom the idea was born to write a textbook in cooperation.

Even if there are a number of disadvantages to this form of edition, such as less uniformity in language and ideas, these are nevertheless largely compensated by the fact that each chapter has been written by an author well qualified in his particular field.

Although many minds have participated in the edition of this volume, every endeavor has been made to make it as complete and uniform as possible and to avoid unnecessary overlapping. Some omissions, nevertheless, were necessary, as for reasons of convenience the size of the book had to remain within certain limits.

It is our hope that this book will be of value not only to those who take their first steps in the field of allergy, but also to those who wish to broaden their knowledge on some particular phase.

Progress in allergy is slow and it calls upon qualities of the highest order, yet it is not devoid of spiritual rewards for those who have been able to master the many facets of its practice.

J. M. JAMAR

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Brussels

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ANAPHYLAXIS

By

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São Paulo

The phenomenon of anaphylaxis was first described by Portier and Richet (1902) in a dog receiving sub-lethal doses of an extract of sea actinia. Richet named the toxic substance in these extracts actino congestine, because it produces abdominal pains, emesis and bloody diarrhea. When a small sublethal dose is first injected, the animal survives; if the same small dose is again injected 20 to 30 days after the first one, it produces severe symptoms which may lead to death. The symptoms described by Richet were somewhat similar to those produced by the actino-congestine itself, namely bloody diarrhea, tenesmus, vomiting, prostration and death. It appeared to Richet that instead of becoming "protected" or "immunized" the dog developed just the reverse condition. Portier (1952) described the origin of the name given by Richet: "When the phenomenon had been solidly established from the experimental standpoint, M. Richet decided to baptize it. I tried to persuade him of the inutility of creating a neologism, since there were already so many in the scientific literature, and especially as we had forgotten our Greek.

You might be right, answered Richet, if the phenomenon we have discovered is only a rarity, but if it presents a certain general interest, we have to have a name for it.—At this moment he approached a small blackboard hidden under the stairs and asked me if I knew the Greek word for "immunity", "protection".—No, I said, I might have known it but I have forgotten.—It is φυλαξις (phylaxis), and now let us affix a privative α.—The resulting word a phylaxie not being very euphonic, we decided to adopt the word *anaphylaxie* (anaphylaxis). At that moment we could not dream of the great value attached to this expression." Later on, it was shown that the phenomenon of Richet might be produced in a dog by the repeated injection of nontoxic material, such as serum protein or egg albumin, as had been shown in the rabbit by Arthus (1903) and Arthus and Breton (1903) and in the guinea pig by Otto (1906) and Rosenau and Anderson (1906).

The symptoms. Since a first injection of such harmless materials as horse serum and egg albumin fails to produce any symptom, and only does so after a long latent period of 15 to 20 days, or when repeatedly injected into the same animal or at the same site (Arthus local phenomenon), the symptoms of anaphylaxis could not possibly be due to any primary effect of the agent. The symptoms are mediated by an immunologic reaction, producing antibodies which will react with the primary agent, the antigen, reinjected a few days or weeks later. In 1941, Dragstedt defined anaphylaxis as "an autointoxication by physiologically active substances normally resident in various tissue cells and liberated therefrom by some change in cellular permeability brought about by the antigen-antibody reaction". There is a term, coined in 1933 by Sir Henry Dale, to indicate such phenomena that develop as a consequence of the release of active substances normally present in the organism in an inactive form. This term is "autopharmacology" and, therefore, anaphylaxis might be understood as an autopharmacological phenomenon, arising from the combination of the antigen with the antibody formed during the period of sensitization. The expression "hypersensitivity" is inappropriate, though widely used, because the symptoms of anaphylaxis can have no bearing on the primary effects of the eliciting agent. They can arise out of nothing and are rather typical of the species in which the experiment is made, quite unrelated to the nature of the aggressor (antigen).

Each animal species has its own *pattern* of reacting to the different antigens. In the dog, besides the symptoms described by Richet and Portier (1902), a sudden fall in blood pressure is typical of anaphylaxis, when the antigen is given intravenously (Richet, 1909; Biedl and Krans, 1910). The heart continues beating with an accelerated rhythm while the blood accumulates in the abdominal vessels, with a sharp decrease in cardiac output. The liver is especially concerned with anaphylaxis in the dog, showing increase in size, and stagnation of blood in the portal region (Pearce and Eisenbrey, 1910; Manwaring, 1910). The role played by the liver as shock organ in the dog was extensively studied by Weil (1912–17), who demonstrated that stagnation in the portal region is quantitatively enough to explain the fall in blood pressure: "The condition of the liver dominates the pathological impression and presents a picture which is rarely if ever seen under any other circumstances. The organ is tremendously swollen and its color intensively cyanotic. Upon section the cut surface bleeds freely" (Weil, 1917). The gastrointestinal symptoms described by Richet as the dominating feature of anaphylaxis in the dog were considered by Weil to be secondary to blood stagnation in the portal region. Removal of the liver, either

by an Eck fistula (Voegtlin & Bernheim, 1910; Denecke, 1914) or by a ligature of the supra-hepatic veins (Simonds and Brandes, 1927) strongly attenuates the shock. However, a milder but sometimes definite anaphylactic shock can be observed in the dog after surgical removal of the liver (Waters, Markowitz and Jaques, 1940 46). A typical symptom of anaphylaxis in the dog is the decreased coagulability of the blood due to an increase in its anti-thrombin titer (Quick, 1936) caused by a discharge of heparin from the liver mast cells (Jaques and Waters, 1941).

Although the first demonstration of anaphylaxis in the rabbit was a local aseptic inflammation, known as the Arthus phenomenon, a general anaphylactic reaction can be elicited in the rabbit as well as in the dog. If the animal is prepared by a few previous injections of the antigen and then 20 days later the antigen is reinjected intravenously, the animal develops shock with fall in blood pressure and death by circulatory collapse (Arthus, 1909). However, the liver of the rabbit does not show any marked changes. The pathological picture is dominated by an acute dilatation of the right heart, which appears filled with dark blood. The whole heart appears immobile, which suggested to Auer (1911) the idea of a "heart death" as the primary cause of the circulatory failure. However, if the heart is isolated and perfused with blood or Locke solution it promptly recovers its normal beat (Gley and Pachon, 1909; Cesaris-Demel, 1912, and many others). In 1914, Airilla showed that the primary circulatory change in anaphylactic shock of the rabbit was an increase of pressure in the pulmonary artery bed. This fact was confirmed and explained by Coca (1919) as being due to a constriction of the thick smooth muscle coating of the rami of the pulmonary artery of the rabbit. Another factor might contribute to the apparent "heart death" described by Auer. If both vagus nerves are cut, the blood pressure rises and the animal recovers from anaphylactic shock (Rocha e Silva, 1940). Therefore, some central stimuli coming through the efferent fibers of the vagus nerves might play a part in slowing down the heart and aggravating the situation in the pulmonary circulation.

As to the mechanism of production of the *local anaphylaxis* in the rabbit, usually known as the Arthus phenomenon, some conceptual changes have been introduced by recent investigations. It was a known fact that a parallelism existed between the precipitin titer and the intensity of the skin reaction (Opie, 1924; Cannon and Marshall, 1941) consisting of hyperemia, edema formation, necrosis and scars. The idea that the complex formed by the combination of the antigen with the antibody is cytotoxic, as suggested by previous workers, was discarded as a consequence of the fine experiments

by Aronson (1933) and Meyer and Loewenthal (1937), who have shown that this complex is completely innocuous when formed in contact with living cells isolated and transplanted into cultures. The experiments of Rich and Follis (1940) producing the Arthus phenomenon in the rabbit's cornea submitted to an intensive artificial vascularization by previous application of an irritant, definitely showed that the phenomenon depends upon the "organization" of the tissue. Following accumulation of leukocytes and blood stagnation, there occurs small hemorrhages and necrosis, by impairment of the nutrition of the cells. Judging from experiments with anaphylaxis in the rabbit, in which there has been shown a general tendency for leucocytes (Abell and Schenck, 1938; Dragstedt et al., 1940) and platelets (Graña and Rocha e Silva, 1945; Rocha e Silva, 1950) to agglutinate in the capillaries of the organs, one might assume that the primary reaction leading to vascular damage in the local Arthus phenomenon is the formation of microthrombi of leucocytes and platelets which subsequently rupture, releasing substances such as histamine or serotonin and proteolytic enzymes which will damage the capillary walls. Experiments by Ovary and Briot (1951) and Ovary and Bier (1952–53) in the guinea pig and rat substantiated the idea that the Arthus reaction is one which involves circulating antibodies and also damage to the walls of the small vessels. On the other hand, the so-called "passive cutaneous anaphylaxis" is a much more superficial reaction, needing a long latent interval between the intracutaneous injection of the antibody and the intravenous injection of the antigen. This reaction can only be revealed by the use of a simultaneous injection of a dye, such as Geigy blue or Evans blue.

In the guinea pig an entirely different picture develops as typical of anaphylactic shock when the antigen is reinjected intravenously, a fortnight after the first sensitizing dose. A persistent dyspnea is the dominating symptom. In a few minutes the animal shows symptoms of asphyxia and dies after violent scratching of the nose, deep respiratory movements and asphyxial convulsions. The physiological analysis by Auer and Lewis (1909–10) showed that death was the consequence of an acute constriction of the bronchiolar tree, immobilizing the lungs in deep inspiration. All efforts made by the animal to expel the air contained in the pulmonary alveoli are fruitless and the final appearance of the lungs is one of an enormous emphysema filling the whole thoracic cavity. The heart continues beating with an accelerated rhythm, even if it is separated from the body. That the phenomenon is mainly peripheral was demonstrated by Dale (1912–13), who showed that even in the isolated perfused lungs, taken from a sensitized guinea pig, the emphysema could be

produced by injection of the antigen. Further experiments by Dale and Kellaway (1922) indicated that anaphylactic shock in the guinea pig is the consequence of an acute constriction of the smooth muscles present in the bronchiolar tree, without much participation of the circulatory system, which plays such a pronounced role in anaphylaxis in the rabbit and the dog. A fall in blood pressure as a secondary effect of the lung distension, however, has been observed by Auer and Lewis (1909–10) and others. When the antigen is given intraperitoneally, the animal does not show very marked signs of respiratory collapse, but will die in a few hours, after a long period of coma, during which it remains prostrate with perceptible and regular respiration (protracted shock). On section, the lung collapses as a normal organ, showing no appreciable emphysema. The abdominal organs show extensive hyperemia, and the liver and intestinal tract are engorged with blood. The predominant symptom in this protracted shock in the guinea pig appears to be the fall in blood pressure, with a drop in body temperature. As the rabbit, the guinea pig can develop a very typical Arthus phenomenon, but since this species is more sensitive to the general effects of the reinjection of the antigen, many die without reaching the stage of the aseptic inflammation and necrosis. The "reverse Arthus phenomenon" has been studied by Ovary and Briot (1951) and Ovary and Bier (1952–53) by injecting minute amounts of antibody in the skin, and the antigen plus Geigy blue intravenously. No latent interval is required and this suggests that the combination of the antibody with the circulating antigen, at the level of the small vessels, can start immediately the succession of phenomena leading to vascular damage and hemorrhages.

Anaphylaxis in other animal species, such as the pigeon (Hanzlik, Butt and Stockton, 1927), the rat (Longcope, 1922; Suden, 1934; Halpern et al., 1955; Mota, 1957) and the mouse (Fink and Rothlauf, 1955; Fink, 1956), although they present interesting features which are typical of each animal species, will not be discussed *in extenso*.

The endogenous mediators. Since anaphylaxis, in the definition of Dragstedt, results from an auto-intoxication by "physiologically active substances", it has been a primary concern of physiologists and pharmacologists who have studied anaphylaxis to identify those principles involved in the production of the symptoms.

First, we shall deal with the nature and site of release of these substances; the mechanism of release being discussed later.

As the main characteristics of anaphylactic shock in most species of animals concern reactions of the smooth muscle, edema formation resulting from increased capillary permeability and fall in blood pressure, it was natural to look for a principle having such pharma-

cological effects. Another important symptom, especially occurring in anaphylaxis in the dog, is the decreased coagulability of the blood which is certainly due to heparin released from the liver mast cells, as mentioned before. The indication that histamine might be one of the important principles released in anaphylaxis, was already suggested as early as 1910–11 by the fundamental experiments by Dale and Laidlaw on the physiological action of β-iminazolylethylamine: "It may be noted that the symptoms and post-mortem examination in the guinea pig correspond in a suggestive manner with those described by several workers as the effect of poisoning in that animal by Witte's peptone, or by serum or other protein in the sensitized guinea pig (anaphylactic shock)". The evidence for participation of choline or acetylcholine (Went and Lissak, 1936) is meager and probably unimportant. By perfusing the sensitized guinea pig lung with the antigen, a slowly reacting substance (SRS) is released (Kellaway and Trethewie, 1940), this substance has been studied more recently by Brocklehurst (1956) under the name of "SRS-A" and appears to be different from bradykinin and substance-P. In the blood of the dog submitted to anaphylaxis, Beraldo (1950) detected a slowly reacting substance resembling bradykinin and this principle was also released when the plasma taken from a sensitized dog was incubated with the antigen. Lately, some evidence has been presented that serotonin might also participate in the genesis of anaphylactic reactions of the mouse. It is of interest that the increased susceptibility of mice receiving the *H. pertussis* vaccine to anaphylaxis and to the toxic effect of histamine (Parfentjev and Goodline, 1948; Malkiel and Hargis, 1952; Kind, 1953; and others) could also be observed in relation to the toxicity of serotonin (Kind, 1957; Munoz, 1957), in accordance with the idea that both substances or, predominantly, serotonin (Fink and Rothlauf, 1955, Fink, 1956) might be of significance in mouse anaphylaxis. Release or activation of proteolytic enzymes has been consistently detected in anaphylaxis.

At present we shall discuss the anatomical origins of these physiologically active principles, presumably participating in the anaphylactic reactions. Where do they come from in the various animal species?

Let us start with histamine. The first evidence for the release of a hypotensive and smooth muscle stimulating principle was suggested by the experiments by Manwaring, Hosepian, O'Neil and Moy (1925), showing the release of such an agent when the liver taken from a sensitized dog was connected to the circulation of a normal animal; when the antigen was injected, an increase in intracystic pressure and fall in blood pressure were observed. Dragstedt and

Gebauer-Fuelnegg (1932) identified histamine in the lymph of the thoracic duct in a dog submitted to anaphylactic shock. Later on, this substance was detected in the peripheral blood of a dog (Dragstedt and Mead, 1936; Code, 1939). The final demonstration that histamine is discharged from the dog's liver in anaphylactic shock was presented by Ojers, Holmes and Dragstedt (1941). Pieces of liver taken before and after the shock, showed drastic reductions in the histamine content, indicating that a liberation on the order of several milligrams takes place during the shock. These experiments have been confirmed and extended to similar kinds of shock such as peptone shock (Holmes, Ojers and Dragstedt, 1941) and the shock produced by extracts of *Ascaris suum* (Rocha e Silva and Graña, 1946). Perfusion experiments of the isolated liver of the dog with Tyrode or Locke solution gave disappointing results (Rocha e Silva and Graña, 1946) since only a few micrograms of histamine were obtained from the entire liver. If the liver is perfused *in situ* better results are obtained, but the highest histamine release still is obtained when total silicone blood is perfused through the liver in anaphylactic shock (Scroggie and Jaques, 1949) or by adding peptone (Rocha e Silva, Scroggie, Fidlar and Jaques, 1947). Another characteristic of anaphylactic shock in the dog is leucopenia (Welb. 1924) and thrombocytopenia (Rocha e Silva and Graña, 1946). Accumulation of these blood elements in the liver and rupture of platelets following the injection of Ascaris extracts in connection with the release of histamine, was described by Rocha e Silva, Porto and Andrade (1946). Since total blood as close to its natural form as possible is important for the histamine release from the liver of the dog in anaphylaxis, it has been suggested that the formation of microthrombi of leucocytes and platelets with their subsequent disintegration is the prelude to the sequence of reactions leading to the discharge of heparin and histamine from the liver mast cells. However, some extrahepatic components might aggravate the condition, since it has been shown that under circumstances of Eck fistula, a fall in blood pressure may occur in dogs submitted to anaphylaxis (Waters and Markowitz, 1940; Waters, Markowitz and Jaques, 1946).

The interdependence of the blood elements and the liberation of histamine has been better demonstrated in the rabbit. The blood of the rabbit is an important source of histamine (Code, 1937) and it was repeatedly shown that the rabbit's platelets are very rich in histamine (Minard, 1937; Zon, Ceder and Crigler, 1939). A clumping of leucocytes in the rabbit's blood when in contact with the antigen was shown by Abell and Schenck (1938) and in experiments of lung perfusion by Dragstedt et al. (1940). In the intact rabbit, Rose and Weil (1939) have demonstrated that concomitantly with a

fall in leucocytes there is a substantial fall in the total histamine extracted from blood. As far as platelets are concerned, Kopeloff and Kopeloff (1941) showed a correlation between thrombocytopenia and the severity of the shock in rabbits. Finally, when the antigen is added to the sensitized rabbit's blood, there is a shift of histamine from the white blood cells to plasma, as shown first by Katz (1940). This simple and reliable technique has been extensively utilized in the study of the mechanism of histamine release. Therefore, when the white microthrombi accumulate in such a structure as the capillaries of the lung, the histamine released from platelets might act directly upon the thick smooth muscle coating of the pulmonary artery bed, producing the constriction typical of anaphylaxis in this animal species. Moreover, the mechanical plugging of capillaries with microthrombi formed by agglutinated elements might constitute an aggravating factor. We know that serotonin is present in platelets in reasonably high concentrations (Humphrey and Jaques, 1955; Pletscher et al., 1955) and that it might contribute to aggravate the effects of histamine, since it seems that serotonin might also act by increasing capillary permeability (Rowley and Benditt, 1956) and that it also can release histamine from the tissues (Feldberg and Smith, 1953). Here, too, the idea that the whole anaphylactic crisis is confined to the blood and lung circulation is too narrow, since Schachter (1953) has shown that by perfusing the limbs of a sensitized rabbit with Tyrode solution plus antigen, histamine is released from the tissues. Obviously, those findings concerning the general anaphylaxis of the rabbit might also apply to a better understanding of the mechanism of the local Arthus phenomenon, since the clumping of leucocytes and platelets with a subsequent local liberation of histamine, and other products of white cells disintegration, might constitute the *primum movens* for the increased capillary permeability, hemorrhage and necrosis characteristic of the *local anaphylaxis* in the rabbit.

Many of the classical concepts of the mechanism of anaphylaxis resulted from experiments on the guinea pig, and from the beginning the analogy was stressed between the symptoms of anaphylaxis and the pharmacological actions of histamine upon the respiratory system in this animal species. It is well known that to demonstrate a phenomenon similar to anaphylaxis in the guinea pig it is sufficient to inject half a milligram of histamine intravenously, and this analogy was clearly indicated in the first publication by Dale and Laidlaw (1910–11) as mentioned above. Nonetheless, at the beginning of the second decade of this century two apparently opposite conceptions were conflicting in the endeavor to explain anaphylaxis

in the guinea pig. According to Friedmann (1909) and Friedberger (1909) the incubation of the specific precipitate with the serum of a normal guinea pig could generate a toxin which they called anaphylatoxin. This material when injected in a normal guinea pig could reproduce a symptomatology very similar to that of anaphylactic shock. This substance—anaphylatoxin or serotoxin—became the foundation of the *humoral theory of anaphylaxis.* This theory was strongly sponsored by the Belgian immunologist Jules Bordet, who contributed a great deal to the development of this concept of the mechanism of anaphylaxis. According to Bordet (1913) it is not necessary to use the specific precipitate; the incubation of the normal guinea pig serum with agar or starch being sufficient to activate anaphylatoxin.

The humoral theory of anaphylaxis was strongly opposed by Dale and his school on the basis of experiments made on the isolated organs of the guinea pig (Schultz, 1910; Dale, 1913). The direct contact of the antigen with a sensitized piece of smooth muscle, in the complete absence of blood, was enough to elicit a strong contraction, followed by desensitization. This effect was understood as a result of the release of histamine previously bound to the cells, when the antigen combined with the antibody anchored to the reacting cells.

Since the effects of anaphylatoxin on the isolated smooth muscle were not very constant, and since this material did not contain histamine or had nothing to do with it, and since histamine was apparently the most important mediator of anaphylaxis, anaphylatoxin could not possibly be involved in the mechanism of anaphylaxis (Dale and Kellaway, 1922). In the subsequent years, the balance shifted in favor of the cellular theory of anaphylaxis, as evidence accumulated to show that the histamine from the tissues, especially from the lung, can be released by contact with the antigen (Bartosch, Feldberg and Nagel, 1932; Daly, Peat and Schild, 1935; Schild, 1939 and many others).

The hint as to the mechanism by which anaphylatoxin produces its lethal effects in the guinea pig, was given to us by the experiments of Hahn and Oberdorf (1940) showing that anti-histaminics prevent the shock produced in guinea pigs by an anaphylatoxin prepared by incubation of guinea pig serum with inulin. In 1951, in collaboration with Bier and Aronson, we started a series of experiments showing that considerable amounts of histamine are released from the guinea pig lung when perfused with an agar-prepared anaphylatoxin. Later on, it was verified that rat anaphylatoxin, which is much more potent than guinea pig anaphylatoxin, produced strong contraction of the guinea pig ileum through the libera-

tion of histamine (Rocha e Silva, 1942; Rothschild and Rocha e Silva, 1954; Rocha e Silva and Rothschild, 1956).

The argument commonly presented against anaphylatoxin as a possible mediator in the release of histamine in anaphylactic shock in the guinea pig, refers to the so-called *latent interval* of passive sensitization. In 1913, Dale had demonstrated that if the uterus was taken from a normal unsensitized guinea pig, it could be made "passively sensitive" to the antigen, after a prolonged contact with the specific antibody. A minimum of 3 hours was necessary to make the muscle responsive to the added antigen. Also *in vivo,* to produce a passive sensitization of the guinea pig, Doerr and Russ (1909) showed that an interval of time must elapse between the injection of the antibody and the assaulting injection of the antigen. This "latent period of passive anaphylaxis" would indicate that the antibodies must anchor to some specified structure (the isolated uterus or the lung of the guinea pig) in order to elicit the reaction when combining with the antigen. An excess of antibodies in the bathing fluid or in the circulation of the animal would rather prevent the development of the symptoms. In the *in vivo* experiments even a period of 48 hours between injections of the antibody and the antigen might be necessary for the production of a maximal shock in the guinea pig. These early experiments were made without much consideration of the quantitative relationships between antibody and antigen. Experiments by Kabat and Landow (1942) indicated that extremely minute amounts of antibody-N, on the order of 0.01 μg, could sensitize the horn of a guinea pig uterus to react with a large excess of antigen. To sensitize a guinea pig passively, it was enough to inject 30 μg of antibody-N; however, to produce a strong reaction, not less than 1 mg of egg-albumin (0.16 mg N) had to be injected, an amount at least 50 times as great as that necessary to precipitate all the antibody injected. The conclusion was drawn that the best anaphylactic response occurs in the region of large excess of antigen. Since in that zone it is doubtful whether a precipitate can be produced at all, it seems obvious that the release of histamine might not depend upon such a precipitation but upon a chemical reaction involving the two reacting materials ($A \times A$). However, an interesting fact that might have a bearing on our ideas about the intimate mechanism of the reaction, has recently been presented by Germuth Jr. and McKinnon (1957). An immediate passive anaphylactic shock in the guinea pig, without a latent interval, can be elicited by injecting the antigen-antibody mixture intravenously, provided a *great excess* of antigen is present. Therefore, no latency is needed for the antibody to anchor to the cells of the guinea pig's lung; not even a precipitate need be formed. It is possible that the

latent period, as shown previously, was the time needed by the cells to metabolize some of the antibody injected, in order to shift the balance to the zone of an excess of antigen.

We do not know whether anaphylatoxin is a necessary step in the release of histamine in the guinea pig anaphylaxis (this point will be discussed later). We know that anaphylatoxin does not act as a histamine releaser in the rat (Mota, 1957) and it is very doubtful whether rat anaphylatoxin can act in the dog. But anaphylatoxin is such a powerful agent in duplicating the symptomatology of anaphylaxis in the guinea pig, that we have to consider it as a possible mediator in the chain of events leading to the death of the guinea pig by anaphylaxis.

If we consider the participation of histamine in anaphylaxis in other species of animals, such as the rat or the mouse, our knowledge is not so complete. The production of anaphylaxis in the rat can be easily demonstrated (Halpern, Liacopoulos and Castillo, 1955) and the fact that anaphylaxis in the rat involves damage to mast cells and release of histamine as a predominant symptom was recently demonstrated by Mota (1957). Since serotonin is also released from mast cells in the rat's skin (Bhattacharya and Lewis, 1956; Parrat and West, 1956), it is to be expected that there is a participation of 5-HT in the production of the symptoms, inasmuch as it has been shown that the so-called "passive cutaneous anaphylaxis" of the rat is extremely resistant to anti-histaminics (Brocklehurst et al., 1955) and can also be produced in an animal with its skin histamine store strongly depleted (Rocha e Silva and Rothschild, 1955).

A cautious, but illuminating picture of the complexity of the intimate mechanism of anaphylaxis is contained in the words of Dale (1955): "We must regard it as practically certain that an injury of adequate severity will cause an activation of intracellular enzymes and that products of proteolytic cleavage may be formed in the protoplasma and diffuse from the cells into the tissue fluids, or that the enzymes may themselves be liberated, to exercise their digestive activities outside the cells. The discovery, that substances as active as histamine were present in normal cells had tended for a time to discount the evidence, much of it of a not very critical kind, which had been put forward for the formation of such active products by enzyme-action. More recently, however, the case for their existence, and for their physiological and pathological significance, appears to have been greatly strengthened by the separation in states of relative purity—though with no claim as yet for chemical isolation—of intensely active cleavage products of a peptide nature, such as those which have been described as "kallikrein" and "bradykinin". The activity of both these substances, while much slower in onset and

development than that, for example, of histamine, is nevertheless of such intensity as to preclude an attribution of either to adherent traces of histamine, which could further be excluded by qualitative differences in the details of their actions."

"It must be obvious that the liberation of histamine and the other preformed agents from the epidermal cells of the skin, or, as some would have it, from mast cells in the immediately subjacent derm, will account for no more than the initial stages of many local allergic reactions, or of the similar vascular responses to local injuries of other kinds ... this initial phase is succeeded by a much more persistent local vasodilatation, such as could much more plausibly be attributed to the effect of agents of a different kind. And it would seem that the slower and more persistent effects of the active products of a protein cleavage by locally liberated enzymes, the production of which may further continue for an unknown period after the initial trauma, might offer a possibility of explaining some, at least, of these later phases of such reactions."

Conclusion. Our endeavor was to sketch our ideas about the intimate mechanism of anaphylaxis. Since our purpose was limited, this review is far from complete. It may be that with the deliberate intention to make sense out of such a variable collection of symptoms and ideas, we have unduly left aside interesting details which will become important in the future for the description of the phenomenon. Emphasis was given more to those facts which have been confirmed in different laboratories, without exhausting the sources of the available literature. A certain number of tentative interpretations can be embedded in that network of undisputed facts. These theories might change with time and individuals, but the facts will remain as the solid ground for further developments in this most interesting field of Experimental Medicine.

Present Status of the Mechanism of Histamine Release in Anaphylaxis and Allergy

The mechanism by which histamine is released in anaphylaxis and allergy is still in the dark, in spite of the large number of papers dedicated to this problem.

For the pharmacologist it is understandable why the problem is not as yet solved. Our knowledge of the mechanism of release of other pharmacologically active substances is indeed no more complete. How is acetylcholine, serotonin, adrenaline or arterenol released in the physiological conditions of the living cell? We know more about the mechanism by which bradykinin is released by the

esterase activity of trypsin or snake venoms, because we can prepare or isolate from the plasma globulins the precursor which releases bradykinin on incubation with those enzymes. This precursor, or substrate, containing bradykinin in a bound, inactive form, can be precipitated, denatured by boiling with acetic acid, washed with distilled water and dialysed for any length of time (van Arman, 1955; Hamberg and Rocha e Silva, 1956). In the case of histamine, however, it has never been possible to isolate a substrate, or precursor, which would set histamine free. As soon as one starts trying to extract any material having histamine in a bound condition, it is released very promptly. Extraction with any solvent, even in the cold, or by heating or simply grinding the tissue with sand or distilled water, will set most of its histamine free.

Therefore, inferences about the mechanism by which histamine is released from tissues have been drawn rather on the basis of indirect evidence by using different kinds of releasing agents, such as proteolytic enzymes, snake venoms, basic compounds, or by submitting the intact or chopped tissues to conditions in which the action of enzymes might take place. But again, if one tries to identify which enzyme is involved, we are only left with more or less indirect evidence based on the effect of temperature, of inhibitors such as iodo-acetate, parachloromercuribenzoate, soybean trypsin inhibitor, and so forth.

In the special case of the release of histamine in anaphylaxis and allergy, we have to assume the interplay of many factors which might be operative under the mild conditions of the living tissue. As an aid to the following discussion, I would like to start with a general equation of the phenomenon:

$$\left\{\begin{array}{c}\text{I}\\ \text{Antigen}\\ \times\\ \text{Antibody}\end{array}\right\}\left\{\begin{array}{c}\text{II}\\ \text{Activation}\\ \text{of}\\ \text{anaphylatoxin}\end{array}\right\}\left\{\begin{array}{c}\text{III}\\ \text{Activation}\\ \text{of}\\ \text{enzymes}\end{array}\right\}\left\{\begin{array}{c}\text{IV}\\ \text{Release of histamine or}\\ \text{other active substances}\\ \text{(heparin, serotonin, slow}\\ \text{reacting substances)}\end{array}\right\}$$

To accept this equation as the final answer to the problem is not at all the intention; it is even doubtful whether the above equation can be applied to all animal species. I would like only to stress that the four processes indicated in the above scheme have been, at one time or the other, described in connection with the anaphylactic process. It is rather a mould or pattern upon which we are going to shape the following discussion.

Let us analyze the facts upon which the general equation is based.

Cellular versus humoral theory. I would like to outline briefly the origins of the "histamine theory of anaphylaxis". Since the dis-

covery of histamine by Windaus and Vogt (1907) until the demonstration in 1932 of its release in the tissues of the sensitized animal by contact with the antigen, the evidence for a participation of histamine in anaphylaxis was mainly based on analogies between its pharmacological effects and those which are typical of anaphylaxis. This analogy was already stressed in the first report by Dale and Laidlaw (1910–11) on the pharmacological properties of histamine. Even the so-called *in vitro* anaphylaxis, performed with isolated pieces of plain muscle of the intestine and uterus of the guinea pig, the so-called Schultz-Dale experiment, was still an indirect evidence of the participation of the histamine released from the surviving tissues by contact with the antigen. Since the pieces of intestine or uterus were freed by perfusion from any traces of blood, and still gave strong responses by contact with the antigen, Dale (1912–13) concluded that anaphylaxis is a cellular phenomenon resulting from the combination of the antigen with the antibody anchored to the muscle structure, releasing histamine or a closely related substance existing pre-formed in the cells of the isolated organ (Dale, 1920, 1929).

This cellular theory of anaphylaxis, so intimately dependent upon the discharge of a histamine-like substance from the sensitized tissues, was naturally opposed to the "humoral theory" set forth by Friedemann (1909), Friedberger (1910) and Bordet (1913). When the serum of a normal guinea pig was incubated with the specific precipitate or with polysaccharides such as agar, starch or inulin, a toxic principle was generated which causes a shock very similar to anaphylactic shock when injected into a normal guinea pig. The name of anaphylatoxin was given to this principle, thus implying its participation in the genesis of anaphylactic shock.

I cannot describe in detail the main arguments put forward in favor of or against the humoral or the cellular theories. The reader is referred to reviews on this subject by Rocha e Silva (1952), Hahn (1954), Rocha e Silva (1954) and the book by Rocha e Silva (1955): *"Histamine, Its Role in Anaphylaxis and Allergy"*. I will only stress the fact that with the increasing evidence that histamine was the main agent released in anaphylaxis, the anaphylatoxin theory was almost completely forgotten for many years.

Release of histamine in anaphylaxis. Among the experiments showing the release of histamine in anaphylaxis, I would like to recall those by Dragstedt and Gebauer-Fuelnegg (1932) showing the appearance of large amounts of histamine in the peripheral blood of the dog and those by Bartosch, Feldberg and Nagel (1932), on the release of histamine by perfusion of the isolated lung of the guinea pig with the antigen. There followed a series of demonstrations by

Daly, Peat and Schild (1936), Code (1939), Ungar and Parrot (1936), Schild (1939) and many others on the release of histamine in many conditions of *in vitro* and *in vivo* anaphylaxis. In the sensitized rabbit, Katz (1940) developed the technique of adding the antigen to samples of blood and estimating the histamine shifting from cells to plasma. This reaction has been extensively studied by many workers and we now know that the histamine in the rabbit's blood is mainly confined to the platelets, and its release in anaphylaxis is somehow concerned with the damage inflicted to platelets by the contact with the antigen. A similar *in vitro* technique was applied to samples of human blood taken from individuals sensitive to ragweed (Katz and Cohen, 1941). A combination of both techniques, using rabbit's blood as a reservoir of bound histamine and studying the *in vitro* release of histamine by adding sera of individuals sensitive to ragweed, was utilized by Spain, Strauss and Neumann (1950).

Release of histamine by snake venoms and proteolytic enzymes. As the evidences accumulated showing the release of histamine in anaphylaxis and allergy, the participation of histamine in other kinds of shock or poisoning has been described. In Australia, Feldberg and Kellaway (1937) described the release of enormous amounts of histamine by perfusion of the guinea pig lung with snake venoms such as the venoms of *Denisonia superba* and *Naja naja.* Later on the work was extended to show the release of histamine by perfusion of several different organs of the cat, dog and monkey, with cobra venom. In our laboratory, we have studied similar effects produced by trypsin (Rocha e Silva, 1939–40) and papain (Rocha e Silva and Andrade, 1943). In collaboration with Dragstedt, in 1940–41, we have studied the release of histamine by trypsin in samples of rabbit's blood, using the technique devised by Katz (1940). This ability of trypsin to release histamine has been confirmed many times and it is interesting to recall, as stated by McIntire (1955), that crystalline trypsin is the *only pure enzyme which has been demonstrated to release histamine.* Also peptone was shown to release histamine when injected into a dog (Dragstedt and Mead, 1936) or perfused through the isolated lungs of the guinea pig (Feldberg and O'Connor, 1937).

The importance of these experiments with animal venoms, proteolytic enzymes and peptone derived from the fact that they mimetize, in many respects, the symptomatology of anaphylaxis. *In vitro,* they produce contraction of the isolated smooth muscles of the intestine or uterus of the guinea pig, followed by desensitization, and in many instances they have been shown to act by the release of histamine. It is no wonder, therefore, that the problem of the mechanism by which histamine is released from its link with the cells,

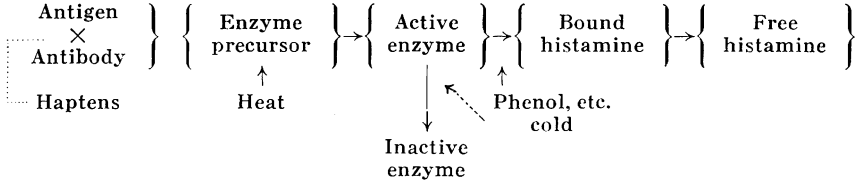
was first brought forward in connection with the action of such venoms and enzymes.

The mechanism of histamine liberation was first described as one of increased cell permeability following injury by the antigen-antibody interaction or by any agent damaging the cell structure. The histamine contained inside the cell boundaries would be in a free state and be discharged to the outside fluid as the cell wall disintegrated under the action of damaging agents. From the work done with snake venoms and proteolytic enzymes, however, two main theories have arisen assuming activation of enzymes as a prelude to the release. On the basis that lysolecithin, the hemolytic agent generated by the interaction of the lecithinase of some snake venoms with lecithin or egg yolk, also releases histamine (Feldberg and Kellaway, 1938), and since lysolecithin appears to produce hemolysis by breaking down the so-called lipoprotein complex presumably existing at the red cell surface, Feldberg (1941) advanced the hypothesis that the binding of histamine to the cells might depend upon the integrity of this lipoprotein film at the cell surface. In favor of this possibility was the parallelism found by Trethewie (1939) between the hemolytic effect of several venoms and their capacity to release histamine. However, this *lecithinase theory* could not explain the release of histamine in other phenomena such as anaphylaxis, allergy and peptone shock, in which hemolysis is no more than a rare event.

Enzymatic theory of histamine release. But if the view sponsored by Feldberg (1941) that histamine is retained by a sort of lipoprotein film at the cell surface or at any particulate structure inside of the cell is correct, damage produced by proteolytic enzyme could also release histamine. This possibility is generally known as the proteolytic theory of anaphylaxis (Rocha e Silva, 1944, 1954) and had its main argument in the fact that trypsin and papain release histamine and also that anaphylaxis is somehow connected with activation of proteolytic enzymes (Bronfenbrenner, 1944; Rocha e Silva, Andrade and Teixeira, 1946; Unger, 1947; and others). There was and still is a growing literature showing activation of proteolytic enzymes as a consequence of the interaction of the antigen with the antibody. We might properly say that this activation of proteolytic enzymes in phenomena connected with anaphylaxis is even more fundamental than the release of histamine, and whatever may be the link between histamine and the cell constituents (peptide linkage or van der Waals forces), disintegration of the cell structure by the action of these enzymes can obviously play a role in the genesis of the symptoms.

There are many indications that the release of histamine under

the conditions of anaphylaxis and allergy involves chemical and enzymatic reactions. It is now an established fact that histamine is not released *in vitro* from pieces of lung taken from a sensitized guinea pig, by the added antigen, when the temperature is lowered to 2° C at the moment of the addition of the antigen, henceforth an enzymatic action is probably required. Recently, Mongar and Schild (1957 a) investigated the effect of a previous heating of the sensitized tissues on the subsequent histamine release by contact with the antigen, and found a striking temperature band (from 20° C to 45° C) in which the histamine release can take place. If the tissues (guinea pig lung or isolated ileum or uterus) are kept for 25 minutes at 42°–43° C, the capacity of releasing histamine on further contact with the antigen is completely lost. From these data they have concluded that the enzymatic system involved in the mechanism of histamine release in anaphylaxis has a higher activation energy (45,000 calories) than that found in isolated enzyme systems. It also appeared quite clear from Mongar and Schild's experiments that the mechanism involved in the release of histamine by octylamine and the basic releasers of the 48/80 type is quite different from that occurring in anaphylaxis, since the temperature affects this release in a definitely different way. The following scheme of events has been suggested by Mongar and Schild (1957):



It appears quite certain therefore that the release involves an enzymatic system, highly sensitive to the effect of temperature. Opinions diverge on the nature of the enzymes or the enzymatic system involved. By utilizing -SH reagents such as iodacetate and p. chloromercuribenzoate, Mongar and Schild (1955) had concluded that some oxidation-reduction enzymes requiring free -SH groups would be involved. In a more elaborate attack on the problem, Mongar and Schild (1957 b) have shown that other substances such as cyanide, antipyretics, phenol, cinnamate, urethane, etc., can stop the release of histamine without apparently affecting the desensitization phenomenon due to the combination antigen-antibody. The correlation between blocking of the cell respiration and histamine release, however, is not complete since dinitrophenol was found to inhibit O_2 consumption in much lower concentration than it was

found to block the release of histamine. It seems likely that the blocking of the histamine release by cyanide and oxygen lack might rather be concerned with the state of organization of the reacting cell, since it has also been proved by the British workers that the release of histamine from a sensitized cell (guinea pig lung) by the antigen will not take place if the cell is disintegrated and the mitochondria (mast cell granules) separated by centrifugation. The opposite is verified if these cell debris are treated with basic compounds of the 48/80 type. On the other hand, the -SH reagents might block the release by acting upon an entirely different step of the process, as discussed in a later paragraph.

Along different lines, Humphrey and Jaques (1955) studied the release of histamine (and serotonin) from rabbit platelets by the antigen-antibody reaction. The platelets were separated from the blood and resuspended, after washing with Ringer's solution, in heparinized plasma which had been submitted to several experimental procedures, such as heating at 56° C for 30 minutes, or treatment with several reagents such as oxalate, versene or citrate to remove calcium ions. Adding the antigen-antibody mixture to the plasma in the presence of the suspension of platelets, the histamine releasing activity was studied under such controlled conditions. If the antigen-antibody mixture was added directly to the suspension of platelets in Ringer's solution, no release was observed. Calcium ions were found necessary for the release, and addition of the proper amount of calcium chloride was sufficient to reverse the inhibition of the release by the previous treatment with oxalate or versene, but not if the plasma was previously treated with citrate. Trypsin (40 μg/ml) rapidly and completely released histamine from platelets suspended in Ringer's solution. On the contrary, the histamine liberator 48/80, in concentrations up to 200 μg/ml, did not release histamine in conditions in which the antigen-antibody complex gave the normal complete release. Treatment of plasma with agar was followed by developments of histamine-releasing activity and also of proteolytic activity. Activation of proteolytic activity was regularly found in most instances in which the plasma acquired the histamine-releasing activity. From these experiments, the following sequence of events was outlined by Humphrey and Jaques (1955):

$$\left\{\begin{array}{c}\text{Antigen}\\ \times\\ \text{Antibody}\end{array}\right\} \xrightarrow{Ca^{++}} \left\{\begin{array}{c}\text{Fixation of some}\\ \text{component of}\\ \text{complement}\end{array}\right\} \longrightarrow \left\{\begin{array}{c}\text{Activation}\\ \text{of}\\ \text{protease}\end{array}\right\} \longrightarrow \left\{\begin{array}{c}\text{Histamine}\\ \text{serotonin}\\ \text{released}\end{array}\right\}$$

If one compares this scheme with the one given at the beginning as the fundamental equation of the phenomenon, a striking analogy can be noted. Of course, what Humphrey and Jaques call "fixation

of some component of complement" might as well be said "activation of anaphylatoxin" which is prevented by heating the serum or plasma for 30 minutes at 56° C.

Mode of action of anaphylatoxin. It is surprising that the mode of action of anaphylatoxin had to wait 40 years, since its discovery in 1909, to be understood. In 1949, Hahn and Oberdorf tried antihistaminics in two different kinds of shock in the guinea pig. The first was the so-called inverse anaphylaxis, resulting from the injection of the Forssman antibody (anti-sheep rabbit's serum) which produces a shock very similar to anaphylactic shock by combination of the injected antibody with the so-called Forssman antigen, present in the lung tissue of the guinea pig. The second kind of shock selected by the German workers was the shock produced in the guinea pig by injecting anaphylatoxin, prepared by incubating normal guinea pig serum with inulin. In both cases, the animals received a protective dose of neo-antergan. Surprisingly enough the first kind of shock was not influenced by the previous injection of the antihistaminic, while the second one (by anaphylatoxin) was completely prevented by the protective treatment.

These experiments were the clue to try the effect of anaphylatoxin on the isolated lung of the guinea pig. Experiments in our laboratory (Rocha e Silva, Aronson and Bier, 1951; Rocha e Silva and Aronson, 1951) have shown a considerable discharge of histamine by a single injection of a few ml of guinea pig's serum activated by agar. The amounts of histamine released from a single lung can be very great indeed, amounting to 100 μg after a single injection of anaphylatoxin. Confirming the finding of Novy and De Kruif (1917) we have demonstrated that anaphylatoxin prepared with rat's serum is from 4 to 10 times more potent in releasing histamine than the one prepared from guinea pig's serum, and nearly all the characteristics of the old anaphylatoxin could be found in the histamine releaser activated in normal plasma or serum by contact with agar (Rocha e Silva, 1952).

However impressive the amounts of histamine released by anaphylatoxin from the perfused lung of the guinea pig, Dale (1952) cast doubt as to the validity of this argument for the possible role of anaphylatoxin in true anaphylaxis of the guinea pig. According to Dale, it is not a question of *quantity* of histamine but rather the *place* where it is released that matters. In the perfused isolated lung of the sensitized guinea pig, though the amounts of histamine released by the antigen were small, the observed bronchiolar constriction due to spasm of the plain muscle was very potent and exceeded that observed with agar anaphylatoxin (Dale and Kellaway, 1922). A discussion on the subject can be found in the Ciba symposium on

Histamine (1955). Nevertheless, Halpern et al. (1956) have demonstrated desensitization of the guinea pig to true anaphylaxis by a previous treatment of the animal with successive injections of anaphylatoxin.

Whatever may be the role played by anaphylatoxin in true anaphylaxis in the guinea pig, it seems beyond doubt that the above experiments bridged the gap between the cellular and the humoral theory of anaphylaxis, since in both cases the final mediator appeared to be histamine itself. One of the strongest arguments against anaphylatoxin was that the product resulting from the incubation of the plasma with the antigen-antibody complex or with polysaccharides, is not very active on the isolated plain muscle of the guinea pig. We have shown that this is mainly a question of concentration; if, instead of the weak anaphylatoxin obtained from guinea pig's serum, we use the potent rat's anaphylatoxin, a powerful contraction of the ileum results from a first addition and the reaction becomes weaker after new additions of anaphylatoxin. Antihistaminics, but not atropine, block this effect, which has been understood as a consequence of a histamine release from the tissues of the guinea pig ileum. Using this effect of anaphylatoxin, it has been possible to study the conditions conducive to the activation of rat's anaphylatoxin by polysaccharides (Rocha e Silva, 1952; Rothschild and Rocha e Silva, 1954; Rocha e Silva and Rothschild, 1956). In particular, the effect of anions and cations upon the phenomenon was extensively studied. It was found that spontaneous activation takes place by adding two volumes or more of distilled water to the normal heparinized rat's plasma. On the contrary, by increasing the ionic strength to twice that of plasma, activation by agar does not occur. In this respect, calcium among the cations and citrate among the anions are the most potent in presenting activation. The process is very sensitive to temperature, being completely stopped at 2° C. The release of histamine by anaphylatoxin, when added to slices of the normal guinea pig lung, is also sensitive to temperature, being stopped by keeping the tissues at 2° C. It was shown by Hahn and Lange (1955) that the precursor of anaphylatoxin can be found in the fraction I, II, III of Cohn (albumin-free globulins) precipitated with 15.2 vol. % of ethyl alcohol. From this complex, the active fraction could be precipitated into the fraction III-O by 27.7 % of alcohol in presence of zinc. In a more recent paper, Giertz, Hahn and Lange (1956) have shown that formation of anaphylatoxin depends on the presence of two fractions: the fraction III-0, thermolabile and possibly enzymatic in nature, and the other contained in the remaining I–III-1, 2, 3. Anaphylatoxin would result from the interaction of both fractions, depending on the enzymatic reaction of the first one.

This demonstration that anaphylatoxin belongs to the protein complex of the plasma is interesting because it discards the possibility of its functioning as one of the basic compounds which will be studied in the next paragraph. It was already clear that this could not be the case, since anaphylatoxin does not release histamine from rat's skin, and works most suitably in the guinea pig, although the basic compounds, of the 48/80 type, do just the opposite: they work satisfactorily on the rat's skin, depleting it of most of the stock of histamine, and are very poor releasers when perfused through the guinea pig lung. It would be reasonable to assume, as suggested by Ungar (1955), that anaphylatoxin activates a protease in the guinea pig lung, and that this would be the ultimate agent in the release of histamine, though a direct proof of this final step is still lacking. It is also relevant that the release of histamine from lung slices by anaphylatoxin is blocked by -SH inhibitors such as iodacetate and p. chloromercuribenzoate, as shown by Moussatché and Danon (1956) and confirmed in our laboratory. Of considerable interest is the work by Haining (1956) on the inhibition by salicylate and 3.hydroxy-2.phenylcinchoninic acid (HPCA) of the release of histamine from rabbit's blood cells by the antigen-antibody complex and by dextran sulphate, and also the action of anaphylatoxin upon the guinea pig ileum, which has been demonstrated to be due to a release of histamine. In this respect, HPCA is a much stronger inhibitor of both phenomena than salicylate. When comparing the effects of different dextrans and agar on the release of histamine and activation of proteolytic enzymes, Haining (1955, 56) has found a discrepancy, since one of the dextrans utilized (Dextran-D) is able to release histamine and to form anaphylatoxin, but could not show any detectable protease activation in rabbit's serum. We have also a few indications that activation of proteolytic enzymes is not concerned with anaphylatoxin formation, and this has been shown in parallel experiments with bradykinin release and anaphylatoxin formation in rat's serum (Rocha e Silva, 1955). Since both phenomena have an independent course, we can assume that they are not interdependent, otherwise each time anaphylatoxin would be activated (by polysaccharides), some bradykinin should be released, which is not the case.

Release of histamine by basic compounds. In the late forties it became common knowledge that many basic substances, such as D. tubocurarine, atropine, strychnine, adrenaline, and so forth, liberate histamine from certain biological structures, especially the striated muscle of the rat and from the rat's skin. An extensive study of the conditions of the release of histamine from the diaphragm and the hind legs of the rat, by D. tubocurarine was made by

Rocha e Silva and Schild (1949). A number of substituted amines, diamines and diguanidines release histamine when injected into the cat or the dog (Mac Intosch and Paton, 1949). In 1951, Paton described a similar release by the compound 48/80, first described by Baltzly, Buck, De Beer and Webb (1949) as a condensation product of p. methoxyphenethylmethylamine with formaldehyde. So far, 48/80 is considered the most potent histamine releaser for certain structures, such as the rat's skin or diaphragm. When injected through the perfused hind legs of the rat, a few μgs of 48/80 are able to release a comparable amount of histamine or more, and since its molecule is many times larger than that of histamine, this indicates that one molecule of 48/80 is able to release several molecules of histamine. However, this compound is surprisingly inactive upon the guinea pig lung or the digestive tract.

Histamine release from mast cells. The metachromatic granules of the mast cells, or the Ehrlich's basophil cells of the connective tissue, were known since Wilander (1938) to be depots of heparin. Recently Riley and West (1952–53) described a striking parallelism between the content of histamine and the number of mast cells observed in any structure. Mast cell tumors, for instance, can give as much as 1 mg of histamine per gram. The ox pleura, in which mast cells swarm, can have as much as 200 to 300 μg of histamine. When a lethal dose of a fluorescent histamine liberator such as stilbamidine is injected into a rat, the fluorescent material can be detected inside the mast cells as a prelude to their disintegration (Riley, 1953). A correlation between disruption of mast cells and histamine liberation was thus very probable. These findings, of course, could be related to previous findings by Wilander (1938) that in peptone shock in the dog, concomitantly with the release of heparin, there is a disruption of the granules of the mast cells, and the correlation between release of heparin and of histamine from dog's liver has been shown in direct *in vitro* experiments (Rocha e Silva, Scroggie, Fidlar and Jaques, 1947) by perfusing the dog's liver with natural blood kept unclotted in silicone flasks and to which peptone was added immediately before the passage through the isolated dog's liver. More recently, disruption of mast cells in the lung of the guinea pig was demonstrated in anaphylaxis by Mota and Vugman (1956), when large amounts of histamine were released from the lung of the sensitized animal receiving an injection of antigen. A similar disruption of mast cells in the mesentery of the rat following injection of 48/80 has been described by Mota, Beraldo and Junqueira (1953) and also in the rat's skin by injection of peptone (Mota et al., 1954).

It seems, therefore, that disintegration of mast cells is always con-

nected with the release of histamine. We do not know for certain if the converse is true, i.e. if every release of histamine depends upon destruction of mast cells. In the rabbit's blood, for instance, histamine is mainly bound to platelets and its release depends upon an action on these elements. But the important question is to know whether in the mechanism of release of histamine in anaphylaxis, one might postulate the interaction of a mediator of the nature of these basic releasers of the 48/80 type. Here we find a few striking discrepancies. Mongar and Schild (1952) showed a certain parallelism between the percentage of histamine released in different tissues of the guinea pig by contact with egg white and with the compound 48/80. However, a previous application of 48/80 to pieces of intestine increased considerably the output of histamine following a further contact with the egg albumin, while by inverting the order of addition, the egg albumin had no effect upon further release produced by 48/80. Furthermore, by using minced lung from animals sensitized to egg white, Mongar and Schild (1955) have shown that although addition of iodoacetate prevents the release of histamine in anaphylaxis, the addition of the same agent almost doubled the release of histamine by 48/80 or octylamine. Also impressive is the difference described by Mota and Vugman (1956) between the mechanisms by which guinea pigs die from anaphylactic shock and from an injection of 48/80; although in the first instance the symptomatology recalls strongly that produced by histamine, the injection of a lethal dose of 48/80 induces in the guinea pig a sort of collapse, without gross impairment of the respiratory function. On autopsy, the lungs in both groups of animals are quite different; in the first group a strong emphysema could be observed, while in the animals submitted to 48/80 shock the lungs were collapsed. Furthermore, and what seems to be more striking, is the fact that in the guinea pig submitted to anaphylactic shock, the mast cells were almost completely destroyed in the lungs, while in the group of animals receiving the lethal dose of 48/80, the cells appeared little affected.

In the rat, the discrepancy is also impressive, but in another way. As shown by Ovary (1952) one can reproduce in the rat's skin a reaction called "passive cutaneous anaphylaxis", by injecting intradermally minute amounts of antibody, and a few hours later, intravenously, a mixture of the antigen + Geigy blue, or trypan blue. A positive reaction is indicated by a strong blue staining of the skin at the sites of injection of the antibody. Using this reaction, we have recently shown (Rocha e Silva and Rothschild, 1955) that this anaphylactic reaction is not in the least affected by a previous treatment of the rat with 48/80, although this completely prevents any further effect produced upon the skin by an intracutaneous injection of

TABLE I

Processes possibly involved in the mechanism of histamine release in anaphylaxis and related phenomena.

Biological structures involved:	Main processes			
	I	II	III	IV
Guinea pig's lung	Antigen × Antibody	Activ. of anaphylatoxin	Activ. of enzymes SH enzymes? SH activator?	Histamine release (blocked by iodoacetate, etc
	Polysaccharides (agar, starch, etc.)			
		Basic compounds (48/80, ovomucoid, etc.)	Activ. of enzymes (No block by SH inhibitors)	Histamine release (increased by iodoacetate)
Rat's skin (P.C.A.)	Antigen × Antibody	Activ. of anaphylatoxin	Activ. of enzymes Proteolytic?	No histamin release Positive blue test
	Polysaccharides (agar, starch, etc.)	Depletion of anaphylatoxin		No skin reactio to AxA.
		Basic compounds (48/80, ovomucoid, etc.)	Activ. of enzymes in plasma	Histamine release (no heparin)
			Disruption of mast cells	
Rabbit's blood	Antigen × Antibody	Activ. of anaphylatoxin	Activ. of enzymes (protease?)	Histamine and serotonin release
	Polysaccharides	Peptone	Trypsin, papain.	Histamine release
Dog's liver	Antigen × Antibody	Total blood needed (leuc., platelets?)	Activ. of enzymes in plasma	Histamine and heparin released
		Peptone		

48/80 itself, ovomucoid or dextran. Similar results have been published recently by Brocklehurst, Humphrey and Perry (1955), who have found that antihistaminics did not block the passive cutaneous anaphylaxis in the skin of the rat, and that depletion of the skin histamine had no effect either. It is therefore even doubtful whether anaphylaxis in the rat is mediated by a histamine release.

Whatever might be the explanation for these discrepancies, it appears quite clear that anaphylaxis follows a route which does not

necessarily pass through a stage where a basic simple agent similar to 18/80 or mono or diamines is released to account for the liberation of histamine.

Concluding remarks. I would like to complete this review of the many aspects of the problem of histamine release, by presenting a general picture of the phenomenon as it appears in different animal species currently employed in experimental anaphylaxis. I take, as a basic pattern, the four processes indicated at the beginning of this review. The way to read the scheme presented in Table I, is the following: in the horizontal line we may have the natural sequence of events leading to the release of histamine or of other pharmacologically active agents. In the vertical direction, we have somehow "equivalent" processes. For instance, in the activation of anaphylatoxin, polysaccharides can take the place of the Antigen × Antibody complex, therefore polysaccharides are presented in column I. The basic releasers, such as 48/80, ovomucoid or dextran, do not activate anaphylatoxin, but appear to work through an enzymatic system. This enzymatic system is not inhibited by -SH blocking reagents, such as iodoacetate or p. chloromercuribenzoate. Neither does peptone activate anaphylatoxin. Therefore, they are "equivalents" (not in the exact meaning of the term, but in their position in the "pattern") to anaphylatoxin and are placed in column II. Trypsin and papain, and possibly other proteases, act directly upon the cell structures to which histamine is bound, and therefore they are placed in column III. The final step, the release of histamine in column IV, might not occur, as in the rat's skin in the passive cutaneous anaphylaxis. In fact, process IV indicates the final agent producing the observed symptoms, such as contraction of smooth muscle, increased capillary permeability, vascular collapse, non-coagulability of the blood, and so forth. Thus the "equivalent" to histamine in this final process, could be serotonin, slowly reacting substances, heparin, or unknown mediators as they occur in the rat's skin reaction.

It is to be hoped that the apparent complexity of the scheme of Table I will not induce a general feeling of discouragement as to the prospects of a future clarification of the whole problem. The mechanisms involved in muscle contraction or in coagulation of the blood are infinitely more complicated. We know for certain that Nature is not playing any tricks with us and that one day we will probably be able to unveil all the details of the phenomenon, and our grandchildren might be able to say: "What a wonderful and simple mechanism Nature invented to elude our grandfathers!"

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THE PHYSIOPATHOLOGICAL ROLE OF HISTAMINE IN MAN

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I. HISTAMINE, A NORMAL CONSTITUENT OF THE ORGANISM. DISTRIBUTION AND METABOLISM

1. Histamine (H) is a normal constituent of human tissues. It is held in a bound form, pharmacodynamically inactive; the nature of this binding, physiochemical rather than chemical, is not fully understood. On fractional centrifugation, bound histamine accompanies the mitochondrial "particle" fraction (Ciba Symposium on Histamine, 1956). The histamine content in tissues varies considerably in various organs and according to the individual who has provided the samples. The *skin*, studied by Craps and Inderbitzin (1957) and by Stern (Symp. All., 1957) contains 2 to 20 μg/g., its concentration being highest at the cephalic extremity (eyelids, forehead and neck). Mast cells, normal or tumorous, are particularly well supplied (Hamrin, 1957). The *central nervous system*, systematically analyzed by Werle (Ciba Symposium, 1956) shows a variable content according to the zone concerned, the greatest amount being found in the superior cervical sympathetic ganglion (10 μg/g.), whereas the posterior medullary roots and the medulla itself contain practically none (0.5 to 0.05 μg/g.). The lungs contain between 8 and 20 μg/g. (Schild et al., 1951)—those of a fetus less than 2 μg/g. (Werle and Meitinger, 1950)—while 10 to 20 μg/g. are found in the nasal mucous membrane (Baxter and Rose, 1953). In the digestive tract, 10μg/g. are found in the mucous membrane of the prepyloric area, 6 μg/g. in the fundus (Code, Ciba Symp., 1956), and 40 μg/g. or more in the small intestine. Free histamine is also present in the gastric juice where its concentration varies between 0.8 and 8 μg./litre (Adam et al., 1954).

2. Histaminemia is the sum of the plasma histamine and histamine bound to the leukocytes. These two constituents vary independently of each other (Code, 1952).

The most rigorous techniques for the determination of plasma

histamine are at present that of Lowry and collaborators (1954), in which no biological reaction is used, and that of Adam and collaborators (1957), in which the dosage involves a surfusion of a guinea pig ileum. Their results are comparable and determine the value of plasma histamine in its free form to be less than 3 μg/litre. The γ-globulins can nevertheless fix a considerable quantity (Parrot, Ciba Symp., 1956).

3. Histamine has been shown to be present in the urine, in which it is found in the free and in the acetylated form (Urbach, 1949). Schayer and Cooper (1956) have moreover shown that 1. methyl-imidazole-4 acetic acid is the principal metabolite found in the urine after an intradermal injection of radio-active histamine. Small quantities of ribosyl-imidazole-4 acetic acid, imidazole acetic acid, 1. methyl 4-(β aminoethyl) imidazole, methyl-histamine and finally free histamine are also present.

With the technique of Düner and Pernow (1956), the elimination of free histamine in the urine varies from 3.3 to 12 μg/24 hours and in a combined form from 1 to 32 μg/24 hours. There is no correlation between this elimination and the diuresis.

4. The presence of derivatives of imino-acetic acid in human urine confirms the fact that part of the histamine is destroyed by the action of amino-oxydase. This action is, however, less important than the methylation process (Schayer and Cooper, 1956).

Various human tissues contain histaminase, particularly the kidneys, suprarenals, liver, intestine and blood platelets, while plasma is practically devoid of it (Ciba Symposium, 1956). The placenta (Decidua Compacta) contains large quantities which normally pass into the blood stream of the pregnant woman, endowing it with an important histaminolytic property (Van den Driessche, 1953).

5. Slow intravenous infusion of exogenous histamine does not necessarily give rise to an increase in plasma histamine, even if the infused quantity reaches 116 μg/kg/min., as exagenous histamine is rapidly fixed and destroyed by the tissues. It is, however, followed by an increased free histamine content in the urine, representing approximately 1 % of the infused quantity (Adam et al., 1954). The ingestion of histamine produces a rise in the value of acetyl-histamine, formed in the intestine by bacterial activity.

Summarizing: the metabolism of histamine can be outlined in the following manner: tissue histamine arises from the decarboxylation of histidine. It is bound to certain cellular constituents; the mast cells are particularly well supplied. It is constantly released in small doses in the blood plasma; it is either destroyed by histaminase, methylated, or undergoes further transformations before being eliminated in the urine.

Ingested histamine is either acetylated and excreted as such, or deaminized in the intestinal mucous membrane and excreted in the form of imidazole acetic acid. Histamine administered parenterally appears in the urine in the form of free histamine, accompanied by various metabolites; it is not fixed by the tissues. The increase of free histamine in the urine henceforth is a good indication of its previous presence in the blood plasma and of its release from the tissues.

II. The Pharmacodynamic Properties of Histamine in Normal Individuals

1. The intradermal injection of a small quantity of histamine (above 1.10^{-6} g.) causes the appearance of a *complex vascular response*, consisting of three independent reactions: the triple response of Lewis (1927). One observes a local dilatation of the small vessels (central macule), an increase in their permeability (papule) and finally at some distance a dilatation of the adjacent arterioles (peripheral erythema). While macule and papule depend on a direct action of histamine, the erythema denotes a reflex mechanism of which the involved fibres are not definitely known. The various participating mechanisms have been described by Parrot and Reuse (1954).

In addition to the vascular phenomena, histamine produces *pruritis* (above $0.3.\ 10^{-4}$ g.) (Broadbent, 1955). The threshold of this symptom is generally higher than that of the papule and it usually disappears before it. In the same dose (0.16 to $0.25.\ 10^{-4}$ g.) histamine gives rise to a sharp transitory *pain*, resembling that of a burn (Rosenthal, 1949).

2. The effects of a *rapid intravenous injection* of a single dose of histamine become more marked when the injected dose increases (Weiss et al., 1932). By this means it is possible to provoke: cephalic vasodilation with hypotension, tachycardia, lipothymia, syncope, cold sweat, at times bradypnea, vomiting and diarrhea. The return to normal systolic values is accompanied by bilateral throbbing headaches. At times a secondary arterial hypertension may be noticed. The return to normal levels is slower in sympathectomized patients (see Fig. I). With large doses—0.5 to 1 mg.—a cardiovascular collapse may be observed.

These symptoms can be better analyzed when slow, prolonged infusions of histamine are administered in increasing doses.

3. Slow intravenous administration of histamine (above $1\mu g$/minute), causes complex reactions, chiefly affecting the cardiovascular system (Weiss et al., 1932; Pickering, 1933; Wakim, 1949; Lecomte, 1956).

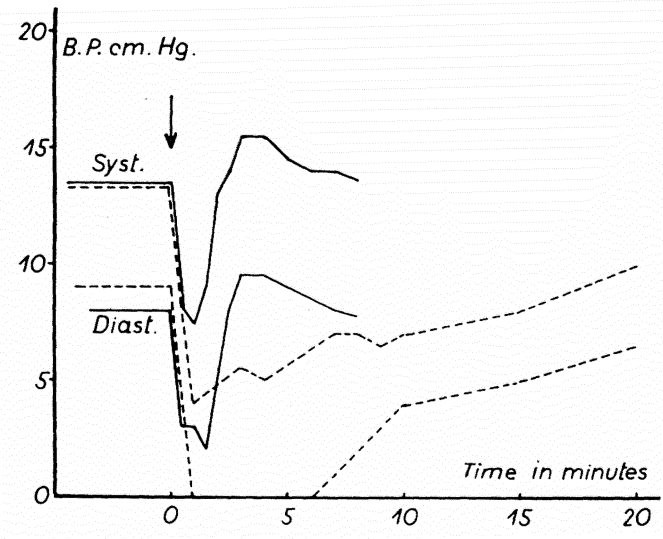

Fig. 1.
Comparison of the effect of the injection of a small dose of histamine (150 μg.) on the systolic and diastolic arterial pressure in a normal and a sympathectomized patient.

Ordinate: arterial pressure, expressed in cm mercury.
Abscissa: time, in minutes.
Full line: graph of pressure in a normal subject.
Broken line: graph of pressure in a patient with bilateral sympathectomy.
At time 0: a rapid intravenous injection of 150 μg. of histamine bichlorhydrate was given.

The fall in pressure is more marked and more prolonged in the sympathectomized subject, who also showed signs of an incipient cardiovascular collapse. In the normal subject, the initial hypotensive phase is followed by a transitory, secondary increase in pressure. The histamine tolerance of the sympathectomized patient is greatly diminished, as compared with the normal subject.

a. With doses under 20 μg/min., the vessels of the cephalic extremity experience a major vasodilatation, both venous and arterial, indicated by a sensation of warmth and an intense flushing, sometimes cyanotic; the cerebral vessels become dilated too. This vasodilatation extends progressively towards the extremities and is not accompanied by pruritus or pain. It is followed by an increase in capillary pressure, whereas the venous pressure remains unchanged; the pulse rate is accelerated and the cardiac output increased.

b. Above 20 μg/min., this generalized vasodilatation is accompanied by an arterial hypotension, proportionate to the administered dose; at the same time an intense tachycardia occurs. With stronger

doses, lipothymia and syncope may appear when the hypotension is pronounced. The electrocardiogram shows a progressive flattening of R and T waves.

c. The phase of vasodilatation may be followed by a sudden rise in systolic arterial pressure due to a compensatory sympathetic reaction with secretion of sympathetic adrenal medullary amines into the plasma.

The increase in systolic pressure at the end of the infusion is accompanied by an intense bilateral temporo-parietal headache, caused by distension of the dilated branches of the internal and external carotid arteries by the increased systolic output. This has been particularly studied by Wolff (1955).

d. The infusion of histamine, above 0.07 to 0.13 μg/kg/min., lasting 2 hours (Adam et al., 1954), causes hypersecretion of gastric acid, accompanied at higher doses by violent vomiting, colic and urgent micturition and defecation.

e. Bradypnea and bronchial wheezing are occasionally observed.

f. The uterine tonus is unaffected, even in pregnant women.

g. Basal metabolism and glycemia are increased; these variations are perhaps dependent upon a concomitant hyperadrenalinemia.

h. Hematocrit values are increased, there is leukocytosis with polynucleosis; circulating eosinophils disappear and thrombocytemia is increased.

i. Indirect and direct signs of adrenocortical stimulation are evident after administration of high doses (0.5 to 1 mg.), notably eosinopenia (Perlstein, 1955).

4. The *intra-arterial administration of histamine* (1 to 20μg/min.) in the forearm causes an increase in the circulatory rate in the perfused region proportionate to the injected dose (Duff and Whelan, 1954). If the quantity of histamine is considerable, vasodilatation is accompanied by cutaneous edema and urticaria with erythema.

5. *Aerosols of histamine* (1 to 2 %) cause bradypnea with prolongation of the expiratory phase; this dyspnea rapidly disappears at the end of the administration. The transpulmonary resorption of the amine is marked by intense cephalic vasodilatation and gastric hypersecretion (Dautrebande, 1951).

6. The *ingestion of histamine* (1 to 5 mg.) does not give rise to symptoms. No peculiarity is seen on X-ray examination of the stomach after a barium meal.

7. The antagonists of the effects of histamine are the same in clinical medicine as in animal pharmacodynamics. They can be divided into physiological antagonists, which counteract certain histamine properties by opposite effects; thus, epinephrine and the sympathicomimetic vasoconstrictors reduce vasodilatation and hypotension, and suppress bronchospasm by their bronchodilating

action. The synthetic antihistamines (AHS) electively neutralize certain effects of histamine; their posology, side-effects and duration of action vary. As a rule they suppress the pruritus, the pain and the Lewis triple response which follow the intradermal injection of H. They also reduce the arterial hypotension and the bronchospasm and exert an important anti-edematous action, which according to Halpern (Proc. 1° Int. Congress All., 1952), is beyond the limits of a strict antagonism against H. They do not influence the secretion of gastric acid.

Summarizing: histamine causes in normal individuals vasodilatation of the arterioles and capillaries, an increase in capillary permeability and a rise in the tone of certain smooth muscle fibres (digestive and respiratory tract). It induces a hypersecretion of gastric juice and stimulates the cutaneous prurigenous and algogenic nerve endings.

Furthermore, it indirectly brings about compensatory sympathetic reflexes, with adrenaline and adrenocortical hormone secretion.

The quantity of histamine present in the tissues is sufficient to reach the threshold of the various pharmacodynamic properties of the amine. Its release can thus *a priori* be indicated by a symptomatic pathognomonic entity.

III. The Role of Histamine in Human Physiology

Participation of histamine in the normal functioning of certain organs has often been postulated; it is however rarely established with certainty.

1. Histamine constitutes the normal physiological stimulant for the gastric acid secretion (Code, Ciba Symposium, 1956).

2. Its role in the vasodilatation following the stimulation of the posterior roots is contested (Parrot and Reuse, 1954).

3. The amine intervenes in the provocation of pruritus of peripheral origin. It is one of the normal excitants of certain pain-sensitive nerve endings. The cutaneous regions which have the highest H content are also those most sensitive to pain and require a greater amount of local anesthetic (Stern, Symp. all., 1957). It can induce axon reflexes whereby the excitation of various nerve structures is involved; the existence of afferent histaminergic nerve fibres is contested (Parrot and Reuse, 1954).

4. Histamine does not participate in paroxysmal post-ischemic vasodilatation (*reactive hyperemia*) nor in the vasodilatation caused by exposure to cold (Whelan, Ciba Symp., 1956). Nevertheless, as a local hormone, it regulates certain peripheral circulatory circuits (Feldberg and Schilf, 1930).

Appendix:

1. *Diagnostic applications of histamine.*

a. By intradermal injections in stages, histamine (10 μg) serves to determine the degree of residual capillary vascularization in limbs with damaged arterial circulation.

b. By subcutaneous or intradermal route (100 to 500 μg), it influences the secretion of gastric acid.

c. At the same dosage it provokes headaches in certain receptive individuals, or bronchospasm in patients with allergic asthma.

d. Intravenously (100 to 200 μg), it causes an increased systolic tension exceeding 7 to 8 cm. Hg in patients suffering from pheochromocytoma (Roth and Kvale, 1945).

e. The interval between the facial flush and the intravenous injection of histamine serves as a measure for the circulatory rate.

2. *Therapeutic applications of histamine.*

These are variable and are related to:

a. the vasodilating properties of continuous infusions of histamine (acute cerebral ischemia, arterial occlusion, Ménière's syndrome.

b. the adrenocorticoid stimulating property, (rheumatoid arthritis).

c. the diminution of the sensitivity to histamine by repeated injections of small and regularly increasing doses. (Applications of this desensitization are very numerous.)

IV. The Pharmacodynamical Release of Endogenous Histamine

Administration of a histamine releasing agent (1935 L and 48/80) to a normal individual causes the histamine, normally bound in the tissues (endogenous H), to enter the circulation in an active form (Lecomte, 1956). This histamine, passing from the lymphatic spaces into the circulating plasma, is fixed by the tissues and partially eliminated by the kidneys. It produces a series of clinically recognizable signs and symptoms.

1. On *intradermal administration,* 1935 L and 48/80 (above 0.1 μg) cause pain and pruritus, followed by a distinct Lewis triple reaction. The discharged lymph is rich in free histamine. Previous treatment with antihistamines suppresses all local manifestations.

Identity with the clinical effects of histamine, the presence of the latter in the lymph and the antagonistic action of AHS establish the role of cutaneous endogenous histamine in the pathogenesis of this local lesion.

2. On *intravenous administration,* 1935 L provokes a pathognomonic syndrome.

a. The release of a small quantity of tissue histamine produces effects of minor importance. Two to three minutes following its

liberation, the patient experiences a definite cephalic warmth, the face is the site of an extremely unpleasant prickling, face and neck become erythematous, pulse rate and arterial pressure remain unchanged. After 5 to 8 minutes the colour of the skin returns to normal.

b. If the amount of liberated histamine is important, the clinical signs are obvious. From the beginning the patient suffers a prickling and pruritus of the face as well as an intense feeling of cephalic warmth. The face immediately becomes erythematous, the eyes water. Flushing quickly invades the upper thorax, abdomen and groin. Pruritus, localized at first at the cephalic extremity, palms and soles, spreads over the body. Pulse rate is rapid and the arterial pressure is considerably lowered. The patient experiences excruciating headaches, acid vomiting and a feeling of imminent defecation:

After 10 minutes the reaction fades; pruritus and pain diminish, the erythema becomes milder. Urticarial papules of varying size and shape then successively develop on the neck, the shoulders and arms. The face has a swollen appearance; edema invades the eyelids, upper thorax, thighs; lastly the abdomen shows the same papular swellings. After 10 minutes, there is an evident progressive reduction in the cardiovascular signs; erythema, urticaria and finally edema disappear. An unusual feeling of warmth will persist for approximately an hour. No delayed reactions complicate the clinical picture.

3. *Intra-arterial administration* of a histamine releasing substance (d. tubocurarine) is accompanied by vasodilatation with pruritus, followed by urticaria and edema in the irrigated area (Grob, Harvey and Lilienthal, 1947).

4. The application of the same substance to the *nasal mucous membrane* does not induce any reaction (Melon and Lecomte, 1958).

5. The symptoms produced by the release of histamine may be described as follows:

a. *Cutaneous manifestations.*

α) Prickling is the first sensation perceived, it is transitory and never passes beyond the upper thorax. It differs from pruritus.

β) Pruritus appears shortly after the prickling on which it is often superimposed. Its location is at first limited to the face and neck, but if the dose is increased, it spreads to the thorax, epigastrium and abdomen, finally covering the entire cutaneous surface. It appears before the erythema and precedes by 3 to 5 minutes the development of urticaria. One may however observe urticarial papules without particularly violent pruritus.

γ) Erythema, due to vasodilatation, spreads on the skin according

to the following topography: immediately visible at the cephalic extremity, it extends progressively to the neck, thorax, abdomen and upper parts of the thighs, sparing the distal portion of the lower limbs. Erythema is always most pronounced on the neck and forehead.

δ) Clinical characteristics of the urticaria vary according to the area. It begins at the upper thorax in the form of peripilary nodules, which punctuate the erythema. These nodules unite into small papules, whose volume, continuously increasing, soon reaches remarkable dimensions. The fusion of these papules causes a true hard edema of the face, filling the upper and lower palpebral fossae; forehead and lips are swollen (Quincke's edema).

Thereafter the urticaria spreads to the flexor sides of the upper extremities, the upper part of the back and abdomen; it finally covers the interior side of the thighs but never extends below the knees. Pressure points are electively occupied by cutaneous nodules.

b. *Circulatory manifestations.*

α) Vasodilatation, the cause of erythema, has previously been mentioned. It accounts for the fall in blood pressure.

β) The intensity of this lowering in blood pressure is in relation to the administered dose and varies considerably according to the patient under consideration. It does not seem to depend on age or sex, but on the initial arterial systolic pressure; hypertensives experience a greater fall than normotensives.

There is often a definite relation between the intensity of the fall in blood pressure and the severity of the erythema. When the patient is in a state of cardiovascular collapse, however, the erythema fades considerably.

Return to normal blood pressure is rapid. Occasionally, the systolic arterial pressure exceeds the original level by 2 to 3 cm. Hg. At times, this hypertensive reaction develops after an abortive hypotensive phase and reaches 5 to 6 cm. Hg. In all cases the return to normal values precedes the disappearance of the erythema and the urticaria.

γ) The cephalic headaches are of the pulsating type and are often unbearable. They occur simultaneously with the rise of the arterial pressure rather than during the hypotensive phase. No hemicranial tenderness is revealed.

c. *Respiratory manifestations.*

Bradypnea is often the only symptom; in the majority of cases, it is indicated by an increased expiratory effort accompanied by a

definite sensation of retrosternal oppression without bronchial or tracheal rales.

d. *Digestive manifestations.*

Digestive signs are less frequent; nausea, vomiting, imperative need to defecate and colic may appear when large doses are administered.

The introduction of a gastric tube in the fasting patient submitted to an intravenous injection of 1935 L shows the following modifications of the gastric fluid: within 15 minutes following the injection, the gastric contents generally become strongly acid, while in the control samples the pH usually remains around neutral.

6. These manifestations undoubtedly depend on the rapid release of tissue histamine. Not only do they present close analogies with the pharmacodynamic effects of exogenous histamine (notably gastric hypersecretion), but they are also accompanied by an increase in plasma histamine, and are suppressed by preliminary treatment with AHS (Lecomte, 1956). There are some differences however between the effects of exogenous histamine and those exerted by the liberation of endogenous histamine. The latter is accompanied by local tissue manifestations, such as pruritus, prickling and urticaria, which are generally absent after intravenous infusions.

The release of endogenous histamine induces homeostatic reactions in the adrenal medulla and cortex; the latter are evidenced by a delayed increase in the level of the plasma 17-hydroxycorticosteroids (Roskam *et al.*, 1956).

Increased histaminemia does not necessarily give rise to a syndrome analogous to that following the administration of a histamine releasing substance. Thus myeloid leukemias show a particularly high level of circulating histamine without associated clinical signs. The factor of importance is the concentration of *free* plasma histamine.

The increase in free histamine is often transitory and must be studied by successive determinations (Strengers *et al.*, 1956). Sometimes, when the liberation of tissue histamine is slow or of little importance, no increase in histaminemia is observed in spite of the concomitant presence of local histaminic lesions (urticaria, hypersecretion of gastric acid).

Summarizing: The pharmacodynamic release of endogenous histamine in the normal subject shows a special clinical picture, which includes vasodilatation, increase in vascular permeability, rise in tone of certain smooth muscle fibres, hypersecretion of gastric acid

juices and stimulation of certain prurigenous and algogenous nerve endings.

The determinative role of histamine can be confirmed by:

1. its presence in plasma in a free state,
2. the analogies between its pharmacodynamic properties and the observed manifestations, particularly the hypersecretion of gastric acid,
3. the neutralization of certain effects by antihistamines.

V. The Physiopathological Role of Histamine

The pathogenic role of histamine, often postulated, has only been established with certainty in a relatively few number of morbid phenomena. To demonstrate this role, it is not sufficient to evidence an increased histaminemia; it is necessary that this histaminemia should correspond to an increase in the free form, and be accompanied by some clinical signs analogous to the pharmacodynamic effects of histamine. An increase in free histamine in the urine is also a good indicator of a tissue liberation.

The determination of the endogenous histamine content in pathological tissues is often fallacious because every afflux of leukocytes is accompanied by a contribution of bound cellular histamine, upsetting the results (Craps and Inderbitzin, 1957). The disappearance of any manifestation after treatment with antihistamines or substances of non-specific activity (Halpern, Proc. 1st Int. Congress All.), constitutes only a vague presumption in favour of a histaminic pathogenesis.

We will now consider the pathogenic role of histamine, in non-allergic individuals and then in patients with allergic diseases.

A. *Non Allergic Conditions.*

1. *Local lesions.* Lewis (1927) was the first to establish the role of histamine release in the pathogeny of numerous cutaneous reactions, in which macule, papule and erythema are recognized clinically. Some chemical agents causing similar lesions are shown in Table I.

Urticaria factitia (dermographism) is accompanied by a liberation of histamine (Lewis, 1927; Kalk, 1929). Similarly, cholinergic urticaria is the consequence of the liberation of histamine releasing substances through sweating (Herxheimer, 1957).

The role of endogenous histamine in local inflammatory cutaneous reactions is difficult to judge: the lesions caused by venoms, microbial toxins, septic inflammations, burns, have a complex pathogen-

esis in which histamine probably plays a part. Histamine, by increasing the vascular permeability with out-pouring of plasma, together with its stimulating effect on the reticulo-endothelial cells and on phagocytosis in general (Stern, Symp. All., 1957), contributes to limit the extension of septic lesions (Mechanism of Inflam., 1957).

TABLE I

The following drugs cause local reactions of the histamine type by intradermal injection.

Alkaloids of opium and narcotics:	morphine, codeine, dionine, papaverine, thebaine, penthidine.
Curarising agents:	curare, d-tubocurarine, laudexium, compound 15.
Various alkaloids:	atropine, strychnine.
Antibiotics and chemotherapeutic agents:	licheniformine, propamidine, pentamidine, stilbamidine, antricyde, trypoflavine.
Diamines:	cystamine, diamino-octane and -decane, diguanidinopentane, diisothioureahexane.
Various:	priscol, apresoline, amphetamine, tyramine, 1935 L, 48/80. biliary salts.

It is to be noted that certain irritations of the skin, e.g. exposure to cold, irradiation by X-rays or ultraviolet rays, are sometimes accompanied by a decrease in the local content of endogenous histamine, with no Lewis triple response, as the liberation of H is too slow.

We may also recall that certain insect stings and urticant plants directly introduce into the skin a complex solution of histamine, acetylcholine and 5-hydroxytryptamine.

2. *General reactions.* The extension of certain histamine releasing processes over a large cutaneous surface can bring about general signs of endogenous histamine intoxication. This occurs especially in subjects particularly sensitive to cold after prolonged exposure. This hypersensitivity to cold (often erroneously called "physical allergy") is accompanied, after the patient has been exposed for a long time to low temperature, by cephalic vasodilatation, hypotension, localized urticaria and pyrosis with vomiting (Horton, Brown and Roth, 1936). A constant trend of the gastric pH towards acidity can be shown (Horton and Gabrielson, 1940). These vasomotor reactions occur simultaneously with an increase in histaminemia. They are prevented by previous treatment with synthetic antihistamines.

TABLE II

The intravenous administration of the following drugs causes general reactions.

Histamine releasers "sensu stricto": 1935 L, 48/80.
Hydrolysates of proteins and peptone.
Antibiotics and chemotherapeutic agents:
- licheniformine
- derivatives of acridine
- stilbamidine and diamidines { pentamidine / propamidine
- arsenical trivalents.

Curare and curarising agents:
- d-tubocurarine, compound 15, laudexium

Morphine, atropine (?)

In other cases, however, the liberation of cutaneous histamine is the result of an attack taking place through the blood. Thus, the parenteral administration of certain *drugs* (Table II), the ingestion of certain *fruits* or *shellfish* can, without any preliminary sensitization, provoke a vasomotor and edematous syndrome, comparable with that caused by the intravenous administration of 1935 L and 1880 (Schachter, Ciba Symp., 1956, C.I.O.M.S. Symp., 1957). The nitritoid crisis caused by drugs can be explained by a massive liberation of histamine. Its participation is often identified by the presence of urticaria, indicating that in the majority of cases, the reserves of histamine have been mobilized from the skin.

The resorption of endogenous histamine from damaged muscles (crush syndrome), or from traumatized or burnt tissues, has not been established with certainty. Although in extensive burns the histaminemia is definitely increased, the cardio-vascular collapse and the hemoconcentration are not proportional to it (Algöwer and Siegrist, 1957). Similarly, in spite of a considerable increase in histaminemia after treatment by X-rays, the radiation sickness cannot be explained by a simple histaminic intoxication (Ellinger, 1951), no more than traumatic or post-operative shock (Weiss et al., 1932).

In certain individuals, however, intensive muscular work is followed by the appearance of giant urticarial wheals with plasma hyperhistaminemia which are sensitive to the action of AHS. This is probably explained by the resorption of toxic substances with histamine releasing properties, liberated by an exaggerated muscular activity (Serafini, 1951).

3. Let us now consider the local manifestations due to an abnormal sensitivity of certain vascular structures.

Under the term histamine cephalalgia, Horton (1941) has described a syndrome striking the cephalic extremity and characterized, besides a hemicranial pain, by widespread flushing, swelling of

the nasal mucous membrane, increased lachrymal secretions and perspiration on the corresponding side.

This syndrome, provoked by subcutaneous or intravenous administration of histamine, and sometimes cured by histamine desensitization, is considered as a manifestation of local hyperreactivity to endogenous histamine; its allergic etiology is not definite.

4. Only exceptionally is a massive intestinal resorption of histamine, for instance by eating putrefied meat or fish, accompanied by signs of cardiovascular collapse.

5. Parental injections of histamine have been the cause of gastrointestinal ulcers (Kirsner, 1957).

B. *In Allergic Diseases.*

1. The content of endogenous histamine in tissues prelevated from allergic patients does not differ from control ones. When no morbid manifestations are present, the histaminemia in these patients is normal as well as the amount of free and bound histamine in the urine. However, the histaminemia undergoes large fluctuations (Rose, 1941).

In these patients the threshold of exogenous histamine effects is generally lowered: histamine manifestations occur with subnormal doses and are more pronounced. Asthmatic patients react with a severe bronchospasm after the parenteral administration or the inhalation of a solution of histamine (Curry, 1946). In migraine, certain hemicranial attacks can be induced by histamine (Wolff, 1955). The nasal mucous membrane of patients suffering from pollinosis is more sensitive to H than that of normal individuals, the amine causing pruritus, sneezing and edema (Melon and Lecomte, 1958). In addition to the lowered threshold, considerable disturbances exist in the metabolism of the exogenous histamine: after the subcutaneous administration of H, the increase in histaminemia is greater and more prolonged than in normal individuals (Serafini, 1948). The serum of allergic patients, in contrast to that of normal subjects, does not "fix" histamine (Parrot and Laborde, 1953). Only in allergic individuals does cortisone cause an increased urinary elimination of free histamine and of its various combined forms (Code, Ciba Symp., 1956).

2. The Pharmacodynamic release of endogenous histamine follows a special course in allergic patients, evolving in two phases; the one immediate and important, the other delayed and more reduced (Halpern, Symp. All., 1957). It shows in addition a special clinical aspect depending on the "terrain": in asthmatic patients, it produces an attack of intense expiratory dyspnea, analogous to that caused

by contact with specific antigens (Lecomte, 1956); it causes edema in those suffering from urticaria (Halpern, Symp. All., 1957). It is probably a matter of special sensitivity of the receptor organs to the liberated histamine.

TABLE III

Symptoms caused by histamine powder in contact with the nasal mucous membrane.

Case N	Pruritus	Sneezing	Watering of the eyes	Congestion	Edema	Nasal obstruction	Rhinorrhea
			A. *Healthy subjects.*				
1	+	+	—	—	—	—	—
2		—	—	—	—	—	—
3	+	—	—	+	+	—	—
4	+ +	++	+	+	+	—	+
5		—	—	+	—	—	—
6		—	—	—	—	—	—
7	+	—	—	+	—	—	—
8	+	—	—	—	—	—	—
9	+ + +	++	—	+++	—	+	—
10		—	—	—	—	—	—
			B. *Patients with Pollinosis during a period of apparent clinical cure.*				
1	+ ++	+++	++	+	+++	+++	+++
2	++	++	—	+	++	++	+
3	+ ++	+++	+++	+	+	—	++
4	++	+	—	+	+++	++	++
5	+ ++	++	—	+	+++	+++	+++
6	+ ++	++	+	+	+++	+++	+
7	++	+	+	+	+++	+++	+++
8	+	+	—	+	+++	+	+
9	+	+	—	+	++	+	+
10	++	+	—	—	++	+	+

The mechanism of endogenous histamine release differs according to the process which induces it. For instance, the injection of pollen in a skin site previously treated with a histamine liberator causes, nevertheless, a Lewis triple response of weakened intensity. It may well be that tissue histamine is fixed in different ways according to selective affinities (Ciba Symp., 1956).

3. Certain allergic reactions in man are accompanied by a release of free histamine, which can be measured in the plasma, the urine and also in the lymph leaving the region where the antigen-antibody reaction has taken place.

Lymph collected during positive intradermal reactions with pollen

contains free histamine (Katz, 1942). Likewise plasma to which white blood cells from a sensitized patient are added (Katz and Cohen, 1941; Noah and Brand, 1954) and saline solution in which a fragment of pulmonary tissue from an asthmatic is immersed (Schild et al., 1951), become richer in histamine as soon as the corresponding antigen is added. Histaminemia increases when specific intradermal reactions, carried out in series, become positive (Serafini, 1948), as well as in patients suffering from giant urticaria or anaphylactic shock (Lecomte, 1956). It also increases in the course of certain serum sicknesses with an edematous component and inconsistently at the onset of certain asthmatic attacks (Rose, 1950; Rocha e Silva, 1957). The histaminuria increases after an anaphylactic shock and in the course of Loeffler's disease (Düner and Perrow, 1956). Mast cell tumors, during certain allergic reactions, constitute an important source of easily liberated histamine (Hamrim, 1957).

Technically it is difficult to evidence a reduction in histamine content in the tissues of man submitted to an antigen-antibody reaction. Besides, leukocyte infiltrations of inflammatory origin, a source of bound histamine, invade the reaction foci and thereby constitute considerable disturbance. Nevertheless in urticaria, the skin has been found to be poor in histamine (Nilzén, 1947); no relation, however, has been found between the histamine content of the nasal mucous membrane and the intensity of the local allergic reaction (Baxter and Rose, 1953).

The release of histamine is often accompanied by the passage to an active state of heparin and of less well-known substances, the *slow reacting substance* of Brocklehurst (Ciba Symp., 1956), whose pathogenic role has still to be determined.

4. The pathogenic role of histamine released during certain allergic reactions can be affirmed when the clinical picture, which develops at the same time, reveals clear analogies to the syndrome associated with the pharmacodynamic release of histamine, and if the synthetic antihistamines inhibit the above reactions. These conditions are fulfilled in the anaphylactic lesion of the immediate type, in particular, the Lewis triple response caused by specific scratch and intradermal tests, in those which are the consequence of the passive transfer of the Prausnitz-Küstner type, urticaria attacks, sudden cutaneous erythemas, nitritoid crisis, anaphylactic shock (respiratory and circulatory form), certain manifestations of pollinosis, manifestations of shock with paroxysmal cold hemoglobinuria and accidents of blood transfusions due to incompatible types of blood.

Release of histamine cannot, however, explain the entirety of

TABLE IV

Symptoms of allergic diseases related to histamine liberation (adapted from Rich, A., Proc. 1st Congress Allergy, 1951).

	Shock and immediate reactions	Serum sickness	Sensitization to		Rheumat. purpura	Periarteritis nodosa	Rheumat. fever	Lupus erythematosus	Rheumatoid arthritis
			Sulfonam.	Iodine					
A. *Symptoms analogous to signs of liberation of endogenous histamine.*									
Cardiovascular collapse	++++	—	—	—	—	—	—	—	—
Erythema	++++	++	+	+	—	—	—	—	—
Urticaria	+++	++	++	++	++	+	+	+	+
Edema	+++	++	+	+	+	+	—	—	—
Hyperperistaltism	++	—	—	—	+	—	—	—	—
Bronchospasm (asthmatic manifestations)	++	—	—	—	—	±	—	—	—
B. *Symptoms different from those signs.*									
Fever	±	++	++	++	++	++	+++	++	++
Arthritis	—	+	++	+	++	++	++++	++	++++
Exudative erythema	—	+	++	+	+	++	++	++	+
Purpura	—	+	++	++	+++	++	+	++	—
Paresia	—	+	?	+	—	+	+	++	—
Eosinophilia	—	++	++	++	—	++	++	—	—
Degeneration of collagen	—	++	++	++	++	++	++	++	++
Aschoff nodules	—	?	+	?	++	+	+++	++	+
Endocarditis	—	+	+	?	+	+	+++	++	++
Myocarditis	—	++	++	++	++	++	++	++	++
Inflammation of serous membranes	—	+	+	?	+++	++	++	++	++
Pneumonia	—	++	++	?	+	+	++	++	—
Arteritis	—	+	+	+	++	++	+	++	++
Lymphoid necrosis	+	+	++	++	+	+	+	?	?
Glomerulo-nephritis	—	+	+	+	+	++	+	++	±

The denomination "shock and immediate reactions" refers to allergic affection which follow immediately upon exposure to the antigenic agent responsible for the reaction.

symptoms observed in the course of these reactions; leukopenia and thrombopenia, activation of fibrinolysin and noncoagulability of the blood observed during anaphylactic shock cannot be explained by a histaminic mechanism, nor the leukocyte infiltration of polyps prelevated in patients with pollinosis (Pepys, 1951).

The part played by endogenous histamine is very reduced in the development of reactions of the serum sickness type. Pruritus, urticaria, certain types of erythema are explained by a similar autopharmacodynamic mechanism, but the associated arterial lesions in no way depend on it (purpura, allergic disseminated angiitis).

Finally, the allergic bacterial reactions and those which accompany diseases involving auto-antibodies do not show any histaminic participation.

Summarizing: In normal individuals release of endogenous histamine can be observed in the course of certain toxic or localized inflammatory reactions. It also accompanies parenteral administration of certain drugs. This liberation is accompanied at times by an increase in histaminemia, and always by concomitant pharmacodynamic manifestations due to liberation of histamine (for instance, hypersecretion of gastric acid).

In allergic patients, histaminic reactions have a more complex interpretation; the metabolism of histamine is disturbed, as shown by the special lability of the histaminemia. The individual sensitivity to the effects of released histamine is also variable, the attacks sometimes provoke a collapse, a bronchospasm, or again an attack of giant urticaria. Some antigen-antibody reactions bring about a release of tissue histamine, giving rise at times to an increase in plasma histamine. Clinically this is manifested by vasomotor crises, cardiovascular collapse and shock, which are the symptoms of an endogenous histamine intoxication. These manifestations are characteristic of anaphylactic accidents.

The release of histamine is only one of the phenomena induced by the antigen-antibody reaction, nevertheless its role, although limited, is essential in certain allergic diseases.

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It is impossible to give a complete list of the publications dealing with the pharmacodynamic properties of histamine and its liberators, and we apologize to the authors omitted.

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ALLERGY AND IMMUNOLOGY

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Introduction.

The term allergy, as originally coined by von Pirquet in 1906, designated the altered response of an individual toward a specific material resulting from prior experience with that material. In the ensuing years allergy has come to mean things to many people—yet withal, the most widespread preoccupation of the allergist has been in relation to the wheal and erythema types of response occurring spontaneously in the genetically susceptible few.

During this same period many immunologists were preoccupied with the immune response, chiefly as it related to infectious disease and the prevention or recovery therefrom. Following upon the introduction of effective antimicrobial agents in the therapy of infectious disease, there occurred a renewal of interest on the part of the immunologist in the phenomena of altered tissue reactivity—allergy as originally conceived—in its broad biological sense. It is appropriate therefore to consider the recent advances in this area as they relate to the understanding of altered tissue reactivity and disease states.

The immunologist's interest in the problems specifically associated with conventional hypersensitivity reactions (i.e., reactions related to a measurable antibody) has been stimulated and broadened in scope by information acquired from attempts at the solution of problems of a general biological nature. This arises from observations relating to such diverse phenomena as the cellular origins of antibody, homograft rejection phenomena, acquired tolerance to foreign cells, allergic encephalomyelitis, agammaglobulinemia, spermatogenesis and reactions to autologous antigens. This chapter will consider in some detail the impact which this extension of interest has had both upon the courses of action in immunologic investigation and the current concepts of altered tissue reactivity.

The Known Types of Allergic Inflammatory Responses.

Three main categories of allergic inflammatory response have been separable largely on the basis of the presence of a measurable antibody in the serum of sensitized individuals. The allergic responses associated with the presence of a detectable circulating serum antibody fall into the category of "early responses"—a designation suggested by Chase (7) to signal the prompt appearance of a visible response in the sensitized subject following exposure to antigen. The "early responses" are further subdivided into the wheal and erythema type of response and the Arthus or anaphylactic type of response.

The allergic response of the wheal and erythema type is distinctive in that it occurs spontaneously in nature, for all practical purposes exclusively in man and usually in those human subjects susceptible on the basis of genetic transmission. This type of allergic response is classically seen in hay fever and certain types of bronchial asthma, clinical states which are provoked in susceptible individuals by specific plant pollens. The serum antibody found in association with this type of response—the so-called "wheal and erythema" antibody or "reagin"—is heat labile at 56° C and does not form a precipitate when reacted with antigen *in vitro*. Some intimation of its quantity can be estimated by titrations of human sera with the Prausnitz-Küstner technique—a circumstance dependent upon the fact that the wheal and erythema response can be transferred passively with serum to non-sensitive individuals.

The Arthus or anaphylactic type of response, whether produced intentionally in laboratory animals or inadvertantly in man, is uniquely an iatrogenic allergic inflammatory response. It is an exaggerated phase of the normal immune response to the parenteral injection of soluble foreign antigens, the heat stable serum antibody produced will precipitate in the presence of antigen and the response can be transferred passively with serum. The Arthus type of response usually follows repeated administration of the same antigen and its intensity, in the host—as well as the capacity of the host's sera to transfer the response, has been shown by Benacerraf and Kabat (1) to be a function of the titer of precipitating serum antibody.

The least well understood of the known allergic inflammatory responses is the delayed tuberculin type of response characteristically associated with bacterial allergy (26). It has suffered a tenuous connection with conventional immune responses because of the absence of a detectable antibody. Indeed, the delayed type of response has been regarded as an immune response largely on the basis of its

occurrence only in the specifically sensitized subject. The delayed type of response, although characteristically associated with bacterial infections also follows viral, fungal and spirochaetal infections and sensitization to certain plant materials and simple chemicals.

The similarities and differences between the known types of allergic inflammatory responses are summarized in Table I.

It may be seen that the main distinction between the types of allergic response relates to the presence or absence of a measurable serum antibody separating the "early" from "delayed" types of response. The physicochemical characteristics of this serum antibody further subdivides the "early" responses. This may be an artificial and deceptive separation arising from the limiting sensitivity of the *in vitro* method for the detection of precipitating antibody. It is possible for example that the skin reaction seen in delayed allergy detects the presence of an immune response with a degree of sensitivity which is not currently available for the detection of minute quantities of circulating antibody.

It has been reported many times (39) that in delayed allergy there is a direct specific cytotoxic effect of antigen upon the cells of the sensitized host. Cytotoxicity has thus been taken as another cardinal point of difference between the delayed and the Arthus and wheal erythema types of response. In recent years the inconstancy of this phenomenon and the unphysiological modes of its demonstration when present, have raised the question whether cytotoxicity exists and if so what meaning it has, if any, in relation to events *in vivo*. Stetson (41) has posed this question clearly by pointing out the high concentrations of tuberculoprotein necessary to demonstrate the phenomenon and the frequent injurious effects of the same concentrations upon normal tissue. He regards the noxious effects of tuberculoprotein on sensitive tissues as representing a real phenomenon but questions the relation of such effects to the presence of delayed allergy in the donor.

The occurrence of delayed reactions in the avascular cornea of the sensitized animal, in contrast to the requisite for vascularization of the cornea before an Arthus reaction can be elicited (39), provided cogent experimental reasons for concluding that this represented an *in vivo* manifestation of *in vitro* cytoxicity. Here again, this interpretation is brought in question by Schlossman and Stetson (40) in a recent histological study of the vascularization of the cornea during delayed reactions. They observed vascularization of the normally avascular cornea as early as six hours after, in response to the trauma of injection of Ringer's solution. The vascularization was more intense following the injection of specific antigen into sen-

TABLE I*

Types of allergic inflammatory responses.

	Early Responses		Delayed Responses
	Wheal and Erythema	Arthus or Anaphylactic	
Clinical state	Hay fever, asthma	Serum sickness	Tuberculosis, lymphogranuloma, histoplasmosis, syphilis, poison ivy
Sensitizing material	Pollens	Soluble proteins, carbohydrates	Bacteria, viruses, fungi, spirochetes, plant materials, simple chemicals
Antibody	Present in serum Non-precipitable Heat-labile	Present in serum Precipitable Heat-stable	Absent in serum Absent in cells Unknown
Transfer of sensitivity	With serum	With serum	Not with serum With cells
Cytotoxicity of antigen for explanted sensitive cells	None	None	Present

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sensitized animals preceding the positive corneal reaction associated with delayed allergy by many hours. These authors conclude that delayed reactions in the cornea do not occur in avascular tissue, and blood vessels participate in this as in other immunological reactions.

The requirement of considerable numbers of intact bacterial cells and focal necrosis of host tissue for the induction of delayed allergy is also in question as the results of recent experimental observations. In nature these conditions prevail in bacterial, fungal and viral infections. In the experimental animal it was originally observed that one needed intact bacterial cells to induce delayed allergy—injected preferably intradermally or subcutaneously, since intravenous injection was without effect. If the soluble constituents of bacteria were used to sensitize the animals then the Arthus type of sensitivity resulted. This notion was modified by the findings of Dienes and by those of Freund and his associates (15, 16). More recently Uhr, Salvin and Pappenheimer (36, 43) have produced delayed allergy without injecting the soluble protein antigen into a tuberculous focus or mixing the antigen with Freund's adjuvant. Their technique entails the use of specific antigen-antibody precipitates made in the region of antibody excess. The injection of this material into the foot pads of guinea pigs results in the induction of delayed allergy to the antigen without the concomitant production of serum antibody. This experimental model offers a unique opportunity for the analysis of the delayed type of allergic inflammatory response uncomplicated by the presence or contribution of conventional serum antibody.

Another of the cardinal differences between hypersensitivity reactions of the immediate and delayed types relates to the incapacity of serum and the effectiveness of cells of the leucocyte series in the transfer of delayed hypersensitivity. Since the original observations initiated by Landsteiner and Chase and Chase (7, 8) the cellular transfer system has proved an effective technique in the study of delayed hypersensitivity reactions. More recently Chase and others have adopted this technique to the study of the synthesis of conventional serum antibody.

Thus it may be seen that Table I serves as a scaffold continuously undergoing alterations in one section while other sections maintain the essential structure of the whole. As such it is a useful aid in defining, at least, the areas of our ignorance. With this discussion as a background, I would like to consider a series of observations and concepts derived therefrom which have evoked interest and enthusiasm in the study of the immune response in general and its aberration, hypersensitivity reactions in particular.

Cellular Origins of Antibody.

In relation to the cellular origins of antibody there has been considerable evidence collected to suggest the association of a variety of cell types with various phases of the immune response (22). Earlier studies by Sabin suggested that the macrophage might have an important role in antibody formation insofar as the disappearance of a coloured antigen phagocytosed by these cells coincided with the appearance of serum antibody. More recently, McMaster's findings clearly demonstrated the production of antibody in lymph nodes and the lymphocyte then assumed prominence in relation to this problem. Evidence collected along several lines has demonstrated that the lymphocyte is concerned in the production of antibody in as yet some unknown fashion. This view results from the finding of antibody in efferent lymph draining nodes stimulated with antigen as shown by Ehrich and Harris. Additional evidence of antibody production using thoracic duct lymphocytes has been secured by Wesslén and using splenic white pulp lymphocytes by Keuning and Von der Slikke. In support of the role of the lymphocyte in the production of antibody have been the findings initiated by Chase (8) and extended by Harris and by Dixon, demonstrating the synthesis of antibody in recipients of transferred cell suspensions obtained from lymph nodes. The cell populations consisted mainly of lymphocytes although other cell types were present.

The plasma cell is currently undergoing intensive investigation as the cell type most intimately connected with antibody production. This cell in addition to being associated with chronic infection and inflammation has been demonstrated to appear in response to antigenic stimulation and to be associated with the production of gamma globulin. There has been accumulated a considerable body of indirect experimental evidence in man and the experimental animal linking the presence or proliferation of plasma cells with the production of serum antibody. Recent direct evidence obtained by fluorescine techniques has been secured by Coons (11) and his colleagues, demonstrating specific antibody in plasma cells in lymph nodes and spleen of animals undergoing antigenic challenge. Of interest in this connection is Good's (19, 20) demonstration that the agammaglobulinemic patient who is unable to respond to antigen with the formation of detectable serum antibody, has a demonstrable parallel deficiency of plasma cells.

The capacity of the macrophage to ingest and metabolize foreign particles which happen to be antigenic is clear. So also, the lymphocyte and antibody production is in some way closely associated. However, there appears to be a more direct relationship between the

appearance and proliferation of the plasma cell and antibody synthesis on the basis of the evidence secured to date. The gaps in our information revolve around the relationship of these events to each other and the origin and developmental potentials of the cells involved.

Allergies of the Immediate Type.

An advance in the understanding of wheal and erythema allergies and the properties of the reaginic type of antibody has been made by Kuhns and Pappenheimer (23–25), (35). This illuminating series of studies accrued from the application of a known antigen-antibody system, diphtheria toxin-antitoxin, to the study of allergic responses of the wheal and erythema type. This immune system has the following advantages not possessed by the usual pollen allergens and their respective antibodies: 1) The antigen is highly purified, 2) The test for antibody (i.e. neutralization of toxin in rabbit skin) detects small amounts of antibody, 3) Both the antigen (toxin) and the antibody or reagin (antitoxin) have biologic properties which indicate their presence in addition to detection by conventional immunological techniques.

Kuhns and Pappenheimer found that the secondary response to immunization of human subjects with diphtheria toxoid may result in the production of antitoxin which does not precipitate in the presence of antigen and which has the capacity to produce the wheal and erythema response on passive transfer. It is of interest that subjects with a clinical history of antecedent allergies of other types, were apt upon initial testing to have a wheal and erythema response. The reaginic antitoxin was found to neutralize toxin as effectively as the precipitating variety. This latter property of reaginic antitoxin is heat stable whereas its skin sensitizing capacity is heat labile. There also occurred a blocking antibody in some of the subjects immunized which differed from the reaginic antitoxin and the precipitating antitoxin. The blocking antibody has no great avidity for the skin, it is heat stable and appears in the gamma globulin fraction of serum. The study of the immune response of allergic and normal subjects to well characterized antigen-antibody systems which permit a biological as well as an immunological measurement as this study has done, affords a fruitful approach to the understanding of the mechanisms mediating this type of allergic response.

Allergies of The Delayed Type.

Bacterial Allergy: The recent advances in the field of hypersensitivity of the delayed tuberculin type have done much to relate this

type of immune response, not associated with a detectable antibody, more closely to conventional immune responses which are associated with measurable antibody. The investigations of Gell and Hinde (17, 18) have suggested that delayed hypersensitivity evoked by repeated testing with protein antigens is an initial and incomplete phase of the immune response which, if testing is continued, is followed by the production of serum antibody and the Arthus type of hypersensitivity. It is of interest that the delayed reactions to the initial application of antigen were characterized by a mononuclear type cellular response. Such delayed sensitivity was amenable to transfer with cells of the leucocyte series, but not with serum. However, concomitant with the development of detectable serum antibody to the same antigen and Arthus type hypersensitivity, the mononuclear cell population characteristic of the delayed reaction was replaced by plasma cells.

In studies of the induction of delayed allergy Uhr, Salvin and Pappenheimer (43) have devised a system whereby delayed hypersensitivity can be studied in the absence of serum antibody. To accomplish this, specific precipitates of well characterized protein antigens are prepared in the region of antibody excess. When such precipitates are injected into the footpads of guinea pigs or skin of man delayed allergy is induced and serum antibody production is suppressed for a variable period, usually a month. The chief advantage of this experimental model is that it affords the opportunity to exclude confusing reactions of the combined delayed and Arthus type that occur incident to the presence of serum antibody found in other modes of induction of delayed hypersensitivity.

Our understanding of the mechanisms involved in the induction of delayed hypersensitivity has been advanced by a series of studies carried out by Good and his associates (19, 20) and by Porter (37) in patients with agammaglobulinemia. Briefly, individuals afflicted with this disorder are incapable of responding to antigenic stimuli with the production of serum antibody and are therefore prey to recurrent bacterial, but not recurrent exanthematous viral infections. Associated with the incapacity to synthesize detectable serum antibody is a parallel absence of plasma cells in such individuals. It has been shown recently that despite the incapacity of these subjects to form serum antibody they do respond to antigenic stimulation with the acquisition of delayed hypersensitivity (tuberculin, dinitrofluorobenzene, diphtheria toxoid). Moreover, the actively induced delayed hypersensitivity can be transferred from the agammaglobulinemic individual to normal subjects by means of peripheral blood leucocytes. These observations would suggest that delayed

hypersensitivity is not dependent for its induction or transfer upon the presence of a capacity to synthesize conventional serum antibody.

One of the chief impediments to an understanding of the mechanisms underlying bacterial allergy has been the inability to detect an antibody which parallels the tissue damage incident to this type of altered response. Chase (8) provided a fundamental contribution which supplied the most direct evidence that tuberculin sensitivity is mediated by an immune mechanism intimately bound to cells of the leucocyte series. He observed that tuberculin sensitivity is conferred on normal animals following the injection of leucocytes obtained from blood, spleen, lymph nodes or peritoneal exudates prepared from sensitive animals. The sensitivity transferred to the recipient was transient and disappeared in 3–5 days—its intensity paralleling the intensity of sensitivity in the donor and the volume of cells used. Transfer of sensitivity could only be effected by living cells. These findings have been confirmed repeatedly in animals and extended to include delayed hypersensitivity to other bacterial antigens.

The application of the cellular transfer system to the study of bacterial allergy (tuberculin, streptococcal proteins) in the human subject also resulted in similar findings with, however, several significant species differences (29). The transfer of delayed sensitivity in man requires a volume of leucocytes, which in relation to the surface area of the recipient is relatively minute. The duration of the transferred sensitivity is also greater in man in terms of persisting for months to 1–2 years. Finally, extracts of leucocytes have been shown as effective as viable leucocytes in the transfer of delayed sensitivity in man (28, 13). This property of the human leucocyte extract has allowed attempts to be undertaken at identification of the factor in human leucocytes concerned in the transfer of delayed sensitivity.

To date, such attempts at identification have been successful only in suggesting what transfer factor is not; however, they do give promise of ultimately defining its nature. For example the capacity of human leucocyte extracts to transfer delayed sensitivity is not affected by treatment with the enzymes desoxyribonuclease, ribonuclease or trypsin (28, 29). Using purified diphtheria toxoid as antigen, conventional serum antibody is not detectable in the leucocyte extracts used to transfer sensitivity nor in the sera of the recipient at the time of maximal delayed skin reactivity. From this study it is concluded that antibody of the conventional type is not involved in the transfer of delayed sensitivity or it escapes detection by a most sensitive biological test (30, 36). This type of experimental approach employing leucocyte extracts may permit identification of transfer

factor—and with identification the possibility of quantitation of delayed hypersensitivity.

The application of cellular transfer to the study of hypersensitivity in agammaglobulinemic patients has yielded valuable clues to the nature of delayed allergy. It has been shown that delayed hypersensitivity can be transferred by means of peripheral blood leucocytes from normal donors to the agammaglobulinemic individual and also from actively sensitized agammaglobulinemic donors to normal subjects. The transferred sensitivity has persisted in the agammaglobulinemic recipients for as long as two years. These observations suggest that the factor in human leucocytes concerned in the transfer of delayed sensitivity can cause its effects for prolonged periods in the absence of the mechanism necessary for the synthesis of serum antibody. They also suggest that whatever cell or cells of the leucocyte series mediate the transfer of delayed sensitivity, it is not the plasma cell. Of interest in this connection and in relation to the cellular origins of antibody, is the observation in humans that the use of *peripheral blood* leucocytes although consistently effective in the transmission of specific delayed allergy are incapable of causing the appearance of serum antibody to the same antigen in normal (30) or agammaglobulinemic (19, 20) recipients. However, the transplantation of *lymph nodes* from normal donors to agammaglobulinemic recipients results in the transfer of the capacity for serum antibody formation and the development of delayed hypersensitivity as well (31).

The application of the cellular transfer system to other disease states in man has also supplied interesting information concerning the relation of delayed hypersensitivity to disease. For example it has been shown that tuberculin sensitivity may be transferred by leucocytes to anergic patients with Boeck's Sarcoid (44). This finding has done much to clear the confusion engendered by the concept of circulating "anticutins" postulated to explain tuberculin anergy in these patients. In cat scratch fever, a disease presumed to be of viral origin, the delayed hypersensitivity to the cat scratch antigen has also been shown amenable to cellular transfer (45).

Contact Allergy.

This type of delayed hypersensitivity has been thought of as distinct from the tuberculin type, but recent observations have suggested that it is probably mediated through the same pathways as bacterial allergy. The unique features which set this response apart from bacterial allergy lie in the nature of the sensitizing materials and in the elicitation of the response. The sensitizing materials here

are low molecular weight substances, called "simple chemicals", which are haptenes rather than complete antigens. It was suggested from the findings of Landsteiner and Jacobs that such materials are capable of forming protein conjugates *in vivo*. Eisen and his colleagues (12) have recently furnished direct experimental evidence that this is actually the case. It was demonstrated by this study that the capacity of low molecular weight chemicals to elicit delayed hypersensitivity was related to their ability to combine with protein of the skin. The inability of serum and the effectiveness of leucocytes in the transfer of this delayed response has been repeatedly demonstrated by Chase (7, 8, 10) and others in animals. After two unsuccessful reports, recent studies (14, 19, 20) have demonstrated the transfer of delayed allergy of the contact type with peripheral blood leucocytes in man. It would appear that for the cellular transfer of contact allergy in humans the degree of sensitivity of the donor and the volume of leucocytes injected into the recipient govern the degree of success achieved, as had been demonstrated in relation to bacterial allergy (29).

Chase (7–10) has made interesting observations in relation to simple chemical sensitization which have a bearing on the variety of hypersensitive responses provoked in patients exhibited drug reactions. He has called attention to the fact that the type of sensitivity produced (immediate or delayed) is determined by the chemical nature of the sensitizing substance. One group of chemicals may have the property of producing predominantly the delayed type of sensitivity, while another group may produce immediate type sensitivity and still other chemicals may produce immediate and delayed sensitivity at the same time to the same material. He also showed that the type of sensitivity produced in the donor animal governed the type transferred to the recipient by means of cells. By this means he was able to transfer both immediate and delayed sensitivity simultaneously to the same chemical using the same cells. This variable hypersensitive response to different chemical groupings suggests an explanation for the diversity of responses provoked in patients by drugs. It may also explain many of the negative reactions obtained in patients sensitive to a particular drug, if only the delayed contact type of sensitivity is looked for by means of the patch test.

The problem of hypersensitivity reactions to antibiotic agents such as penicillin and streptomycin in patients is even more complicated. Here in addition to the pathways of sensitization open to low molecular weight materials, one has the extra complication of sensitization of the type associated with fungal antigens, which is predominantly delayed in type.

Chase (9) also observed that animals which had been fed the particular chemical before sensitization was attempted, became and remained refractory to sensitization by the usual means. The only way in which this refractory or tolerant state could be overcome was by means of cell transfer with leucocytes obtained from sensitive donors. This observation may have its counterpart in drug allergy observed in patients. For example, it is not known whether the sensitivity reactions to penicillin—or other topically or parenterally administered drugs—could also be inhibited by this means.

Reactions to Homologous Tissues; Homotransplantation Immunity.

If an individual is confronted with another's tissue as exemplified by the application of a skin homograft, a definite and predictable sequence of events will ensue. Initially the graft will take and appear viable until about the 10–12th day when a brisk inflammatory response occurs with resultant necrosis and rejection of the graft. If the same individual is again confronted with skin from the same donor this response will be more intense and occur with an accelerated tempo (4–6 days) (2, 27).

In a series of classical experiments Medawar (32–34) and Billingham, Brent and Medawar (2, 5, 6) have established that the phenomenon of homograft rejection is mediated by an immune mechanism. The immune response to foreign tissues or cells exhibits many similarities to bacterial allergy of the delayed type, namely the requirement for specific prior sensitization, the temporal sequence of events in the primary and accelerated rejection of tissues, the inability to transfer the response with serum (vide infra) and the successful transfer of accelerated homograft rejection by means of cells from regional lymph nodes of sensitized donors. There is also much evidence collected to support the notion that the serum antibodies inevitably formed to tissue antigens, may play a role in mediating homograft rejection (2). However the most direct evidence for this possibility has only recently been secured by Stetson (42) who demonstrated the local passive transfer of accelerated homograft rejection by means of hyperimmune sera in rabbits and mice.

The problem of the antigen(s) that incites this type of altered tissue reactivity and the antibody(ies) that mediates it are currently under intensive investigation.

Acquired Tolerance.

An entirely new area of immunologic investigation has been opened by the demonstration by Billingham, Brent and Medawar (6) that exposure of the foetus to cells of a prospective donor allows

the former, after birth, to tolerate that donor's skin homograft indefinitely. This actively acquired tolerance may then be interrupted if lymph node cells from a normal mouse are injected into the tolerant mouse. The rejection of the previously tolerated homograft will occur slowly if the lymph node cells are obtained from non-sensitized donors and rapidly if obtained from donors specifically sensitized to the same homograft. This work has provided direct experimental proof of the postulate of Burnet and Fenner (3, 4) that antigens introduced into the embryo at an early period will be recognized as "self" and therefore be incapable of provoking an immune response. The far reaching implications of this and subsequent observations have a practical bearing on the ontogeny of immune mechanisms and the hitherto unsuspected immunological conditioning which may be exerted by the mother upon the foetus.

Reactions to Autologous Tissues.

If an adult animal is exposed to certain of his own tissues in a particular fashion there will result a specific hypersensitive state developed by the recipient against these tissues. The experimental study of this phenomenon in relation to tissues of the central nervous system was given impetus by the clinical observation of the development of allergic encephalomyelitis following certain viral infections and viral immunization procedures. The experimental production of this syndrome has been facilitated by the addition of Freund's adjuvant (21) to the nervous tissue (brain or spinal cord) reinjected into the donor animal. An allergic neuritis with many of the features of the Guillain-Barré syndrome has also been experimentally produced in animals (47). Similarly allergic uveitis has resulted from sensitization to retinal tissues. The immune response to autologous tissues of this type has in common with the immune response to homologous tissues, many similarities to hypersensitivity of the delayed type. For example, in allergic encephalomyelitis the timing of events and failure to transfer the sensitivity passively with serum from actively sensitized animals are suggestive pieces of evidence. Here, although the sensitivity has not been amenable to transfer with cells of the leucocyte series, Freund has demonstrated successful transfer in parabiotic rats (16).

Allergic aspermatogenesis induced in the guinea pig by Freund (16) by the injection of homologous or autologous testicular materials in adjuvant has many similarities to allergic encephalomyelitis. It differs from the latter, however, in being both species and organ specific and in the requisite for killed mycobacteria for its induction.

Reactions to Autologous Antigens.

It is appropriate to close with a description of recent immunological observations made in a disease of man, thyroiditis (Hashimoto's disease), since they afford an illustration of the practical application of some of the concepts of altered tissue reactivity discussed above. Witebsky and his colleagues (46) observed that the injection of rabbits with thyroid extracts or thyroglobulin prepared from their own or other rabbit thyroid tissue and incorporated into Freund's adjuvant, resulted in the formation of precipitating and complement-fixing antibodies directed against thyroglobulin. Associated with this production of anti-thyroglobulin antibody was the histological picture of thyroiditis and dense infiltration of the gland with lymphocytes.

The finding of elevated gamma globulins in patients with Hashimoto's disease and their subsequent return to normal following surgical extirpation of the gland suggested to Roitt and Donach (38) the possibility of an immunological basis for this disease and resulted in their subsequent demonstration of precipitating antibodies in the sera of such patients directed against human thyroglobulin. Witebsky also found precipitating and hemagglutinating antibodies in the sera of similar patients directed against human thyroid extract.

Roitt and Donach postulate that since thyroglobulin resides within the thyroid follicles, the foetus is not exposed to this antigen *in utero* and therefore on the basis of the Burnet and Fenner "self-marker" hypothesis and the Billingham, Brent and Medawar demonstration of acquired tolerance, it is not recognized by the adult as "self". When in adult life thyroglobulin gains access to the fluids and tissues of the organism, antibodies are formed against it which react with the thyroglobulin of the gland and stimulate lymphocytic infiltration and plasma cell proliferation within the gland itself. There follows further damage to thyroid follicles with further release of antigen. It is suggested however, that there may be involved a cellular hypersensitivity of unknown type in addition to precipitating antibodies to thyroglobulin, to account for the extreme example of the progressive disease with almost total destruction of the thyroid gland.

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DEFINITION—PREVALENCE—PREDISPOSING AND CONTRIBUTORY FACTORS

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I. DEFINITION OF ALLERGY AND BRIEF HISTORICAL REVIEW OF PRESENT CONCEPT

It is obviously most desirable that we should know what is at present meant by and included under the term Allergy.

Allergy includes those illnesses in man and animals resulting from an altered capacity to react in which there is an underlying immunological mechanism, i.e. those illnesses due to an indirect action resulting from an antigen-antibody reaction. It is a comprehensive term including all such reactions.

As has been pointed out by Payling Wright (1953) both hypersensitivity (allergy) and immunity are "dependant on the action of a provocative antigen—the essential difference between them lies in the amount and distribution of the specific immune bodies as between body fluids and cells ... Much evidence supports the belief that whereas a combination of antigen and antibody can take place without any detrimental effect on the individual as long as both are free in the blood or tissue fluids, any union that occurs when either have become fixed is followed by serious disturbances in the cells in whose membrane or interior the process happens."

The present concept of allergy has only taken place gradually as advances in knowledge have been made both by clinicians and pathologists. With increasing knowledge, more and more illnesses have been brought within its scope.

It was therefore felt that a brief historical review would help the reader to appreciate more fully than by definition, not only what is now included under the term allergy, but how this has come about and, it is hoped, may enable the reader to understand and assess future developments in this field.

Idiosyncrasies have been known throughout the ages, for the old proverb "One man's meat is another man's poison" was written in the first century B. C. by Lucretius.

It was in the 19th century that clinical medicine began to appreciate the importance and frequency of idiosyncrasies. Hyde Salter (1868) showed clearly that inhalant and food idiosyncrasies played a part in asthma and that the tendency to such idiosyncrasies might be familial, eighty-four of two hundred and seventeen asthmatics giving a family history of asthma. Charles Blackley (1873) experimented on himself and showed that hay fever was due to grass pollen in the atmosphere. He was the first to use the skin as a means of testing a subject's idiosyncrasy. In the 19th century also, came animal experiments in this field. Magendie (1839) found that animals which came to no harm after a first injection of albumen, were made ill and died by a later injection. A similar type of reaction was also found by von Behring (1893) who referred to it as a "paradoxical reaction".

It was not, however, until the turn of the present century that it became gradually recognized that idiosyncrasies in clinical medicine and these paradoxical reactions in experimental animals were linked together by the same basic immunological and chemical mechanisms and that human idiosyncrasies were linked by heredity.

In a series of classical experiments Charles Richet appreciated that he was dealing with a fundamentally new mechanism of disease which he and Portier (1902) termed anaphylaxis, meaning "without protection". Their basic concept being that a substance which was relatively harmless on first injection might, on reinjection, become severely toxic in its action when given in the same or even smaller dosage after an interval of several days.

In the following year, 1903, Arthus produced local skin necrosis by repeatedly injecting (every sixth day) small amounts of horse serum into the skin of rabbits, a reaction now known as the Arthus Phenomenon. Here was the first example of local tissue necrosis caused by repeated injections of an otherwise innocuous substance. Arthus also showed that the local reaction was linked with general anaphylaxis, for animals sensitized locally were killed by subsequent intravenous injection of horse serum.

In 1905 von Pirquet and Schick described serum sickness, combining the results obtained from animal experiments with clinical findings in man. In the same year Czerny (1905) was linking asthma, vasomotor rhinitis and eczema under the concept of an exudative diathesis and in 1906 Wolff-Eisner suggested that hay fever was linked with anaphylaxis.

The word Allergy was introduced by von Pirquet in 1906. It was

derived from two Greek words, αλλος meaning altered and εργον meaning energy or action. The word, therefore, means literally, an altered action. von Pirquet used the word in the sense of an excessive or diminished action—the changes in condition of the organism brought about by contact with some organic or inorganic toxin or other. Pollen, foods and other organic substances giving rise to idiosyncrasies came within his definition of an allergen, although he was studying human reactions to sera, tuberculin and vaccines.

von Pirquet described in the following year (1907) the delayed reactions to tuberculin which occurred in human cases of tuberculosis and which had been previously reported in tuberculous animals by Koch (1891).

Besredka and Steinhart (1907) described the process and attempted to explain the mechanism of desensitization which they called anti-anaphylaxis, and a few years later (1911) Noon described the first successful use of inoculations as prophylactic treatment against hay fever.

In 1909 Gillette called attention to the similarity between anaphylactic shock and asthma, as did Biedl and Kraus in the following year. It was, however, Meltzer's article in 1910 which brought widespread notice to the similarity between anaphylactic shock in guinea pigs and asthma in man and he suggested that asthma was an anaphylactic reaction. This article focussed attention on the possibilities of a new approach to asthma, linking idiosyncrasies in man with the new understanding of anaphylaxis. Asthma became accepted by many as an "anaphylactic disease".

In 1910 a new contribution was made relating to the mechanism in anaphylaxis—Dale and Laidlaw demonstrating the marked similarity between anaphylactic shock and the effect of histamine in experimental animals.

In the same year, 1910, Eppinger and Hess introduced the concept of vagotonia and Staüble the concept of the "eosinophilic diathesis". Eppinger and Hess instanced asthma as a classical example of vagotonia which also included urticaria. Staüble (1910) using the eosinophil cell as the index linked asthma, eczema, urticaria, angioneurotic oedema and various intestinal disorders. Schloss two years later (1912) reported urticaria, angioneurotic oedema and eczema occurring as idiosyncrasies to certain foods and used skin tests to identify the causative agents.

At the same time Doerr (1913) gathered under the term Allergy, all the phenomena of altered reaction, hypo- and hyper-sensitivity in man and also in animals (animals were not included by von Pirquet).

In 1913 Longcope described lesions resembling glomerulonephritis

in animals subjected to repeated injections of foreign protein. This work was one of the earliest suggesting an allergic mechanism as the cause of nephritis and gave further evidence of a foreign protein, in itself harmless, causing tissue damage on repeated injection.

In 1916 Cooke and Vander Veer conducted a careful study of heredity in asthma and hay fever and this was followed by a number of such studies which brought out the hereditary nature of some of the naturally occurring allergies in man.

In 1920 Coca used the word allergy for the hereditarily occurring human illnesses due to hypersensitivity, anaphylaxis for the manifestations of artificially induced hypersensitivity, and hypersentiveness as the overall term to include both.

This was soon apparent as too narrow a use for the word allergy; however in 1923 Coca introduced the word atopy, a word meaning "strange disease". Atopy was a term to include those allergic diseases of a hereditary nature and which occurred naturally. Coca later (1945) defined atopy as a "type of hypersensitiveness peculiar to man, subject to hereditary influence, presenting the characteristic immediate whealing type of reaction, having the circulating antibody reagin, and manifesting peculiar clinical syndromes such as asthma and hay fever."

The proof that there were "circulating antibody reagins" was discovered by Prausnitz and Küstner in 1921. They showed that a positive skin sensitizing factor was transferable by the serum of a sensitive person to the skin of a non-sensitized person. Küstner was allergic to fish. A small amount of his serum was introduced into the skin of a non-sensitive patient and subsequent testing of this passively sensitized site resulted in a positive reaction, while a control test elsewhere on non-sensitized skin was negative. This was the long awaited proof which had previously only been hinted at.

Coca and Walzer and their colleagues later made extensive studies of this phenomenon and Coca termed these antibodies "atopic reagins". It was by using serum containing atopic reagins transferred to a non-sensitive patient that Walzer (1927) was able to show that unaltered proteins were absorbed unchanged from the alimentary canal and so explained the specificity of foods as allergens.

In the early nineteen twenties also, Zinseer (1921) was carrying out his studies on bacterial allergy. He gave convincing proof of two different types of immunological response to the tubercle bacillus, the anaphylactic type from the nucleoprotein fraction of the bacillus and the delayed tuberculin type from the "residue antigen". Two years later he and Parker recorded the findings of chemically similar substances in other bacteria they investigated.

At the same time, Verkoeff and Lemoine (1922) using lens tissue

for intradermal testing, found positive reactions in patients who developed "endophthalmitis" after operation. Uhlenhuth had shown in 1903 that lens tissue was antigenic. Verkoeff and Lemoine put forward the theory that the inflammatory reaction in the eye following trauma to the lens was caused by the development of a sensitization to lens protein. A few years later, in 1925, Woods introduced skin tests with uveal pigment solutions in sympathetic ophthalmia, and following this with further contributions to the understanding of allergy in ophthalmology.

In 1923, Duke recorded a series of observations showing how physical agents, light, heat, cold and mechanical irritation, were capable of producing various symptoms such as asthma, rhinitis, urticaria, etc. He introduced the term physical allergy for such reactions. However, no antigen-antibody reaction was proven and so the inclusion or otherwise of this concept as an allergic mechanism has remained controversial.

Around this time, also, studies in contact dermatitis were being actively pursued. In 1924 Low described how primula leaf when first applied to the skin gave no reaction, but when repeated, a dermatitis was produced after a few weeks. Two years previously Spain (1922) had found that when the oil of poison ivy was applied to the skin of adults sixty-five per cent reacted but that the skin of infants did not react to the first test. He thus excluded the action as being primarily an escharotic effect. In 1926 Block and Steiner-Wourlisch showed that by repeated application of an extract of primula to a limited area of the skin they could sensitize the entire surface of the skin of all their (twelve) subjects. In the following year Cooke and Spain (1927) showed that the alcohol-soluble fraction of poison ivy when applied as a "patch test" produced the typical lesions of dermatitis. Within a few years the use and value of the patch test in dermatology was being demonstrated.

In 1928 Shwartzman described a local tissue reaction to bacterial filtrates now known as the Shwartzman phenomenon. He found that if a bacterial filtrate was injected intravenously, there appeared in four to five hours, at the injected skin site, a local inflammatory reaction developing into a haemorrhagic necrosis. It has since been shown that not only the skin can be affected but many other organs such as the stomach and intestines, the peritoneum, liver, joints and testes. Many other bacterial, viral and other filtrates can produce the same result and the preparing and the exciting factor need not be the same.

Cardiovascular disorders were beginning to be linked together with bacterial allergy when in 1926 Swift correlated bacterial allergens with rheumatic fever, a viewpoint supported by Coburn (1931).

In 1934 Simon and Rackemann showed that there was no absolute differentiation between atopic and non-atopic persons, for by repeated intradermal injection of quite small quantities of guinea pig serum, sensitization occurred in one hundred per cent of their subjects. They also showed that sensitization was first of the "tuberculin or delayed type", and later, after continued injections, positive cutaneous reactions of the "immediate whealing or urticarial type" occurred.

In 1935 Squier and Madison showed that in convalescence from agranulocytosis due to amidopyrine, the application of this substance to the skin produced a fall of white cells with a positive skin reaction. Thus an allergic reaction to amidopyrine was the basis of the agranulocytosis.

In 1934 Burky introduced a new method of sensitizing animals to proteins of relatively low antigenic power by the addition to them of staphylococcus toxin. Lens tissue was incubated in hormone broth and the sterile tubes inoculated with toxin-forming staphylococcus aureus. After ten days incubation, 0.5 per cent trikresol was added and the solution filtered through a Berkefeld V. filter. With this lens toxin solution he was able to produce sensitivity to lens protein in rabbits quite readily and regularly, although in his experimental work during the previous eight years he had been unable to produce satisfactory sensitivity to lens protein by the usual methods with simple lens extracts. In the same way he easily produced a marked sensitivity to ragweed pollen in rabbits, although it was common experience that using pollen extracts only, it was difficult to obtain any satisfactory degree of sensitization in rabbits. Using the same technique he also showed, that rabbits could be sensitized to their own muscle.

In 1936 Swift and Schultz confirmed Burky's observations with other proteins and bacterial toxins. They found a "synergistic conditioning" when diphtheria toxin or streptococcus toxin was used with serum.

In 1936 Landsteiner provided the basis for our present knowledge that a non-protein substance can attach itself to a normal protein of the body, thus forming a new protein substance capable of stimulating the production of an antibody specific for the chemical substance which attached itself to the protein. This explained how previous idiosyncrasies to drugs and other chemicals could in fact be specific allergic reactions.

In 1936 Sikl described myocarditis with many eosinophils in a patient who died of exfoliative dermatitis following arsenic and he suggested that the myocarditis might represent an allergic reaction to the drug, and in the following year Clarke and Kaplen (1937)

described myocarditis in human serum sickness. In 1942 French and Weller showed that hypersensitivity to drugs could produce local collagen degeneration.

In 1942 Rich discussed the role of hypersensitivity in periarteritis nodosa and recorded seven such cases developing during sulphonamide therapy. Later, in the same year, he described another case resulting from a sulphonamide reaction.

In the following year Rich and Gregory showed that destructive and fatal vascular reactions could be produced in animals by subjecting them to a protracted hypersensitization reaction. They produced glomerulonephritis in rabbits with horse serum or egg albumen in amounts that permitted some to remain in circulation until the antibody made its appearance.

In 1942 Harley used the term allergy to include 1. Hereditary Allergy; 2. Bacterial Allergy; 3. Allergic Contact Dermatitis, and 4. Serum Sickness and Drug Allergy. Hypersensitivity was still used as a comprehensive term to include "all forms of increased reactivity in man and the lower animals which are *considered* mediated by special mechanisms."

In 1943 Haxthausen established proof of the existence of antibodies in contact dermatitis in animals. He showed that antibodies from guinea pigs previously sensitized by contact with dinitrochlorbenzene became transferred to the skin of a joined partner.

In 1945 Chase showed that passive transfer of tuberculin sensitivity could be accomplished by transferring washed living mononuclear cells from a sensitized animal to a normal one. This gave the long sought for confirmation that the tuberculin reaction was in fact an antigen-antibody reaction.

In 1946 in their book "Allergy", Urbach and Gottlieb wrote that "In Europe today, the viewpoint is generally accepted that an antigen-antibody mechanism represents the basis of all allergic hyper- or hyposensitiveness."

In the following year, 1947, Cooke in his book "Allergy in Theory and Practice", wrote "Allergy was such a short, neat and expressive word that by a sort of common consent it has been appropriated and is now generally used to designate a special group of diseases in man. On account of the interrelations of the various antigen-antibody reactions of man and of animals and the pressing need for a concise over-all word for all such reactions, "Allergy" should be selected as that word." Cooke suggested the dropping of the cumbersome word Hypersensitiveness and other unsuitable terms such as Hyperergia and Pathergy and Idiosyncrasy. Atopy he suggested should either be dropped or re-defined to designate the immediate whealing type of spontaneous allergy.

In 1949 Cooke defined allergy *as all manifestations resulting from antigen sensitized cell reactions and only these.* He wrote that "substances in themselves usually harmless, by "indirection" (indirect action) produced profound and even lethal effects upon tissues because of the existence of a specific cellular sensitization, for sensitized cells when combined with an antigen seem to liberate some more active substance or poison and the resulting reaction constitutes allergy." ... "But it is necessary to go a step further and appreciate the fact that all antigen-antibody reactions are not identical. The tissue responses vary with the nature of the antigen, type of cell or immunological mechanism involved." He cited three different types of allergy—"that occurring in a ragweed-sensitive hay fever patient, the delayed reaction of the tuberculin type and the dermatitic type by contact with poison ivy."

In 1948 Raffel took tuberculin allergy a stage further when he showed that hypersensitivity similar in all respects to tuberculin sensitivity could be established by the injection of tuberculo-protein mixed with a lipid fraction of the tubercle bacillus. (Neither substance alone will induce this type of sensitivity). He found that a high degree of tuberculin sensitivity could be established without any concomitant enhancement of resistance to infection.

In the last ten years additional work, clinical and pathological, has further strengthened this concept of allergy and has brought out increasingly its importance in medicine. Interest in allergy has been considerably stimulated by the wide range of diseases relieved or modified by cortisone and corticotrophin. Freund (1957) has pointed out how during the last eight years or so a new group of experimental diseases have been discovered, diseases due to sensitization with organ-specific antibodies. Experimentally produced encephalomyelitis, neuritis, uveitis and testicular damage can be produced in animals by the injection of a suspension of the respective tissues to which adjuvants or potentiators—paraffin oil, killed acid-fast bacilli have been added.

There is now much support for the belief that various nervous diseases in humans—encephalomyelitis, the Guillain-Barré's syndrome, various diseases due to demyelinization—result from an allergic mechanism, and some—the Guillain-Barré's syndrome and some induced neuritis—have been shown to respond to cortisone (Graveson, 1957).

In the field of haematology Ackroyd (1952) has shown that thrombocytopenic purpura due to Sedormid is due to the development of an antibody that destroys platelets. He points out that since platelets and capillary endothelium are antigenically related the mechanism whereby the vascular lesion is produced in purpura is

similar to that which causes thrombocytopenia, i.e. an allergic mechanism.

It is hoped that this brief historical review will have given the reader an idea of the present concept of allergy.

Allergens, it has been seen, may be derived from otherwise innocuous substances such as foods or inhalants or non-pathogenic organisms, from drugs and other chemical substances, from tissues altered by adjuvants, or from bacterial or other pathogenic organisms. Some of these allergens only sensitize people who have a natural tendency to become sensitized while others sensitize all people.

It has been seen that various types of tissue reactions occur as the result of allergic mechanisms. A simple and practical classification is: I. The immediate whealing type of reaction, and II. the delayed tuberculin type, which also includes the delayed drug allergies.

Hartman (1956) in a comprehensive review suggested a useful classification of allergic disorders based primarily on the predominant type of tissue reaction. Allergic disorders with:

I Anaphylactoid tissue reactions, e.g. asthma, hay fever, eczema, mild serum diseases, etc.

II Necrotizing tissue reactions.
- (a) cell selective, e.g. Rh sensitization, agranulocytosis, haemolytic, anaemia, etc.
- (b) tissue selective, e.g. acute dermal necrosis, encephalomyelitis, demyelinizing diseases, etc.

III Granulomatous tissue reactions.
- (a) Tuberculoid type, including sarcoidosis.
- (b) Rheumatoid type, including rheumatic fever.

IV Hyalinoid tissue reactions.
- (a) collagen diseases.
- (b) amyloidosis.

Hartman, under the above headings, further classified allergic disorders into three clinical groups. I. Those disorders always or usually allergic in origin such as hay fever; II. Those disorders in which allergy is considered frequently a cause such as glomerulonephritis, and III. Those disorders in which allergy is uncommonly a cause such as scleroderma.

To some, the exhaustive lists of diseases which have been suggested as allergic would seem, possibly, to be too comprehensive, but this only illustrates the difficulty of drawing a sharp line in allergy in our present stage of knowledge; i.e. our present difficulty in deciding how important a part an allergic mechanism plays, and/or

how commonly, in producing certain illnesses at present considered borderline. Only the future can tell.

With the contents of this chapter in mind, the clinician may well follow a simple and conventional subdivision of allergy as follows:

1 The immediate whealing allergies; hay fever and vasomotor rhinitis, asthma, infantile eczema, urticaria and angioneurotic oedema, food allergies and (sometimes) migraine; whether or not there is a hereditary factor proven.

2 Drug allergies—immediate and delayed, including serum diseases and anaphylactic reactions in humans.

3 Allergic contact dermatitis.

4 Bacterial allergies.

5 Anaphylaxis, Arthus Phenomenon and other artificially induced reactions in animals.

By common consent the concept of hypo-allergic reactions has been dropped.

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II. Prevalence of Allergy (Naturally Occurring Type)

An accurate assessment of the prevalence of the naturally occurring allergic diseases is at the present time difficult. There are still difficulties with regard to what should be included. For example there is even now much sincere disagreement as to what manifestations result from food allergies and as to the prevalence of allergic reactions to foods.

As an example of the present diversity of opinion with regard to this, the findings of Loveless (1950) can be instanced. She found from a poll of 191 specialists in pediatrics and allergy in the United States that 1.5 per cent of 245,000 patients were considered allergic to milk whereas the figures suggested by Rowe, Randolph and Rinkel would be five to ten times higher. In the same way she obtained information that ingested corn in the United States caused allergic symptoms in 0.16 per cent of 45,000 patients in contrast to an incidence of 16 per cent to 30 per cent by Rinkel, Randolph, Rowe and Crandall.

At present, therefore, any estimate of the prevalence of allergy in a population can only be a rough estimate and is likely to be affected to a certain extent by the views of the investigator.

Prevalence Studies in the United States.

Vaughan in 1932 estimated the prevalence of allergy in the village of Clover in Southern Virginia comprising 508 individuals. He classed as major allergies, asthma, hay fever, eczema, urticaria, recurrent headaches or indigestion for which foods were known to be responsible. A total of 10.8 per cent were found to have or have had major allergies. Minor allergic manifestations at one time or another were found in 48.1 per cent, making a total of 59 per cent of the population who had or had had allergic manifestations. The manifestation of minor allergy included a great variety of symptoms (quoted Vaughan & Black, 1954, p. 95).

Jimenez (1934) in an investigation of 6,935 students of the University of Michigan considered 35 per cent as sensitized persons. This included those who had or had had asthma, hay fever, rose fever, eczema, gastro-intestinal upsets, food idiosyncrasies, frequent colds and headaches, etc. Based on the family history, another 20 per cent were considered potentially allergic, making a total of 55 per cent being considered allergic or potentially allergic.

A few years later Pipes (1937) at Jackson, Louisiana, investigated 700 residents and students at the secondary schools and university. Forty-nine per cent were found to have allergic manifestations, 1.6 per cent had major allergic symptoms and 35.8 per cent minor

symptoms. As with Vaughan's study, the incidence of food allergy was high.

Service (1939) at Colorado Springs investigated through trained investigators one thousand families, 3141 persons, and found that 22.6 per cent had or had had one or more major allergic manifestation, i.e. asthma, eczema, migraine, urticaria and/or gastro-intestinal allergy.

It is from these early studies and from the subsequent clinical opinions of other workers in this field that there is now general agreement in the United States literature that some 10 per cent of the population are subject to major allergic illnesses and that some 40 per cent to 60 per cent suffer from minor allergies (Vaughan and Black, 1954).

Prevalence Studies in Europe.

Denmark. Schwartz (1952), based on careful personal study of 1,790 persons, estimated the prevalence in Denmark of asthma as 1.01 per cent, hay fever 0.30 per cent, vasomotor rhinitis 1.40 per cent, Besnier's prurigo 0.10 per cent, eczema 4.60 per cent, urticaria 7.20 per cent, Quincke's oedema 1.45 per cent and gastro-intestinal allergy 0.10 per cent, making a total of 16.16 per cent. If migraine at 1.10 per cent is included the total is 20 per cent of the population.

Finland. Eriksson-Lihr (1955) draws attention to the findings of Pellonen and his colleagues at Turku where they found that of 1,832 children aged 7 to 14 years, 6.8 per cent had allergic manifestations, 7.39 per cent of 2,312 boys and 6.23 per cent of 2,520 girls. Infantile eczema had a prevalence of 3.0 per cent, urticaria 3.2 per cent, asthma 0.6 per cent, rhinitis 0.4 per cent, "other allergies" 0.6 per cent, making a total of 6.8 per cent.

Britain. The following figures are quoted from Reports (No. 7 and No. 9) issued from the General Register Office of England and Wales by its Chief Medical Statistician W. P. D. Logan, of analyses of the clinical records from April 1951 to March 1954 of ten selected general practitioners. The figures give an average annual rate of patients consulting their doctors for allergic illnesses. It is to be borne in mind that the services of a general practitioner in Britain are free and that any drugs prescribed are issued at a nominal fee. Thus all patients with active disease requiring either advice or medicinal treatment will attend their doctors. It is, however, probable that mild urticarial cases would not visit their doctors, nor possibly would milder cases of migraine who would no doubt treat themselves with aspirin or codeine. The figures, therefore, will indicate active illness.

In males (all ages) asthma had a prevalence of 0.86 per cent, hay fever 0.44 per cent, urticaria 1.38 per cent, "other allergic disorders" 0.30 per cent, making a total of 2.96 per cent. If eczema 1.43 per cent and dermatitis 1.48 per cent are added, the prevalence would be 4.87 per cent, just under 5 per cent.

In females (all ages) asthma had a prevalence rate of 0.77 per cent, hay fever 0.47 per cent, urticaria 1.62 per cent and "other allergic disorders" 0.43 per cent making a total of 3.29 per cent. With eczema 1.37 per cent and dermatitis 1.53 per cent the total is 6.19 per cent, a slightly higher figure than in the males. The addition of migraine 0.38 per cent in males hardly affects the total figure, while 0.93 per cent in females brings the total figure in females up to 7 per cent.

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The Prevalence of Asthma

Introduction.

Knowledge of the prevalence of a disease not only gives us a measure of the load imposed by the disease on a community, but is of value for the light it may throw on the aetiology and natural history of the disease. Comparative studies by showing similarities or differences may well guide us more surely on fundamental aetiological factors than isolated individual studies.

In asthma, differing climatic conditions, differing environments, differing ways of life and social conditions, differing racial characteristics and sex and age differences have all been considered to play important parts in its aetiology and natural history. Careful comparative studies of the prevalence of asthma in different communities would be one method by which the relative importance of these different factors could be assessed.

In assessing the value and meaning of prevalence studies care must be taken to note the exact definition of asthma used and whether it includes inactive as well as active asthmatics, the methods used to establish the population at risk and the number of asthmatics, the age and sex distribution of the population, and the year of examination. Each of these factors affects the resultant figure and only by most careful comparison can one hope eventually to assess the effect of different modes of life, different climates, etc.

Europe.

Britain: Asthma was the cause of rejection of 0.9 per cent of young men aged 18 to 19 years medically examined for the Armed Forces (Williams, 1952). Among university students, in 1949 50 Rook at Cambridge found that of 1,786 students medically examined, 5.6 per cent gave a history of asthma and 2.4 per cent had active asthma, while at the University of Wales, Hitchens found that of 1,198 students, 3.1 per cent gave a history of asthma and 1.7 per cent had active asthma (Williams, 1952). Grant (1957) in a medical study of 4,571 students at the University of Wales, found that 3.3 per cent gave a history of asthma and 1.9 per cent were still having attacks. Grant (1957) gave figures strongly suggestive that asthma was more prevalent in university students than in the general population at that age-group.

Roughly it would appear that some 2.0 per cent of university students in Britain have active asthma and between 3.0 and 4.0 per cent give a history of asthma.

During 1946–47 Stocks in a two-monthly survey of illnesses in a random sample of a canvassed population of 37,458 persons aged 16 and over, selected with proper regard to regional distribution and representation of urban and rural districts, found the mean monthly prevalence of asthma to be 0.9 per cent (Williams, 1952).

In 1954 two general practitioners from Barrow-in-Furness, an industrial town in the northwest of England, found that in their practice of 4,000 patients, 1.7 per cent consulted them on account of asthma (Hamilton and Bendowski, 1954).

The General Register Office of England and Wales under the guidance of its Chief Medical Statistician, W. P. D. Logan, has published an analysis of the clinical records from April 1951 to March 1954 of selected general practitioners. The following is an extract from these publications. The overall figure of the prevalence of asthma 1951–54 was 0.85 per cent as estimated from ten general practitioners covering a population of 36,889 persons of all ages. In 1951–52 in eight practices, the prevalence was 0.97 per cent; in 1952

in 9 practices (with addition of one practice with a prevalence of 0.7 per cent), the prevalence was.0.83 per cent, and in 1953–54 in 9 practices the prevalence was 0.74 per cent. It is interesting to see that the prevalence of asthma is not of necessity constant each year even over a period of three years.

That both age and sex have an affect on the prevalence of asthma is shown in the following table:

Prevalence Analysed by Age and Sex.

Ages	*Males*	*Females*
0–14	0.97 %	0.51 %
15–44	0.64 %	0.70 %
45–64	1.07 %	1.25 %
65 plus	1.00 %	1.18 %

It can be seen that in the 0 to 14 age-groups, males have asthma twice as frequently as females, whereas in the middle-aged and elderly, females have asthma more frequently than males. Asthma is commoner in both sexes over the age of 45 years than under this age.

In *Finland,* Eriksson-Lihr (1955) recorded that of 2,176 recruits for the Armed Forces age 18 years, 0.9 per cent were rejected on account of asthma, a figure almost identical with that of Britain. From school records at Helsinki of 14,668 boys and 13,331 girls aged 7 to 14 years, she found a prevalence of 0.4 per cent in the boys and 0.3 per cent in the girls. She quotes figures from Turku by Peltonen and his colleagues showing that in a population of 4,832 school children aged 7 to 14 years the prevalence of asthma was 0.6 per cent.

In *Sweden,* Kraepelin (1954), from school cards for the whole of Sweden, found the prevalence of asthma in school children 7 to 14 years to be 0.73 per cent in both 1948/49 and 1949/50, populations of 235,437 and 247,000 respectively. In March 1953 in Stockholm, after a personal interview with the school doctors of Stockholm the prevalence of asthma was found to be 1.37 per cent of the population.

In *Norway,* Claussen (1948) in a survey of 295,356 persons of all ages over a considerable area of Norway, chiefly in smaller country districts, found a prevalence of 0.4 per cent. He could find no obvious differences in the frequency of asthma as between coastal and inland districts but noted considerable differences in prevalence in different age-groups. The maximum prevalence occurred in males in the 60–65 age-groups, 1.15 per cent, and in females, in the 55–65 group, 0.85 per cent.

In *Denmark*, Schwartz (1952) in a very careful study of 1,790 persons, calculated the prevalence of asthma at 1.01 per cent of the population.

In the *Netherlands*, Quarles van Ufford (1951) records that of 171,737 young men of military age, 0.93 per cent were found to have asthma. It is of interest that in the larger towns of more than 25,000 inhabitants, the prevalence was 1.18 per cent while in the smaller ones the prevalence was 0.77 per cent; a definite difference.

In *Germany*, Albrecht and Dwerstef (1957) as the result of circularizing doctors in 1953 found the prevalence of asthma to be 0.51 per cent.

North America.

United States of America. One of the earliest estimates of the prevalence of asthma was that of Frankel and Dublin (1917) who, in a survey in the principal cities in Pennsylvania and West Virginia between 1915 and 1917 of those who were ill on the day of visiting, found a prevalence of active asthma of 0.04 per cent in 464,873 people.

Later studies have shown this figure to be excessively low.

Sydentricker (1928) in a study of the prevalence of various diseases at Hagerstown between 1921 and 1924 in a population of 8,587 found asthma to give an annual sickness rate of 0.41 per cent.

Collins (1935) in a canvassed population of 9,000 families, 39,185 persons in eighteen states visited for twelve months between 1928–31, found active asthma to have a prevalence of 0.42 per cent. The following table shows his findings of the differing prevalence rates of active asthma in the different age-groups: –

Under 5 years	0.33 %
5– 9	0.45 %
10–14	0.31 %
15–19	0.07 %
20–24	0.19 %
25–34	0.41 %
35–44	0.37 %
45–54	0.60 %
55–64	0.75 %
65 plus	1.00 %

Bigelow and Lombard (1933) in an assessment of chronic illness in Massachusetts State in 1929–31, in a population of 75,668 based on 13,000 cases, estimated a prevalence of active asthma of 0.45 per cent. Rackemann (1931) based on admission to the hospital clinic at Boston estimated the prevalence of active asthma as 0.5 per cent.

Rowntree et al. (1943) found in World War II, that of 48,585 recruits for the Armed Forces, aged 18–19 years, asthma was present in 0.53 per cent and 0.37 per cent were rejected on this account. This figure for rejection is a lower figure than that for Britain and Finland for the same age-group.

Hyde and Kingsley (1943) found in recruits to the U.S. Army aged 21–44 years, that 0.7 per cent were rejected because of active asthma.

Rowntree (1944) in an analysis of recruits to U.S. Army aged 18–38 years found 0.75 per cent rejected on account of asthma.

Vaughan in 1934, in a careful study of the inhabitants of Clover, Virginia, a population of 508, found 3.3 per cent had or had had asthma (Vaughan & Black, 1954).

Service (1939) in a canvassed population of 3,141 persons in Colorado Springs, found 3.6 per cent had or had had asthma.

Rowe, (1937) among university students, population 1,000, found that 3.0 per cent had or had had asthma.

Blanton, et al. (1953) in a study of 37,497 persons 1949/50, who were over the age of fifteen years, found that 2.6 per cent had or had had asthma.

Dees (1957) records that during 1955, of 2,951 first visits or admissions of children to the Pediatric Department of The Duke University Hospital, 274 asthmatics were seen, giving a rate of 9.3 per cent of all pediatric admissions.

A survey of the literature of the prevalence of asthma shows that at present only a very rough comparison can be made.

In Europe, the prevalence of active asthma in England, Denmark, Netherlands and Finland, is, surprisingly perhaps, very similar, all being around or just under 1.0 per cent. In Sweden the figure for children aged 7 to 14 years of between 0.7 per cent and 1.37 per cent would suggest at least a similar prevalence amongst the adults. The figure of 0.5 per cent for Germany is by comparison low, but as the authors point out this figure can only be regarded as a rough estimate as the returns from some doctors were unsatisfactory. The figure of 0.4 per cent for Norway is also rather low when compared with other studies in northern Europe and it would be of considerable interest to see figures of more recent studies from this country.

Present studies suggest that roughly the prevalence of asthma in different countries in northern Europe may well be somewhat similar.

The United States is of course a vast continent as compared with northern Europe, but it would appear that their prevalence figures for active asthma are in general lower than those of northern Europe, roughly 0.5 per cent as compared with approximately 1.0 per cent.

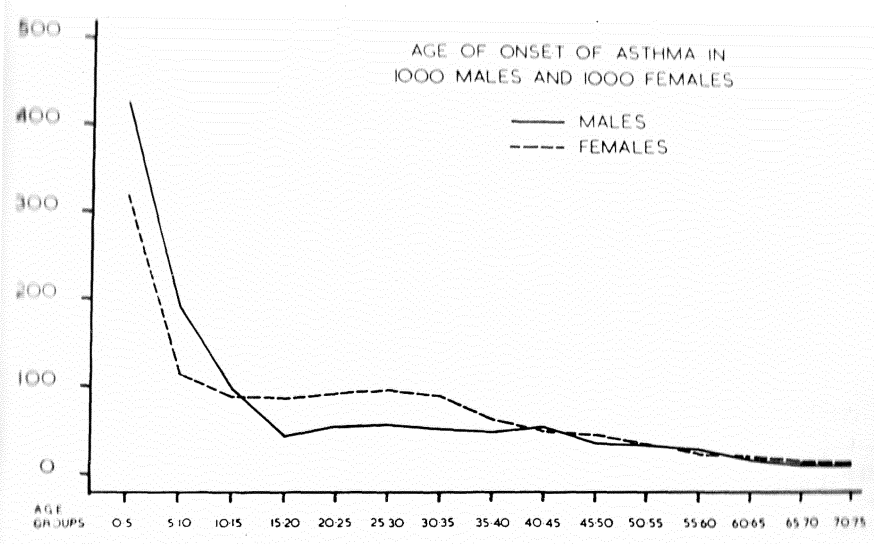

Fig. 1.

Previously published in the Proceedings of the First International Congress for Allergy, Basel, Karger, 1952, page 50.

Age of Onset of Asthma.

Figure I shows the age of onset of asthma in one thousand males and one thousand females as found at the author's clinic. It can be seen that before puberty boys develop asthma more frequently than girls, in a proportion of some 2–1; between puberty and the menopause more woman develop asthma than men, and that after the menopause the two sexes develop asthma approximately equally. More recent studies by the author with Dr. Higgins of the Pneumoconiosis Research Unit Llandough, Cardiff, have shown that of 9,018 males and 16,592 females, asthma started in 38 per cent before the age of 5 years, 54 per cent before the age of 15 years, 67 per cent before the age of 25 years and in 80 per cent before the age of 35 years. A definite sex difference was found, 80 per cent of the males as against 40 per cent of the females developing asthma before the age of 15 years, and 90 per cent of the males as against 75 per cent of the females developing asthma before the age of 35 years. Thus 25 per cent of the women, compared to only 10 per cent of the men developed asthma for the first time after the age of 35 years.

Deaths from Asthma.

The next table (A) shows the death rates from asthma as recorded by death certificates in different countries. The figures represent a

TABLE A

Mean Death Rates from Asthma per 100,000 of the Living Population

Country	Years in Survey	Total No. of years	Mean Rate
Japan	1948–50	3	15.7
Germany (Federal Republic)	1949–50	2	10.8
England and Wales	1946–50	5	7.0
Ireland	1946–49	4	6.8
Scotland	1946–50	5	6.2
Netherlands	1946–50	5	6.1
Italy	1946–48	3	5.9
Denmark	1946–50	5	4.5
Norway	1946–50	5	4.3
Spain	1946–48	3	4.2
Finland	1946–50	5	4.1
France	1946–47	2	2.2
United States of America	1946–49	4	
Total			2.2
Whites			2.2
Others			2.2
New Zealand	1948–49	2	2.2
Australia	1946–49	4	2.1
Canada	1946–49	4	2.0

comparison of the view of a large number of doctors in the different countries, whose medical standards are similar and which can probably be taken as an average comparison in regarding the true death rates from asthma in those countries. They may well indicate the relative severity of asthma in these various countries and possibly be a guide to the relative prevalence. The figures must, of course, be considered with a modicum of reserve. The figures for

TABLE B

Deaths from Asthma Compared with Other Well-Known Medical Conditions in England, Scotland and Wales for 1950.

Condition	M	F	Total
Asthma	1,796	1,628	3,424
Appendicitis	717	535	1,252
Bronchiectasis	1,210	550	1,760
Duodenal Ulcer	2,143	411	2,554
Diseases of Blood and Blood Forming Organs	977	1,763	2,740
Diseases of Liver and Gall Bladder	1,297	1,960	3,257
Gastric Ulcer	2,250	925	3,175
Diabetes	1,383	2,866	2,249

Taken from Registrar General Statistical Review of England and Wales for the year 1950, Volume 1, Medical, London, H. M. S. O.

England and Wales have been largely corroborated by clinical studies of the author.

The next table (B) gives an indication of the relative importance of deaths from asthma as compared with other illnesses (Registrar General, 1950).

The next tables (C. & D.) (both reproduced by permission of Karger, Basel from the Proceedings of the First International Congress of Allergy), show the relative importance of the allergic diseases as compared with other common illnesses with regard to prevalence and incapacity, England and Wales.

TABLE C

Mean Monthly Prevalence Rates per 100,000 Population.

(The Monthly Periods being evenly distributed from May 1946 till April 1947).

Asthma	904	Pernicious Anaemia	140
Hay fever	168	Other Specified Anaemia	4
Urticaria	26	Undefined Anaemia	1,066
Allergic Eczema	9		
Migraine	250	Anaemia, all forms	1,210
	1,357	Heart Disease of Rheumatic Origin	175
Tuberculosis-Pulmonary	280	Valvular Diseases of heart not said to be rheumatic	189
All sites	374	Coronary Disease, Angina	108
Influenza	1,326		472
Gastric Ulcer	476		
Duodenal Ulcer	516		
Peptic & Anastomotic Ulcer	48		
	1,040	High blood pressure	1,352
		Diabetes	291
		Simple Goitre	182
Chronic Bronchitis	3,110	Thyrotoxicosis	14
Chronic Nasopharyngitis	7,452	All Thyroid Conditions	209
Sinusitis	126	Pneumoconiosis	93
Eczema	289		
Industrial Dermatitis	52		
Rheumatoid Arthritis	419		
Osteo Arthritis	39		
Spondylitis	14		
Other Arthritis	1,058		
All forms of Arthritis	1,530		

Taken from Table 15, "Sickness in the Population of England and Wales in 1944 1947", by Percy Stocks, C.M.G., M.D., F.R.C.P., Studies on Medical and Population Subjects No. 2.

Previously published in Proceedings of the First International Congress for Allergy, Basel, Karger, 1952, page 60.

TABLE D

Days of Incapacity in Month per 10,000 from all Causes.

Asthma	206	Pernicious Anaemia	20
Hay fever	–	Other specified Anaemia	–
Urticaria	1	Undefined Anaemia	54
Allergic Eczema	–		
Migraine	23	Anaemia, all forms	74
	230	Heart Disease of Rheumatic Origin	14
Tuberculosis-Pulmonary	72	Valvular Disease of heart not said to be rheumatic	28
All sites	108	Coronary Disease, Angina	16
Influenza	906		58
Gastric Ulcer	124		
Duodenal Ulcer	120		
Peptic & Anastomotic Ulcer	18		
	262	High blood pressure	62
Chronic Bronchitis	858	Diabetes	4
Chronic Nasopharyngitis	51	Simple Goitre	18
Sinusitis	16	Thyrotoxicosis	–
Eczema	32	All thyroid conditions	26
Industrial Dermatitis	33	Fractures, all sites	194
		Pneumoconiosis	11
Rheumatoid Arthritis	61		
Osteo-Arthritis	–		
Spondylitis	–		
Other Arthritis	133		
All forms of Arthritis	194		

Taken from Table 15, "Sickness in the Population of England and Wales in 1944–1947", by Percy Stocks, C.M.G., M.D., F.R.C.P., Studies on Medical and Population Subjects No. 2.

Previously published in Proceedings of the First International Congress for Allergy, Basel, Karger, 1952, page 61.

TABLE E

Summary—31 General Hospitals.

England, Scotland and Wales.

	No.	Total Medical Discharges	Asthma Principal Disease	Asthma as % of Medical Discharges
London Teaching Hospitals	6	32,659	737	2.3 %
Provincial Teaching Hospitals	11	143,313	3,150	2.2 %
Non-Teaching Hospitals	14	64,065	1,283	2.0 %
Total General Hospitals	31	240,037	5,170	2.2 %

Previously published in Proceedings of the First International Congress for Allergy, Basel, Karger, 1952, page 63.

The next table (E) gives the percentage of the total admissions to thirty one hospitals in Britain. The maintenance cost in hospital if the average stay was three weeks was estimated in 1949 as four and a half million Pounds Sterling annually.

There is no doubt that asthma is of considerable social importance.

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Prevalence of Hay Fever

The following are the figures given for the prevalence of hay fever.

Europe:

Britain (Based on patients consulting their doctors in ten general practices in different parts of Britain).

Years	*Males*	*Females*
0–14	0.43 %	0.23 %
15–44	0.56 %	0.67 %
45–64	0.28 %	0.48 %
65 plus	0.30 %	0.12 %
All ages	0.44 %	0.47 %

(Extracted from Medical & Population Subjects No. 9, H. M. S. O. London)

Denmark 0.3 % (Schwartz, 1952).
Italy 0.5 % (Sangiorgi, 1956).
Spain (Barcelona) 0.5 % (Surinyach et al. 1956).

Middle East:

Israel 0.3 % (Kessler, 1954).

America:

United States
4.4 % of 3,000 (Piness and Miller, 1930).
3.0 % of 1,000 (Piness and Miller, 1930).
5.3 % had or had had hay fever (Vaughan, 1954).
10.0 % „ „ „ „ „ „ (Service, 1939).
10.0 % „ „ „ „ „ „ (Rowe, 1937).
8.0 % of 2.140 school children had hay fever Glaser et al., 1951).
3.0 % had or had had hay fever (Blanton et al., 1953).
2.3 % "conservative estimate" (Alexander, 1947).
1.0 % (Scheppegrel, 1922).

Brazil Nil—no cases of true hay fever among native Brazilians (Lima et al., 1946).

It can be seen that a figure of approximately 0.5 per cent could be taken for the prevalence of hay fever in Europe, but that in the United States, hay fever which includes sensitivity to ragweed, a pollen which does not occur in Europe, results in a much higher

figure, som 3.0 per cent to 10.0 per cent with a past or present history of hay fever.

Urticaria and Angioneurotic Oedema

The following are published figures with regard to prevalence:

Europe:

Britain

	Urticaria	
Years	*Males*	*Females*
0–14	3.47 %	3.75 %
15–44	0.66 %	1.22 %
45–64	0.39 %	0.79 %
65 plus	0.34 %	0.77 %
All ages	1.36 %	1.62 %

(Extracted from Medical & Population Subjects No. 9, H. M. S. O. London)

Finland School children 7–14 years 2.2 % of 109 (Eriksson-Lihr, 1955).

Denmark *Urticaria* 7.2 %
Quincke's oedema 1.45 %
(Schwartz, 1952, p. 253).

United States of America:

3.2 % Angioneurotic oedema and Urticaria (Service, 1939).
0.39 % Angioneurotic oedema (Vaughan, 1954).
4.9 % Urticaria (Vaughan, 1954).
15.7 % of 1,424 College Students had or had had one or more attacks of urticaria (Sheldon et al., 1954).
13.0 % Personal history of urticaria in 1,600 students (Rowe, 1937).
23.6 % of 1,000 persons had urticaria (Swinny, 1941).

Eczema

Europe:

Finland 3.0 % of school children with infantile eczema (ages 7–14 years) (Eriksson-Lihr, 1955).

Denmark 4.1 % eczema.
0.1 % Besnier's prurigo (Schwartz, 1952).

Britain

	Eczema	
Years	*Males*	*Females*
0–14	2.02 %	1.83 %
15–44	1.07 %	1.18 %
44–65	1.26 %	1.46 %
65 plus	1.63 %	1.04 %
All ages	1.43 %	1.37 %

		Dermatitis
0–14	1.49 %	1.62 %
15–44	1.39 %	1.42 %
45–64	1.81 %	1.52 %
65 plus	1.05 %	1.48 %
All ages	1.48 %	1.53 %

(Extracted from Medical & Population Subjects No. 9, H. M. S. O. London)

United States of America:

4.5 % personal history of eczema (Rowe, 1947).
0.6 % allergic eczema (Vaughan, 1954).

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III. Predisposing Factors

A *Heredity and Allergy.*

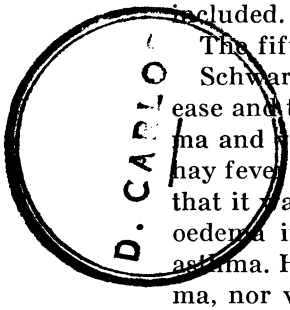
The great majority of clinicians accept heredity as a basic factor, giving rise to the tendency for some individuals rather than others, to develop spontaneous allergic diseases of the immediate whealing type.

The most recent and notable contribution to this subject has been that of Schwartz (1952) who critically (and excellently) reviewed and summarized the literature and studied the occurrence of diseases of known or of suspected allergic nature in the families of 191 asthmatics, 200 "controls" and 50 cases of baker's asthma. All the asthmatics had been fully investigated at the University Hospital, Copenhagen, and all were patients, of all ages, referred to the Medical Out-Patient Department. The majority were seen in 1943.

The illnesses studied in their families are listed below and were as defined:–

1. Asthma.—Paroxysmal dyspnoea accompanied by a wheezing respiration.
2. Hay fever.—Characteristic symptoms occurring each year during the season. In practically all cases the causative agent was grass pollen with only a few spring and autumn hay fever cases.
3. Vasomotor rhinitis.—Paroxysmal, sudden rhinitis and sneezing, itching in the nose and nasal obstruction, at all times of the year.
4. Besnier's prurigo.—"Eczema", recurrent or chronic, characterized by intense itching, prurigo, papular and lichenization in the flexor surfaces of the knees and/or elbows, wrists and face. Only cases considered certain were included, more doubtful ones were relegated to eczema. The majority started before the age of 20 years.
5. Eczema.—Included were: (1) cases where the precipitating factor was known, primula, nickel, turpentine, etc. (2) Cases of typical eczematous eruptions of protracted duration but in which the aetiological factor was unknown. (3) Cases of mixed and uncertain character including eczema during infancy, eczema with ulcer of the leg and eczema solare.
6. Urticaria.—Urticarial wheals with erythema and itching of some hours duration subsiding with sequelae (strophulus not included).
7. Migraine.—Paroxysmal unilateral headache accompanied by nausea and vomiting with scotoma, etc.
8. Quincke's oedema.—Paroxysmal, sudden swelling of the skin or mucous membranes of a few days duration subsiding without sequelae.
9. Gastro-intestinal allergy.—Included were only cases of regular attacks of vomiting, diarrhoea or acute abdominal pain occurring invariably after ingestion of well-defined foods or drugs. All uncertain dyspeptic cases were excluded.
10. Epilepsy.—
11. Ichthyosis.—Included only those with typically cracked, scaly skin; "fish skin disease."
12. Psoriasis.—

The "controls" were subjects who did not suffer from any of the above diseases but were matched by age and sex. There was no social difference in the two groups. Both groups lived in Copenhagen. The "pedigree" or family studies included the patients' and controls' parents, grandparents, parents' children and children. More distant relatives such as first cousins or grandparents' children were not included.



The fifty cases of baker's asthma were similarly studied.

Schwartz came to the conclusion that asthma is an inherited disease and that a genetic relationship was demonstrable between asthma and vasomotor rhinitis, while Besnier's prurigo and presumably hay fever also appeared to be genetically related to asthma. He found that it was possible but not very likely that urticaria and Quincke's oedema in females are in certain instances genetically related to asthma. He found that eczema and migraine were unrelated to asthma, nor were psoriasis, gastro-intestinal allergy, ichtyosis and epilepsy.

It is of considerable interest that in his investigation of the asthmatics he analysed separately those cases of definitely allergic asthma and those cases of asthma in which allergic exciting factors could not be demonstrated, the so-called non-allergic group. He found a striking correlation between these two groups and could find no essential differences between them, concluding that asthma was a disease entity, a genetic entity.

It is also of interest that Schwartz, on the basis of the genetic entity of asthma and its close association with vasomotor rhinitis, Besnier's prurigo and hay fever, and on the common finding of positive cutaneous reactions and eosinophilia in these diseases, considers that the evidence strongly indicated that these diseases are always of allergic origin.

Schwartz' results, as he points out, support Coca's concept of atopy, for Coca has for years been of the view that these diseases differ from other allergic diseases by virtue of their common hereditary background.

Urticaria and Quincke's oedema were found to be genetically linked, to have a positive correlation and may be regarded as identical. This illness and asthma were linked apparently only in females. It was suggested that there were two varieties of this illness, only one of them being hereditary.

Bray (1930) had maintained that asthma was inherited twice as often from the maternal side as from the paternal side, but Schwartz showed from his own material that the diseases he demonstrated to be genetically related, asthma, hay fever, etc., afforded no evidence to support the idea of extrachromosomal inheritance through the

mother, and after considering the evidence, considered extrachromosomal inheritance as unlikely.

The work of Cooke and Vander Veer (1916) and Spain and Cooke (1924) suggested that patients with allergic predisposition from both the paternal and maternal side manifest the allergic disease before puberty, that in patients with unilateral allergic predisposition the disease does not occur until shortly after puberty, and that patients without obvious allergic predisposition develop their illness at a more advanced age. Wiener, Zieve and Fries (1936) presumed the existence of two allelomorphic genes, H. (normal) and h (allergic). H H. is the normal and h.h. always develops allergic disease before puberty, with all the intermediate combinations. Schwartz analysed their basic studies and condemns them on the basis of their material and also on their assumption of an incidence of seven per cent of allergic diseases in the population, which is used for the calculation. Further, Schwartz could not find in his own material that the presence or absence of allergic predisposition influenced the age of onset of asthma. He therefore rejects the theory of Wiener, Zieve and Fries. Schwartz also ruled out the possibility of sex-linked inheritance in these diseases.

The possibility of dominant or recessive heredity in the asthma group is discussed in detail. He concludes that the genetically related diseases: asthma, vasomotor rhinitis, Besnier's prurigo and hay fever are transmitted by Mendelian dominance with failing manifestation. As far as asthma is concerned there is, moreover, a "localization factor" of genetic nature.

In discussing the localization factor, attention is drawn to the previous work of Clarke, Donally and Coca (1928), who had found that whereas there appeared a heredity correlation between asthma and hay fever, asthma seemed to occur with preference in some families and hay fever in others. Schwartz draws attention to the agreement of his figures, that among the relatives of asthmatics the predominant disease is asthma, and therefore supports the suggestion of this localization factor in asthma, i.e. that asthma tends to occur in the relatives of asthmatics more commonly than the other allergic diseases.

The degree of manifestation of these hereditary diseases is about forty per cent. From this he calculated the following risks. If one parent had asthma and the other was healthy, fifty per cent of the children would be carriers of the gene but only forty per cent of this fifty per cent, i.e. twenty per cent, would acquire manifest allergic disease, thirteen per cent would develop asthma and the remaining seven per cent vasomotor rhinitis, Besnier's prurigo or hay fever.

If both parents are asthmatic, seventy-five per cent to one hundred

per cent of the children would be carriers of the gene and so thirty to forty per cent would manifest one of the allergic diseases, asthma occurring in twenty to twenty-five per cent.

In cases of healthy persons from families with asthma or one of the other allergic diseases, calculation of the risk must be uncertain for it is impossible to know whether or not they are carriers of the gene. At the usual age of marriage the probability of being a carrier of the gene is between thirty and fifty per cent. If two carriers of the gene marry, seventy-five per cent of their children will be carriers so that thirty per cent will manifest an allergic disease, twenty-two point five per cent as asthma.

Bowen (1953) has studied fifty-nine pairs of identical (monozygotic) twins over a period of fifteen years. He found co-existing allergies in twins to be the exception. In only seven instances was there a true bilateral allergy of similar pattern while in fifty-two cases the allergic condition existed only in one twin.

Ratner and Silberman (1953) review their own material and the literature and discuss Schwartz' article. They agree that there is no relationship between the type of family history and the age of onset of symptoms and Ratner also draws attention again to his previous findings (1951) that fifty-nine per cent of children with allergic eczema later have respiratory allergy (asthma and hay fever).

Their general conclusions are that the difficulty in obtaining adequate material, the inadequate definition of essential criteria and the difficulty in dissociating acquired from genetic factors make it impossible at present to fit any genetic hypothesis to the existing data. Schwartz' views, however, are of considerable importance and an acceptable hypothesis.

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B. *Exposure to Allergens as a Factor in Allergic Diseases.*

It is obvious that before a person becomes allergic to a substance, he or she must have been exposed to it.

It is generally accepted that differing substances have differing degrees of antigenicity, but unfortunately there is no method of estimating this factor in man except by clinical observations.

It is also generally accepted that the tendency to develop sensitization depends up to a certain maximum at least, upon the degree of exposure, both quantitatively and over a period of time. Here again accurate observations in man are most difficult to obtain. The outbreaks of "epidemics of asthma" near factories processing castor-bean, from large quantities of castor-bean dust escaping into the air, show how large quantities of a highly antigenic dust can rapidly produce asthma, and even in people not naturally susceptible (Ordman, 1955).

Phillips (1939) has shown that clinical sensitivity to beet pollen -Beta vulgaris—developed in a number of persons after only two seasons of exposure. In his district, domestic beet was introduced for the first time in 1936 when some 1,800 acres were planted. In 1937, 3,200 acres and in 1937, 5,500 acres were planted. The pollen production was enormous. Two years of preparation with an adequate exposure in the third year were required to elicit symptoms of sensitivity to beet pollen; nearly seventy per cent of a group of allergic patients so exposed being affected. In the following year Phillips (1940) gave evidence on similar lines that for the spores of Johnson grass smut (Sphacelotheca sorghi, S.cruenta or S.holci) at least five seasons of exposure to its spores were required to induce cutaneous and clinical sensitization.

Clark and Leopold (1940) analysed the percentage of ragweed hay fever sufferered in 103 American-born patients and 98 foreign-born patients in respect of the time of onset of symptoms after they had been exposed to ragweed pollen. Both groups had spent their American years in or near Philadelphia where the ragweed is a never failing crop. Although 33 per cent of the American-born and 30 per cent of the foreign-born ragweed hay fever patients had their symptoms within ten years, the peak time of developing symptoms was after an exposure time of eleven to twenty years when 36 per cent of the American-born and 47 per cent of the foreign-born patients developed their hay fever.

In a study of vasomotor rhinitis due to orris root and horse dander Rackemann (1925) found the period of sensitization varied from a few months up to seven years. In bakers and others working with wheat there have been many studies made concerning the period of

sensitization. There is general agreement that the period of sensitization is about ten to fifteen years but in any individual it may vary from one year to forty-two years (Schwartz, p. 217). It has been estimated that some ten per cent to twenty per cent of persons working with flour become sensitized to it.

These are examples of published work which give us an idea of approximately the length of time necessary for exposure to certain inhalant allergens before symptoms of sensitization occur. In practice it is perhaps worth emphasizing that when a child or adult develops asthma, it is the common inhalants such as house dust, feathers, animal danders, etc., i.e. inhalants with which the patient has been in common contact for some time, which are likely to be the cause of asthma. It is most exceptional for an unusual inhalant which has been introduced very recently into his environment to be the cause of symptoms, and enquiry on those lines is likely to be abortive. Whatever finally precipitates symptoms, the development of inhalant sensitivity occurs gradually over a period of time. Food allergies usually develop at an early age, often in infancy, but here again, sensitivity to one of the common foods, eggs, milk, wheat, potato is far more likely to be the cause of symptoms than unusual foods.

Exposure to poison ivy will produce a contact dermatitis in some fourteen days (Field and Sulzberger 1936) and to primula within three weeks (Low, 1921).

Schwartz writes that dermatitis from wearing apparel begins usually five days or more after the garment has been worn and that in an occupational dermatitis, such dermatitis must be shown to have developed after an incubation of at least seven days after first exposure to the sensitizing substance (Schwartz, 1947, page 265).

The role of length of exposure to the varying antigenicity of various sensitizers, and the question of inheritance, are and need to be increasingly studied because of their importance in occupational diseases, for the number of occupations where such a hazard exists is very numerous.

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C. *The Effect of Climatic Factors and Altitude on Allergic Symptoms.*

One of the first to express an opinion on the effect of atmospheric conditions on asthma was Sir John Floyer. In 1698 Sir John considered that moist air was injurious and dry air beneficial to the asthmatic and that changes in the weather, especially a falling barometric pressure, were likely to precipitate attacks.

Hyde Salter (1860) was of the opinion that low damp areas with abundant vegetation were unsuitable for asthmatics and in more recent times Storm van Leeuwen (1925) considered asthma to be commoner in the more humid areas of Holland than in the drier areas.

Jiménez Díaz and his colleagues (1932) also associated climatic asthma with high humidity and found certain parts of Spain to be particularly so affected. There would appear to be much agreement among both European and American clinicians that climate plays a part in allergic illnesses and in general a warm dry atmosphere is the best for those with naso-respiratory allergy. There is, however, no statistical information to support this, and even if there was its correct assessment would be very difficult, for many other factors may be involved.

Both Storm van Leeuwen and, to a certain extent Jiménez Díaz, favour the possibility of mould spores as a possible cause of increased asthma in humid areas, and in assessing climatic effects full regard must be paid to the role of differing atmospheric content of pollens and mould spores, resulting in freedom or otherwise from symptoms. Harsh (1952) is of the opinion that the chief reason for the greater incidence of respiratory allergy in a humid climate is that the humidity renders house dust and possibly certain other allergens more antigenic, but this view although interesting, has only had very limited support, as others consider house dust antigenically similar the world over (Vaughan and Black, 1954, p. 71). Apart from having to consider possible exposure to or freedom from allergenic substances in different climatic areas, other factors such as racial differences, social differences and differing degrees of urbanization have also to be considered.

The possible effect of altitude is of special interest, for altitude and climate are intimately connected. In the older European literature there was general agreement that asthma was relieved by re-

sidence at a high altitude and a figure of 4,500 feet was frequently mentioned. It has, however, become evident that whereas there may be some truth in this observation with regard to certain mountain resorts, altitude as such does not prevent allergic manifestations.

Baker (1948) working in Mexico City at an altitude of 7,325 feet has pointed out that allergic manifestations not only occurred in Mexico City but in her opinion were more prevalent in that city than at lower altitudes. Other observers have also found that allergic symptoms are not invariably relieved by residence at a high altitude.

The effects of sudden changes in weather, especially sudden changes in barometric pressure, have also interested clinicians, but except for a few isolated observations (Rappaport, Nelson and Welker, 1935) who suggested that sudden barometric variations precipitate asthma, there is as yet little definite correlation.

The correlation is difficult because of other accompanying atmospheric changes such as humidity and also because such changes affect the atmospheric pollen and mould content. Certain weather conditions, such as thunderstorms, produce very high pollen counts for short periods of time (Dingle 1955).

One of the most helpful and recent contributions to the subject of climatic asthma is that of Ordman (1955) in South Africa, who has for some years studied this problem in detail. The greater portion of the Union of South Africa has an elevation of some three thousand feet above sea level, but there is a narrow fringe below 1,500 feet around the coast. He has found that the incidence and severity of the perennial type of respiratory allergy (bronchial asthma and nasal allergy), are relatively greater in this coastal area, than on the plateau, especially on the east coast. He has also found that numerous cases seen both inland and in the coastal areas, have maintained good allergic health inland but become ill on the coast and observes the opposite to be true as well, i.e. sufferers of perennial allergic symptoms on the coast are ameliorated or restored to health when they reside inland.

The possibility of these cases being affected by psychological factors or by differing allergenic factors was considered and after much investigation excluded. Local pollens were excluded by the history, consideration of the local pollens and skin testing. Numerous cases were also tested with a wide range of fungous allergens. No greater degree of sensitivity was found on the coast at Durban, Port Elizabeth and Cape Town than was found in some of the inland cities where similar studies had been made. The atmospheric fungus content as revealed by plate cultures was no different at these coastal towns than had been found over many years inland at Johannesburg. The fungus content of house dust and bedding materials from the

homes of sufferers at the coast was not found to be significantly different from corresponding material at Johannesburg. Ordman also considered the possibility of enhanced clinical sensitivity to house dust as a posible cause, but large numbers of patients from inland and coastal areas showed similar reactions to extracts of house dust derived from either region.

Ordman did not consider that altitude alone was an explanation of the observed clinical differences, for in certain inland districts perennial climatic asthma also occurred. This he suggested might be associated with mists, but is being further investigated.

He came to the conclusion that climate was the agent responsible for the precipitation of symptoms. Climate, he points out, is the cumulative weather state over a period of time and is the resultant of air temperature, barometric pressure, rainfall, relative humidity, hours of sunshine and so on and is closely related to geographical features such as altitude and proximity to the sea or to mountain ranges. Meteorological data were studied in detail and large numbers of charts on such data were drawn up in an attempt to find critical differences between inland and coastal climates. After the study of many charts he found a striking and obvious "pattern". The climate of the South African coastal towns is subtropical and the "pattern" was a "compressed" one showing a temperature range of 55° to 80° F with a relative humidity of 60 % to 80 % showing little variation during the day and night and throughout the year. Some of the inland towns showed a marked change in the month to month temperatures and relative humidity, but even in other inland towns where the month to month variations were not so great, the day-night variations were pronounced.

It is this combination of a high atmospheric temperature and high relative humidity in a constantly narrow range throughout the twenty-four hours and during the year which he considers the significant climate factor in exacerbating naso-respiratory allergy in the coastal area of South Africa.

Spoujitch and Danilovitch (1956) also support the important role played by the climatic factor in the incidence of asthma. The highlands and hilly parts of Yugoslavia, with less mist, are much less injurious to asthmatics than the Panonic plain with its marshes and mists. They also report a higher incidence of asthma in industrial centres. The Dalmatian coast is considered to be favourable to asthmatics. The climate of Slovenia in contrast to other hilly regions, due to local factors such as the mist and the fog of the large forests, is unfavourable.

In England, it has been found that deaths from asthma are commoner in the winter months than in the summer and that incapacity

from asthma is commoner in the wetter areas of the west coast of Britain and in the colder northern areas than in the south eastern area which is a drier and warmer area (Williams, 1956). It would appear from the literature that naso-respiratory allergy at least is influenced by climate.

Sheldon and his colleagues (1953) have found that a pleasant warm location such as Arizona and Florida results in a marked remission quite frequently in atopic eczema, but emphasize that climatic changes should never be advised until careful consideration is given to the patient's environmental and social situation. Marchionini and Borelli (1956) in a study of a hundred patients with neurodermatitis living in Ankara, Hamburg and Munich found a change of climate beneficial in seventy-nine patients. Only if the altitude is above 1,500 feet will a stay in the mountains be of any help and it should last for at least six weeks. They also suggest careful individual study before recommending a change of climate.

In general it would appear that a warm dry climate will benefit many intractable asthmatics and atopic eczemas. Each patient ,however, must be fully investigated from the allergic viewpoint and very careful consideration given to all the factors involved before a change of residence and climate is advised.

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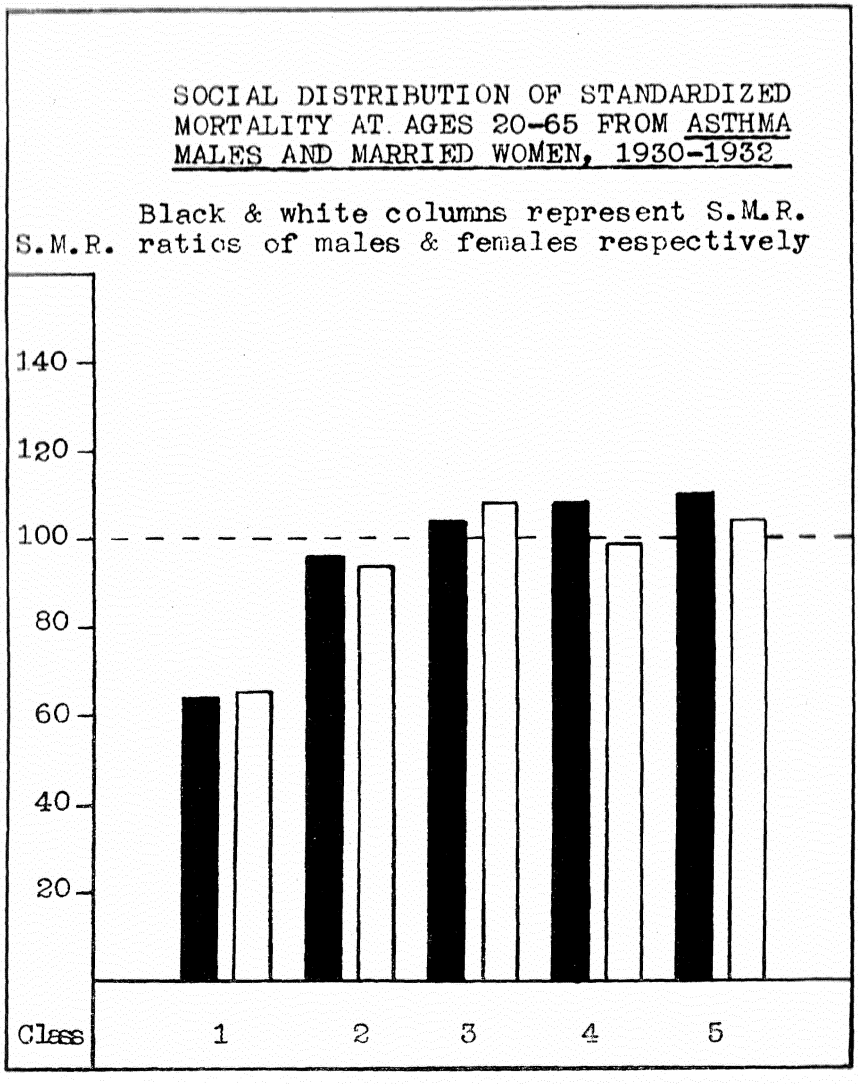

Fig. 2.
Taken from the Registrar General's Decennial Supplement, England and Wales 1931: Part II a Occupational Mortality, Diagram 3.

D. *Social Factors in Allergic Disease.*

Figure 2 shows that in Britain, mortality from asthma is affected by social position. In Class I, the professional classes, there is a distinctly lower death rate than in the other classes.

Table G shows that in Britain the amount of incapacity due to

TABLE G

Incapacity Due to Asthma—Males (Great Britain)—Classified According to Occupations.

Occupations listed in order of increasing prevalence of "spells of incapacity".

	Occupations	Population at risk (1,000)	Spells of Incapacity (1,000)	Spells of Incapacity per cent
1	Administrators, Directors, Managers	373	0	–
2	Professional and Technical	695	1	.144
3	Commerce, Finance and Insurance	1,328	2	.151
4	Agriculture, Horticulture and Forestry .	1,052	2	.190
5	Engineering, Metal Manufacture	2,521	5	.198
6	Workers in Wood, Cane, Cork	484	1	.207
7	Persons Engaged in Personal Service; hotels, clubs, institutions	491	1	.204
8	Workers in Building and Contracting ...	902	2	.222
9	Fitters, Machine Erectors	813	2	.246
10	Clerks, Typists	793	2	.252
11	Road Transport Workers	788	2	.254
12	Warehousemen, Storekeepers, Packers...	363	1	.275
13	Electricians, Electrical Apparatus Makers and Fitters	358	1	.279
14	Painters and Decorators	332	1	.301
15	Railway Transport Workers	316	1	.316
16	Water, Air and other Workers in Transport and Communications	293	1	.341
17	Workers in Unskilled Occupations	1,233	5	.406
18	Coal Miners	630	3	.476
	All Occupations	14,400	35	.243

Information obtained from the Ministry of Pensions & National Insurance, Digest of Statistics Analysing Certificates of Incapacity, 1951–52. Calculations checked by E. Lewis-Faning, D.Sc., Ph.D., F.S.S., Department of Medical Statistics, Institute of Preventive Medicine, Welsh National School of Medicine, Cardiff.

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asthma is affected to a large extent by social position, the amount of incapacity increasing to threefold with declining social position. The first eight occupations (those above the centre line) are all occupations where there is less incapacity than the average for all occupations and those below the line have all more incapacity from asthma than the average. The difference between Group I, Administrators, Directors and Managers, and Group 10, Clerks and Typists, is marked, although the difference in the work and place of work may be slight. It is in the financial and resulting social differences that we must look for the reasons of variations in the amount of incapacity from asthma.

Asthma is an illness which is adversely affected by poor social conditions. It is especially important that we should remember this when advising a choice of occupation for children and young adults. I have for many years advocated that children with asthma should be encouraged to work hard at school and to attend as regularly as possible so that their education later enables them to have a suitable choice of occupation and that they do not become workers in unskilled occupations.

A few articles have supported the viewpoint that allergic manifestations, especially asthma, are commoner in urban than rural areas, that is in the big cities rather than the country districts. However, in a survey of the prevalence of asthma in a sparsely populated country district (asthmatic population 5,939) and in a densely populated mining district (asthmatic population 19,671) in close proximity, it was found that the prevalence of asthma was a little higher in the country than in the mining towns, 1.8 per cent against 1.4 per cent, but the severity of asthma was less in the country district than in the industrialized towns, 8.5 per cent in the country having frequent incapacity (loss of work at least once a month) as against 16.7 per cent in the industrialized towns (Higgins and Williams).

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E. *The Infective and Traumatic Factor in Allergic Diseases.*

It is generally accepted that naso-respiratory infection may precipitate asthma, vasomotor rhinitis and even hay fever and that local trauma or infection also plays a part in the localization and precipitation of allergic dermatitis.

In asthma, many authors have pointed out the frequency with which naso-respiratory infection precedes the first attack. Hajós (1926) found 40 per cent of asthmatics reported an acute respiratory infection preceding their first attack; Kammerer (1927) found an acute infection preceding 56.6 per cent of his cases and Claude (1931) found 44.6 per cent gave a previous history of lung infection or other lung damage. Recently Dr. Lewis-Faning of the Department of Medical Statistics of the Welsh National School of Medicine, and the author, have found that of 487 consecutive asthmatics of all ages attending his clinic, 51 per cent gave a history of bronchitis; 15 per

cent a history of pneumonia and 22 per cent of "other respiratory infections" (influenza, colds, congestion of lungs, pleurisy or croup, but not tuberculosis) preceding the onset of asthma, while the corresponding figures for "controls" matched for age, sex and civil state were 13 per cent, 8 per cent and 10 per cent. Respiratory infective episodes were certainly far commoner in the preasthmatic patients than in the "controls". ("Controls" were patients attending the Accident Unit of the same hospital).

Infection may not only initiate asthma but it may also precipitate further attacks. Many cases of chronic asthma are infective in type.

Chobot and his colleagues (1951) in a study of 400 children found infection to play a part in 87 per cent and to be the sole cause of the attacks in 30 per cent. Pearson (1956), in an analysis of 500 cases of asthma of all ages, found that infection played a part in 45 per cent and that it was the only cause in 17 per cent. Lewis-Faning and the writer in an analysis of 487 asthmatics found the infective factor present in 77 per cent and the sole cause in 11 per cent. It is in the middle-aged and elderly that naso-respiratory infection plays an especially important part.

Prigal and his colleagues (1947) consider infection plays a major role in the production of allergic symptoms of the respiratory tract and is the most common cause of status asthmaticus. Swineford (1954) finds true status asthmaticus at his clinic unusual in the absence of infection. The writer's experience in Britain is similar.

The mechanism by which asthma and other allergic illnesses are precipitated by infection or trauma is a subject which has been much discussed of recent years. Pasteur Vallery-Radot and his colleagues (1956) on the basis of both clinical and experimental findings suggest that infection and trauma play a part in localizing the circulating antibodies. They point out how in special cases, positive cutaneous tests had been obtained with extrinsic allergens but that symptoms did not manifest themselves until an infection or some other form of trauma precipitated symptoms. They also draw attention to clinical observations where the localization of allergic dermatitis has occurred at skin sites previously injured by trauma or infection. Their experimental findings show that local trauma will increase the speed with which an allergic reaction occurs in the tissues when a standard dose of antigen is injected.

Whether or not asthma can be caused by bacterial allergy is still controversial. Gay and Marriott (1947) have pointed out how in cases of infective asthma an asthmatic attack may be precipitated by a small dose of vaccine, especially from an autogenous vaccine, and instance this as one of the most convincing factors supporting the viewpoint that bacteria can act as allergens in asthma. Rackemann

(1952) considers that "in some cases the diagnosis of "bacterial asthma" seems indicated even if hard to prove."

Curry (1950), while acknowledging the importance of the role of respiratory infection in asthma, considers that the role of allergy in bacterial infections associated with asthma is not clear. Spoujitch and Danilovitch (1953) also acknowledge the important part played by infection or bacteria in asthma and suggest that their role is not always the same in all cases, nor is it a simple matter. In certain cases the bacteria may act as allergens, at other times they aid the penetration of other allergens while they may also act as a localizing factor which produces the shock tissue.

There is general agreement as to the considerable value of antibiotics for the acute episodes of naso-respiratory infection in asthmatics, and their lesser value in the chronic infective asthmatic.

The value of bacterial vaccines, either stock or autogenous, has been discussed for many years. There is no doubt that such vaccines are almost universally used in the treatment of the chronic infective case, but their value has been difficult to estimate and there is no agreement as to whether any effect obtained is specific. Frankland and his colleagues (1955) found as a result of a controlled trial in 200 cases of infective asthma that regular injections of an autogenous bacterial vaccine produced no greater benefit than similar injections of carbolsaline, just over 50 per cent in both groups obtaining benefit.

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F. *Hormonal Influence on Allergic Manifestations.*

That there are hormonal influences on allergic manifestations has long been assumed.

That asthma and hay fever develop more frequently in boys than in girls before puberty, and in women more than men after puberty, supports this view. Pregnancy has been found to profoundly affect various allergic manifestations. The recent knowledge of the strikingly beneficial effect of cortisone in allergic conditions has further strongly supported this viewpoint.

The exact role of hormones in allergy is still, however, unknown. Evidence has been sought by many workers that in the allergic person there is either a continuously or intermittently lowered production of hormones from the suprarenal, but the results are as yet inconclusive. There is no doubt that the suprarenal, even in status asthmaticus, responds very actively to corticotrophin stimulation (Davies 1956). There may indeed be a dysfunction of the hypothalamus or of the pituitary which fails to adequately stimulate the suprarenal but this again is as yet surmise.

The role of the thyroid on allergic manifestations has been extensively studied. There is experimental evidence that decreased thyroid activity reduces allergic reactions and increases resistance to histamine and acetylcholine (Nilzen 1955). Some allergic reactions in animals can be abolished by thyroidectomy, circulating antibodies restrained, but other manifestations presumably allergic are not affected (Nilzen 1954).

Nilzen (1955) also showed that destruction of the thyroid inhibited anaphylactic reactions provoked by antigen administration via the respiratory passages.

Long and Sherwell (1954) found that thyroxine increased sensitivity to tuberculin by inducing hyperinsulinism from an increase in the amount of islet tissue.

Long (1956) points out that the ratio of insulin to cortisone output profoundly influences the immunological and allergic responses of guinea pigs to bacterial infection. He also points out that the influence of hormones upon sensitivity to tuberculin is intimately concerned with ascorbic acid-sulphydryl metabolism.

Statistical evidence as to the incidence of allergic diseases in diabetics is inconclusive but, although the two diseases do occur together occasionally, it is the impression of the writer and of some statistics that the incidence of diabetes amongst allergic patients is less than among the general population.

Clinically there is also no general agreement as to the role of thyroid in allergic manifestations. The writer has a few adult asthmatics with undoubted myxoedema of several years standing and has found that when these patients are allowed to become increasingly myxoedematous there is a decreasing liability to asthma while, with increasing doses of thyroxin, there is exacerbation of their asthma.

Quarles van Ufford (1951) on investigating the B.M.R. on 420 asthmatics, found 67 per cent were within normal range; 27 per cent had hypometabolism and 26.7 per cent hypermetabolism. He points out that from the literature and his own investigations, the allergic condition is often complicated by a dysfunction of the thyroid gland. He found that treatment of deviation from normal, although it frequently helped the patient, generally never directly improved the asthma. He concludes that thyroid treatment should never be used by itself as a treatment of asthma, a point of view generally held.

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THE DIAGNOSIS OF ALLERGIC DISEASES

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The expression "allergic diseases" is currently used to cover symptom complexes which may or may not have an allergic etiology. The problem confronting the allergologists—or allergist—is then to find out whether or not these symptoms are present in a patient with an allergic constitution (28) ("Allergiebereitschaft") (18), defined as "the tendency or ability to be sensitized". This is rather a poor definition, but it is just as well that one realizes how little we actually know as to what is happening in the organism of an allergic patient. It should always be kept in mind that asthma, rhinitis, eczema etc. are only symptoms and may all have a non-allergic etiology. Unfortunately we have no specific test for allergy, although numerous investigations have been performed in the hope of finding a deficiency or an appearance of a protein, hormone, blood corpuscle or any other organic or inorganic material which could be pathognomonic for allergy. Even physical examination or the macro- or microscopic picture do not reveal any features which are absolutely specific for allergy.

The question of "allergy or not" is a strange one and appeals to the detecting sense of the physician, because not only must he solve this problem, but if he concludes to an allergic background, he may often find it difficult to discover the offending allergen. Some physicians never think in terms of allergy while some allergologists try to find an allergy in every patient. Much experience is needed to adopt an intermediate position between these two viewpoints. When starting to practice allergy, the physician will sometimes be disappointed because what seems at first to be a simple case may later appear to be a difficult combination of physical and psychological problems which takes much effort to correct, as psychology plays a more prominent role in allergic diseases than in most others. The reward of the allergologist, however, lies in the fact that a number of patients

will have received various treatments from several doctors without success until a careful investigator reviews the whole history and reveals an allergy.

How is it possible to ascertain that the symptoms for which the patient consults are definitely or likely of an allergic origin?

1) The physician must know the symptomatology of the diseases possessing a possible allergic etiology. Although there is some disagreement amongst allergologists about the number of complaints which may be termed "allergic", at least some diseases are uniformly agreed upon as being due to allergy.

With regard to the symptomatology, reference is made to the specific chapters about allergy in the various organs where the differential diagnostic possibilities are discussed.

2) Allergic diseases are intermittent or chronic with exacerbations which makes it very difficult to reveal an allergy from the first attack. However, exposure to a suspected provoking allergen may produce another attack and thus ascertain the "intermittence". True, an infection may also behave in this way, but a great amount of allergic response is involved in the reaction to infection, so that this is only reasonable. Nevertheless, the intervals between the recurrence of symptoms or their localizations will sometimes lead to the suspicion of the involvement of an allergy. If a patient always reacts with characteristic symptoms, known to be of a possible allergic origin, to a substance which is innocuous to other people and whose pharmaco-dynamic properties are unrelated to the symptoms which it produces, it may be termed an allergic reaction. Such patients however are rarely encountered. The characteristic symptoms are always confined to the same organ under the same conditions and occur as a reaction to some more or less specific exposure. Although it is not uncommon to have a combination of two or more types of manifestations (for instance asthma and prurigo, rhinitis and asthma etc.), the symptoms in the same organ are practically always of the same quality even if there may be a difference in degree.

Here is one of the pitfalls in the diagnosis. A patient may often have noticed that he is sometimes sensitive to a substance to which he does not react under other circumstances. This is one of the arguments which is brought forward most often by colleagues who do not believe that allergy is a very frequent condition. This can be explained in various ways. My theory is based on the fact that the human organism has a tendency to be well balanced against whatever may try to disturb its equilibrium. If the allergy is not of a too pronounced degree or the exposure to the allergen is not too intensive, the body will be able to resist the attack by means of its normal control functions, provided that the natural resistance is

unhampered. When the patient is fatigued or exhausted, or when he has been under mental strain or has developed an infection, the controlling resisting forces are engaged in adjusting these deficiencies and the allergy will then cause symptoms. Unfortunately we do not know what a lowered resistance really is or how it can be explained biochemically. As an example, there is the common experience that a patient exposed to cold or to wet feet can be infected by bacteria which he has been carrying in his throat for days without harm. This theory can also be applied to patients who present symptoms on certain days and not on others although there seems to be no difference in exposure during these days (foodstuffs must be included in what is termed exposure). Finally this explains why patients who have been desensitized and are apparently symptom-free may develop another attack under extremely high exposure (see fig. 1).

3) The suspicion of an allergic etiology is increased if the patient presents more than one potential allergic disease. The presence of an eczema obviously provoked by contact with a specific substance, makes it seem more probable that a concomitant rhinitis can be due also to a hypersensitivity, although the symptoms may be perennial and chronic. The cause may be the bread or the cheese which the patient consumes daily.

4) Of less importance, but still "a little evidence", (Rackemann (27)), is a positive family history of allergy. Schwartz (37) has found, that if one of the parents has asthma, 50 % of the children will carry the "asthmogenic" gene and about 20 % of the children will acquire manifest asthma. If both parents are asthmatics 75–100 % of the children will carry the gene and 30–40 % will develop the disease, while the incidence of allergic disease in the general population is 7–8 %.

5) The results of skin tests should be used only as any other laboratory procedure. They should never be performed unless there is some evidence from the patient's history that he is allergic. Positive skin tests will also be encountered in a group of perfectly normal controls with no history of allergy in the family or in their past (Rackemann & Simon (29), Grow & Herman (16)). Positive skin tests alone can never be considered as a proof of allergy, but when allergy is ascertained or strongly suspected, skin testing may be helpful in detecting the substances responsible for the symptoms (43). "No technic is better than the technician who uses it. The diagnostic value of the technics will depend more on the clinician's ability to interpret his results correctly than on the elicitation of positive reactions" (Walzer (42)). Samter (34) has related an experiment in which the etiologic diagnosis was based solely on skin

tests in one group as compared with another where the diagnosis was based on the history or interviews with the patient. In the first group an approximate diagnosis was reached in less than 10 % while in the other an adequate diagnosis was found in almost 70 %. This shows clearly the "validity" of skin tests alone.

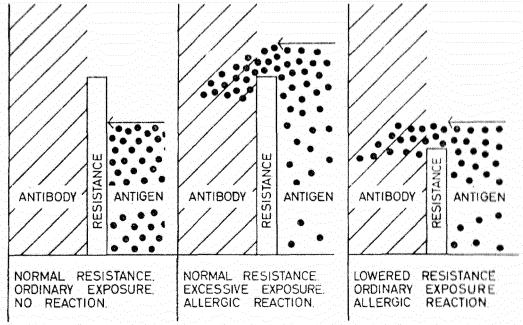

Fig. 1.

6) Eosinophilia in the blood and in various secretions is likewise an indication for allergy and is so far "the chief cellular characteristic of the allergic reaction in man" (Gay (14)), but the absence of eosinophils is by no means conclusive for the rejection of allergy. Eosinophil cells in the nasal secretion, in the bronchial mucus, in the faeces or in the saliva are by some authors (15, 17, 19, 44) considered to be pathognomonic for an allergic condition in the respective organs but no final agreement about this subject has as yet been reached.

7) Many papers have been written in which the results of treatment have been regarded as a proof of an existing allergy. The fact that a patient has responded successfully to an elimination diet, a change in occupation or environment, to a desensitization treatment (all of which are maintained to be specifically "anti-allergic") or to a symptomatic treatment including hormones, is regarded by some authors as proof of an allergic background of the disease. This is not convincing evidence, however, as the psychological effect of an interested doctor who listens carefully and is very understanding, or the many other factors which are involved in any of these types of therapy are not taken into consideration. Another thing is that in very few cases in which the pathogenesis is extraordinarily difficult, helping the patient without being certain about the etiology *may* be resorted to as a final attempt.

Diagnostic Procedures

A) *History-taking.*

The first and most important part in the diagnosis is the history-taking. The first interview with the patient or his parents, which often will last for an hour or more, should best be held in a room where the doctor can ask questions without interruptions from others. This will give the patient an opportunity to think and from the first interview he will have an idea as to what is expected of him and if he is cooperative—and this is usually the case—he will try to think backwards in the way which is intended, namely that he tries to find a cause for each attack he has had, at least the more recent ones. Then, when he comes back for the second interview, which need not last as long, he will be able to correct the information he gave the first day and perhaps add something new. The first interview should enable him to give an accurate account of his past history and his environment. It is necessary that the history-taking should leave a clear impression, not only regarding the particular symptoms for which the patient is consulting, but also of his physical and mental development as well as his environmental conditions. It is essential to determine his eventual contacts with foreign substances and his reaction to them, his behaviour towards the people he meets and his reaction to infections, fatigue and psychological stress. Obtaining a distinct picture of the patient, his symptoms and his surroundings is much more helpful in making a proper diagnosis and solving the problem of the presence of "allergy or not" than any other procedure, including the physical examination, skin tests, laboratory tests or X-ray (Alford (1)).

In all treatises on allergy the importance of taking a careful history is stressed but differences exist as to the best method in which it should be obtained. Some advise "a clean sheet of paper and plenty of time" (Chobot (5)), while others prefer questionnaires or forms (examples are given by Glaser (15) and Harris & Shure (19)). Both methods involve certain disadvantages: 1) without a questionnaire or form pertinent questions may be forgotten and omitted while the patient or mother is speaking steadily, especially if the physician is not well trained in this matter and 2) with a standard form the spontaneous description of the development of the symptoms may be brought to a standstill as the patient is being constantly interrupted in his narration. Valuable details, all of which cannot be included in a form, may be forgotten. Therefore, the best method in my opinion is probably to register first the spontaneously given history and thereafter ask questions whose answers are not already apparent from the patient's statement. One can thus fill in

the questionnaire which is attached to the "blank sheet" and which contains all the necessary details that are so indispensable for the correct diagnosis and no less for the confirmation of the value of the positive skin tests.

Taking a careful history is time consuming and laborious but nevertheless an essential procedure, more so than in any other branch of medicine. It is better to have more information than actually needed at the moment because later on it may be wanted to control the reliability of the narrator or to compare the results of skin tests or of progress with the past history. As the allergologist becomes more accustomed to the history taking of allergic patients, he shall probably find it unnecessary to write down every bit of information, only to make certain that he has written down the most important details.

The past history must include information about infancy, especially concerning infantile eczema and an early tendency to catch colds. If the patient has been suffering from infantile eczema, he should be questioned as to whether or not he was breast-fed and if not, what was the constitution of his diet? Did the eczema start in relation to a change in formula? In childhood it is of interest to know when the first symptoms started even if they did not suggest at that time any suspicion of allergy. It often begins in children with sneezing or coughing, whose only distinction from common colds lies in the chronicity of the complaint. Later on pseudocroupal attacks or periods with febrile bronchitis may appear and very often the disease develops into genuine bronchial asthma. In such a case, it is very important to know if anything else but "common cold" was noticed as a provoking factor of a dripping nose, cough, or hampered respiration. Sometimes the patient or the relative who accompanies him can remember that the first symptoms appeared in relation to some other event in his life or in his environment. Have similar events taken place subsequently and what were the consequences? It is likewise of interest to inquire as to any other preceding disease as well as the exposure to anything which may provoke an allergic attack, such as animals, foods etc. When the symptoms did not commence before adulthood, it is usually easier for him to remember the circumstances under which the first attack was noted and valuable data can be obtained as to exact time of day, year, and in which locality the first unpleasant reaction had been noticed. Any information concerning the first attack may be relevant so that it cannot be described in too much detail.

Several questions may arise about the patient's reactions to similar situations and exposures to the same allergens but under different circumstances. It must here be remembered that in infancy and early

childhood, for the most part, foods and infections will produce allergic reactions, aside from contact dermatitis. Allergy towards inhalants is scarcely encountered in this group. With increase in age, the inhalants become of growing importance although pollen allergy seems to occur rarely before the age of four or five.

The importance of foods as a cause of allergy is still under discussion. Some investigators claim that up to 50 % of all allergic manifestations are due to ingestants (31, 40) while others find this figure most exaggerated (5, 8). There is no doubt, however, that food sensitivity is of significance and causes many unpleasant reactions. For several reasons the diagnosis of this type of allergy is much more troublesome than inhalant allergy and is therefore often disregarded. Skin tests with foods are unreliable; only few foods are seasonal such as fruits and vegetables, some are seldomly eaten, such as shellfish, and from the case history it is impossible to discover that the patient is sensitive to milk, cheese, bread, egg, meat or any other daily consumed food. Finally, elimination diets and provocation tests with foods are more dependent on the cooperation of the patient, unless he is hospitalized, and are therefore less reliable.

When reviewing the past history of the patient from early childhood to the present, one should make certain that the following information has been obtained concerning the existing symptoms:

1) The onset: age of patient, period of year and approximately time of day.
2) The first signs and suspected causes.
3) The evolution of the illness and influence of environmental changes and treatment.
4) The seasonal, daily and local variations of symptoms: their appearance in particular rooms or places, during night or day time, at work or while engaged in some hobby.
5) The condition between attacks.
6) The non-specific factors which may disturb the well-being of the patient, weather variations, dusts, fumes and smoke.
7) The patients' psychological state and how symptoms are influenced by emotion, stress, etc.

Inquiry is then made as to the present complaints and symptoms involving the various organs: bronchi, nose, skin or the more rare locations such as headaches, gastro-intestinal symptoms, bleedings, nervous or epileptic disorders. At this time, the suspected allergens should be searched for, including inhalants, foods, colds or other infections, particularly of the upper respiratory tract, drugs or contactants. Questions should be asked regarding the influence of non-

specific factors, as mentioned above, upon the present symptoms, and about the variation of symptoms due to season, time of day and locality.

If possible at the time of the first interview it may also be of great importance to ask about the psychic factors which may be involved, but sometimes it is better to wait until one knows the patient a little better before going too deeply into this question. Some investigators claim that asthma, for instance, may develop without the involvement of an allergy on a purely psychosomatic basis, yet, although several psychologists and psychiatrists have published case reports intended to prove the psychologic origin, especially from maternal rejection, no one has so far been able to find any psychological picture which is not found in an equal manner in children with behaviour disorders or in maladjusted adults. When, through investigation, the provoking allergen has not been evidenced, this is not the fault of the patient, but may be due to a too inaccurate case history, bad testing material or an inadequate technique, however, it is not a proof of the absence of an allergy. It is, therefore, of utmost importance to ascertain the allergic background in cases where psychic factors evidently play a role. It is the opinion of all trained and experienced allergists that psychic involvement may be present in all allergic patients, but to a variable extent. In asthmatic children, for instance, the more or less hidden anxiety seems to be a common finding in most or perhaps all cases, but it is much more likely that the anxiety is secondary to the asthmatic attacks instead of being the original cause (Feinberg (10)). The emotional picture of the asthmatic child can be found to the same degree in children with other disturbances and in the same proportion, but perhaps to a less degree in so-called normal children (45). Just as a psychological "stress" may result in finger sucking or nail biting or bed wetting in some children, it may result in dyspnea if the child has an allergy, so that it may act as a trigger mechanism just as an infection or an exposure to a significant allergen. In every case, in order to provide adequate treatment, it is necessary to know about the psychological and environmental influence upon symptoms.

With regard to the intended treatment, it is advantageous to know how the patient has been treated previously, which examinations he has undergone, especially recently in order to avoid repetitions. Thus it may be of interest to make inquiries at the hospitals and from doctors he has already visited concerning pertinent findings.

For the purpose of substantiating the diagnosis of allergy it is also of importance to ask in detail about the family history. Not

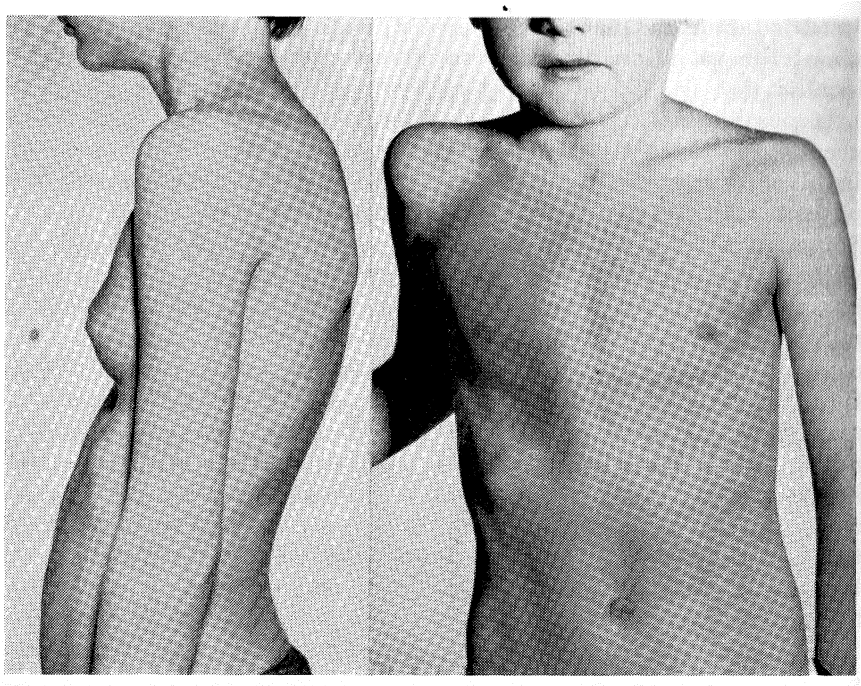

Fig. 2 and 3.
A girl and a boy with asthma.

only are allergic manifestations more common in allergic families but an organ specificity is encountered to a certain extent as well. Children of asthmatic parents are more exposed to asthma than those without this trait in their family.

B) *Physical Examination.*

It is very important to remember that, as previously mentioned, the asthmatic attacks, the sneezing, the itching and so forth are symptoms which may have an non-allergic origin. A thorough physical examination is therefore always a necessity. The dyspnea may arise from heart disease, tuberculosis, bronchitis, emphysema, foreign body etc.; hay fever symptoms may be due to sinusitis; eczema to fungus infection and so on. Accordingly all possible measures must be taken to refute any other etiology by a careful examination which must include blood pressure and X-ray of lungs, sinuses and teeth.

Quite often a more or less perennial rhinitis results in chronic post-nasal drip and blockage of the nose and consequently the child breathes through the mouth. Thus the mucous membrane of the

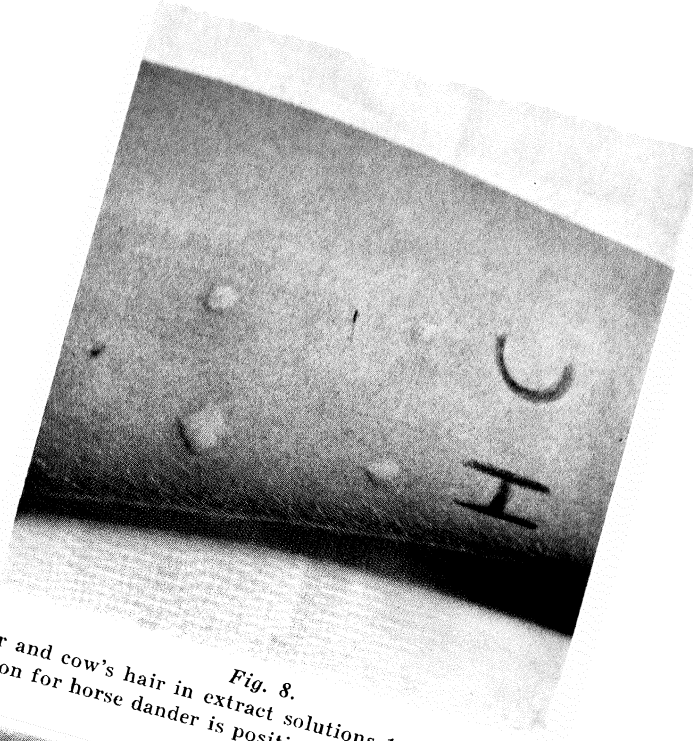

Fig. 8.
Horse dander and cow's hair in extract solutions 1:1,000,000 and 1:10,000.
The reaction for horse dander is positive and negative for cow's hair.

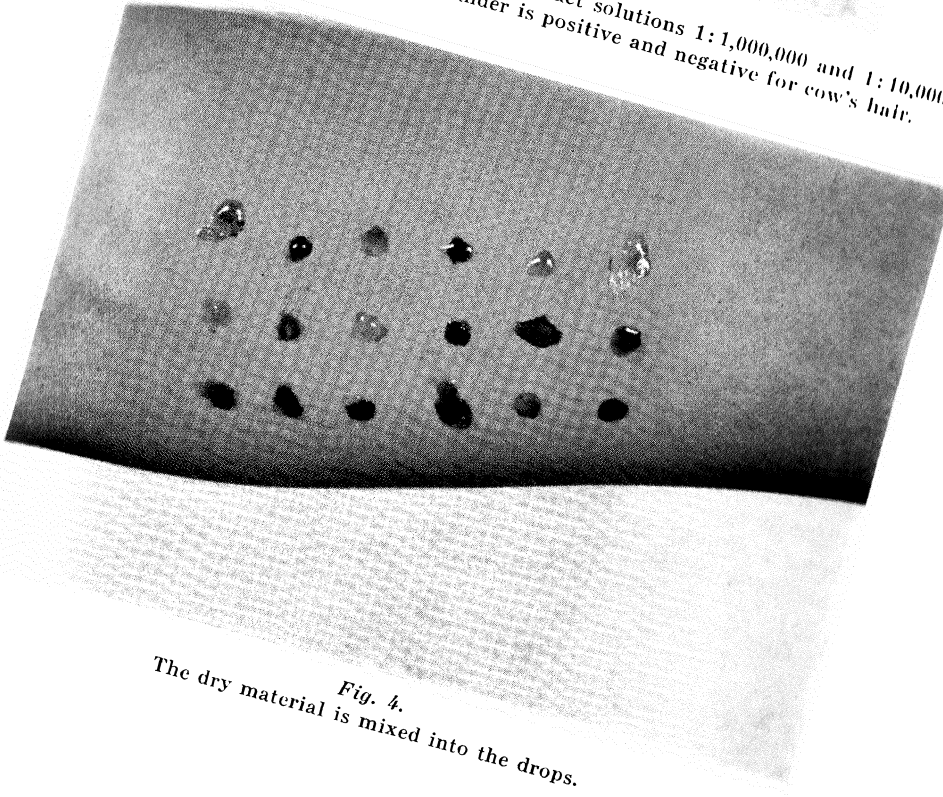

Fig. 4.
The dry material is mixed into the drops.

throat is constantly irritated and the air comes directly into contact with it without being filtered and heated in the nose. Henceforth, a rhinitis may result in a constant cough, perhaps in bronchitis, and subsequently in asthma. This situation may be overlooked in children who very often do not blow their nose but instead sniff the secretion inwards. The earlier this is stopped the better are the possibilities of prevention. A stubborn case of asthma can on rare occasions be clarified by means of a bronchoscopy, which may lead to the discovery of a tumor or a foreign body. At the same time, mucus can be taken for microscopic examination in search of malignant cells or for culturing to determine the bacterial resistance. Bronchography, however, should only be done when a foreign body is seriously suspected, as the contrast material generally contains iodine to which the patient may be allergic. Different laboratory tests and visits to other specialists, such as the ear-nose-throat specialist, cardiologist, dermatologist and psychiatrist or psychologist can be considered.

C) *Laboratory Tests.*

Erythrocyte sedimentation rate and haemoglobin should be determined routinely, and the blood count may also prove to be of interest. Some clinicians use the leucocyte and differential count, while others determine only the eosinophil count; the number of eosinophils seems to show variations during the day in relation to meals and their contents. A great deal of research is still necessary to determine the importance of the eosinophil cells. The finding of an eosinophilia, when no other reason can be evidenced, e.g. a helminthiasis, is regarded as a sign in favour of allergy although in its absence allergy is certainly not to be excluded. Cooke (8) reports that in case of infectious allergy the eosinophilia is more pronounced and the author is in agreement with this opinion. Some authors are convinced that eosinophil cells in various secretions such as in the nose, sputum, or stool, are pathognomonic for an allergic condition, but definite proof is still lacking, especially as the absence of eosinophils, in this case also, does not exclude an allergy (15, 17, 19, 44).

Electrocardiogram and lung ventilation tests may be of importance for the differential diagnosis.

D) *Skin Tests.*

Skin tests are of some value and will give some information in regard to the diagnosis provided they are interpreted in an adequate way. It should always be kept in mind that a positive skin reaction to a certain allergen does not necessarily mean that this substance

will produce symptoms, nor does a negative skin test exclude the possibility that this substance might be the cause of the illness. Skin tests should always be interpreted in relation to the history and eventually with clinical exposure tests. Quoting Bruce Pearson: "Skin tests do not provide a short cut to a speedy diagnosis, and in the hands of those who expect too much they are often misleading" (24).

Skin testing is a valuable procedure as (1) it may confirm the history findings, (2) a patient may be unaware that certain factors influence his allergy, a positive skin test may in this case lead his thoughts in the right direction and make him acknowledge that symptoms appear on exposure to these substances, (3) it may call the doctor's attention to a substance which was not suspected to be of significance so that it can be tested by provocation (43).

A great difference exists between the various allergens in regard to their reliability. The most dependable are the inhalants and substances which produce contact dermatitis. Ingestants on the other hand are considerably less reliable.

Positive cutaneous reactions may be found with allergens which do not provoke symptoms; this is termed "latent allergy" (33). A good example is grass pollen in children, which may show positive skin test, but negative provocation test. The provocation test, however, may become positive within a year or two, although there are still no seasonal symptoms. This condition is called "subclinical allergy" (11, 32) ("semi-latent" (20) or "nonclinical" (39)) and may gradually change into a manifest allergy. This again may return to the latent stage, with or without treatment, as shown in table 1:

TABLE 1

	Cutaneous Reactions	Provocation test, Sniff or Exposure	Clinical Hypersensitivity
Latent Allergy	+	—	—
Subclinical Allergy	+	+	—
Manifest Allergy	+	+	+
Postclinical Allergy	+	—	—

Sometimes positive reactions are obtained due to the presence of irritants in the material, histamine for instance, while at other times the skin reaction remains negative although the food concerned produces evident clinical symptoms. Several reasons can be evoked. The material being used is insufficient, too weak or too old, the testing material has changed during preparation,—for instance Ratner (30) has reported that milk is altered with regard to its allergenic pro-

perties by the evaporation, the skin shows no reaction due to changes in the tissues, dehydration, oedema, inanition, infection, hyperemia, cachexia, etc., or the allergic organism contains no antibodies towards the substance as such, but towards metabolic products derived within the organism as a result of the digestive enzymes on the food. This has been demonstrated by Cooke (7) and by Bloom, Markow & Redner (4) who conclude: "In the search for the aetiologic agent in nonreactive cases, the use of digested extracts for testing purposes will offer no advantage over a thorough and carefully taken history, confirmed by test feedings". Finally it may be mentioned that drugs usually give no specific reaction with scratch, prick or intracutaneous tests while the drugs responsible for contact dermatitis give very typical reactions by patch test.

The first cutaneous tests were performed by Blackley (3), who described how, on July 13th 1865, he did a scratch test with pollen of Lolium Italicum and obtained a positive reaction. Although Bela Schick (35) in 1956 called von Pirquet "the father of all skin testing for diagnostic purposes", Blackley must be given the credit, not only for the skin test, but also for the provocation test which he described in a way which has not been improved since that time. After von Pirquet's scratch test for tuberculosis in 1907 (25), Smith in 1908 (38) introduced, and Walker in 1917 (41) reintroduced, the same technique for application in allergy. Meanwhile Mantoux, 1908 (22) had employed the intracutaneous test with tuberculin and O. Schloss in 1912 (36) resumed this procedure for allergic testing. Finally the prick test was introduced by Lewis, 1924 (21), with histamine only, while Freeman (13) in 1930 applied this method for diagnostic purpose in allergic patients.

Testing Material

Reliable testing material is of the greatest importance. Some allergists prepare their own material while the majority buy their extracts from commercial firms. The processing and preparation of testing materials vary to some extent and differences may be noted in various handbooks. Only by experience can the physician ascertain that the materials he employs are the most dependable. The testing material in Denmark is manufactured by Allergologisk Laboratorium in Copenhagen. Table II indicates the manufacturing process.

The testing equipment should preferably consist of a large variety of extracts, as an examination made with only a few allergens is hardly worthwhile and is apt to create an unfavourable reputation for this otherwise valuable diagnostic procedure.

The allergologist must be able to test the patients with:

a) *Inhalants:*
   1) house dust; some prefer a sample from the patient's home and working place, others use a stock material,
   2) animal hair and dander, e.g. cat, dog, horse, cow, sheep, rabbit, goat,
   3) feathers: duck, goose, chicken,
   4) grass pollen, all the common grasses in the neighborhood, including wheat, rye, corn etc.,
   5) pollen from trees and flowers known to be allergenic, growing in the region,
   6) mould spores of the local types,
   7) clothing material, cotton, linen, silk, kapok, hemp etc.

b) *Ingestants:*
   1) milk, perhaps also lactalbumen, lactoglobuline, and caseine,
   2) egg yolk and egg white,
   3) flour, types most frequently employed,
   4) meat of the locally eaten animals, including birds,
   5) fish and shellfish of various kinds.
   6) vegetables, locally consumed,
   7) fruits, obtainable in the region,
   8) nuts, almonds, chocolate, coffee, tea etc.
   9) cottonseed, flaxseed, grains, spices, and perhaps drugs, e.g. ipecacuanha.

For contact or patch test a completely different equipment is needed. Here the different metals, tars and ointment bases must be at hand as well as a variety of other substances frequently encountered in daily life, paraphenylenediamine, formalin, linseed oil, orris root etc. Last, but not least, adhesive plaster used for the test must be included.

Technique

A) *Scratch and Prick test.*—When prepared solutions are used for the tests, the scratches—2 to 5 mm in length—or pricks are made on the clean skin and on each scarification or prick a drop of the solution is applied. Whenever dry material is used, a drop of N/10 sodium hydroxide is placed in rows on the testing site and the dry powder is mixed into it with a small wooden toothpick which must be changed for every test. A scratch or prick with a sharp needle (a gramophone needle can also be used for this purpose), is made through the drop. After every test it should be cleaned and wiped carefully in order to avoid contamination.

Tests can be made either on the flexor side of forearm, upper side of arm or on the back and spaced 1 to 2 cm apart. If the testing is done on a routine basis with numerous preparations, it may prove advantageous to make intervals between the suspected antigens about 2 cm while 1 cm between the less probable reacting substances is sufficient. Neither scratch nor prick should be deep enough to draw blood. About 15 minutes after the test, the arm is cleaned with ordinary water and the results are read. A positive reaction develops in 10–20 minutes and is characterized by an urticarial wheal with or without pseudopods and surrounded by a red zone. The larger the wheal, or the more pseudopods, the more positive the test is considered to be.

When the reaction is so large that it overlaps those next to it, these should be repeated. For comparison a control test with the diluting fluid must always be done. The reaction begins to fade away within a half hour. Infrequently, delayed reactions occur, mostly with foodstuffs.

It is important to keep in mind that there is not necessarily a parallelism between a large positive skin reaction and a high degree of sensitiveness, even if this is sometimes the case. Unexpected positive reactions should always be repeated.

Prick tests have the advantage of causing less discomfort to the patient which is especially important with children. It is also easier to make identical pricks than uniform scratches. As the reactions are smaller, there is less chance of a general malaise and confluence between adjacent wheals is less frequent.

B) *Intracutaneous tests* are far more sensitive than scratch and prick tests, but are more hazardous, and false positive reactions are more frequently encountered. In addition, they are more time consuming, more difficult to perform and interpret correctly. Nevertheless, many allergologists prefer this method as they consider it more important to obtain some false positive reactions than to omit any significant ones. The results, at any rate, must be compared with the case history and/or with the provocation test.

It is best to use a tuberculin syringe of 1 cc with lines at every 0.01 cc and a small needle, e.g., 20. Care should be taken to make the injection so superficially that no blood will appear and not to inject more than 0.01 to 0.02 cc as larger amounts will make the reaction more difficult to read. The injection may not be done too rapidly and care should be taken not to inject any air as in both cases a wheal, simulating a positive reaction, may appear.

It is recommended to perform the tests on the flexor side of the forearm and not on the back, so that in the case of a constitutional reaction a tourniquet can be placed above the site of injection. Constitutional reactions and their treatment are described in the

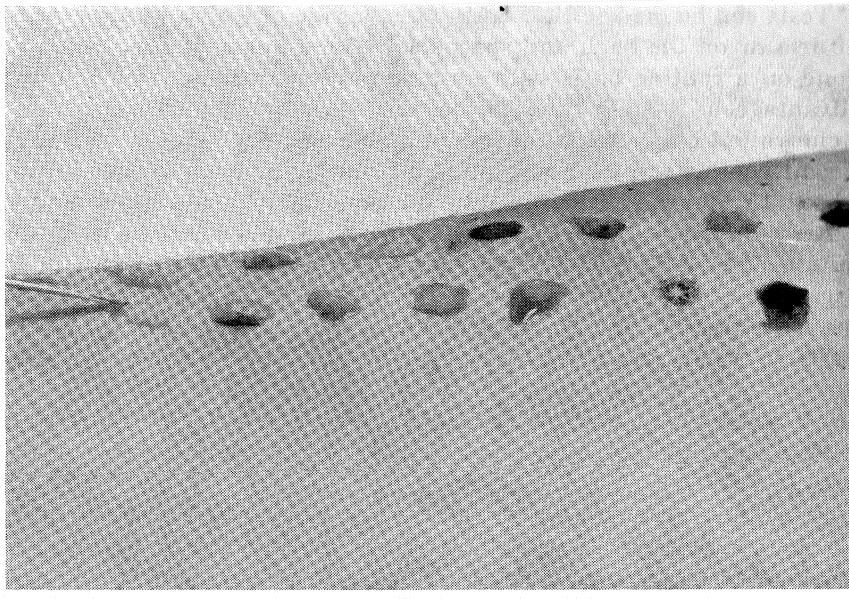

Fig. 5.
The skin is pricked with a scalpel.

chapter on specific desensitization treatment. As shown in fig. 7, the arm is reacting in almost the same manner from a little under the elbow to the lowest ⅓ of the forearm. It is advisable not to perform more than 8–10 tests at the same time if there is a suspicion that any of them will react positively, as an accumulation of strongly positive reactions increases the chances of a constitutional reaction.

In children, intracutaneous tests are regarded as too dangerous and produce far too much discomfort when done routinely. Only if the history raises a suspicion that the child is allergic to a substance and the prick test remains negative, is an intracutaneous injection to be considered. If, on the other hand, the prick gives a dubious reaction, it can be controlled by doing a series of intracutaneous tests with the same substance in increasing concentrations. If the same amount of fluid is injected in various concentrations, the reactions should increase in size in proportion to the concentration, otherwise there is no evidence of a reliable positive reaction. This applies to adults as well. The present author generally uses two injections, 1:1,000,000 and 1:10,000 (weight per vol. —see p. 137) and a definite difference must be noticed before concluding that a reaction is positive (see fig. 8). For food tests it is customary to try concentrations such as 1:10,000 and 1:100 in

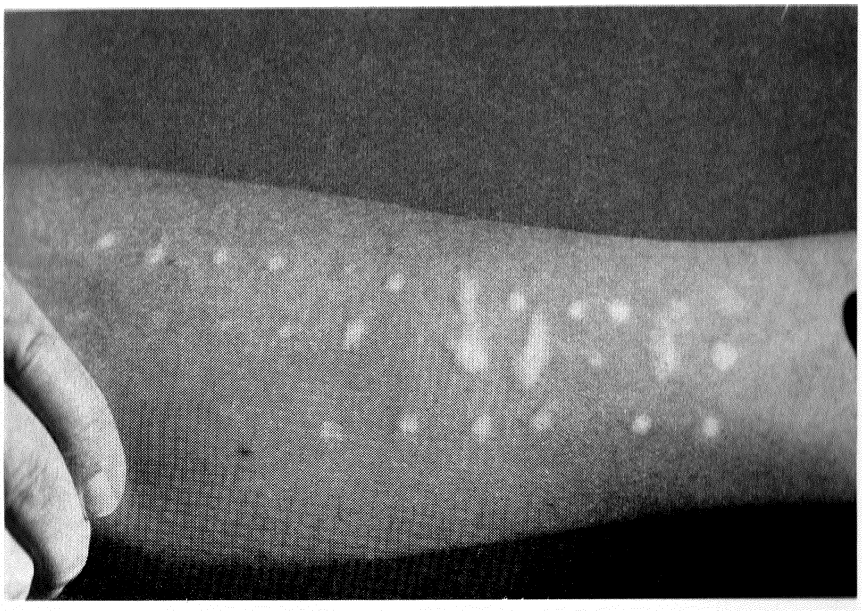

Fig. 6.
Reactions of different strength. Notice the confluence between different wheals. These tests must be repeated.

order to get a positive reaction, but it must be emphasized once more that the reactions must be correlated with the history and/or provocation tests. Only egg, shellfish, nuts and cottonseed should be tried with weaker solutions in comparison to other foods. If the tests mentioned do not give a distinct reaction, skin sensitivity is very doubtful. It must be remembered, however, that this does not exclude a constitutional reaction.

Group tests are used quite often in spite of severe criticism. The purpose in employing mixtures, e.g. one of inhalants, one of meats, one of cereals, one of vegetables and so on, is to diminish the number of tests to be performed. A great disadvantage of this method is that the reaction may remain negative because the one substance which, separately, would react positively, has been diluted by the other allergens in the group. If the group test is positive it is necessary to test all the components individually and it is therefore very doubtful if any time or work is actually saved in this way. Many a time it has been experienced with the prick test that a group reacted negatively while a suspected component, tested separately, gave a positive reaction. With the intradermal test the procedure may be permitted with groups of substances chemically or biologically related, such as grass pollen or fish. It is very seldom, indeed, that a

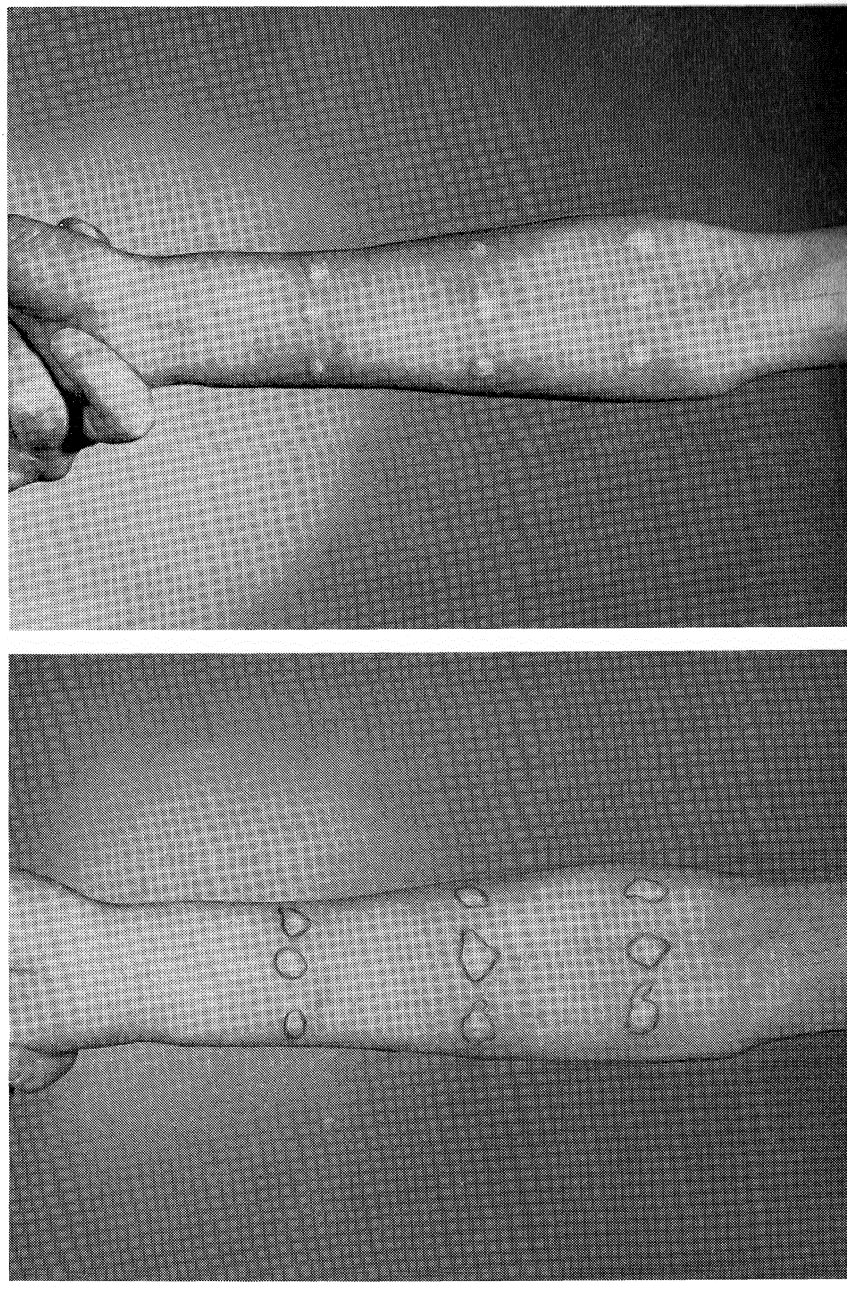

Fig. 7.
The reactions are identical in size from slightly below the elbow to lower ⅓ of forearm.

person is allergic to one sort of grass or to one type of fish only, and as Frankland (12) has shown, the sort of grass to which the patient is allergic is not so important in regard to treatment.

Several attempts have been made to find a test for bacterial allergy and many individual bacteria as well as groups of bacteria or culture material have been tried to prove the existence of allergy towards infection. No convincing evidence, however, has as yet been published although most allergologists believe in its existence. Either the skin tests are positive in all patients who have had a sore throat or a similar infection, or they are dubious or negative.

Standardization of extracts is a problem which has aroused many discussions and many experiments have been carried out in order to find a reliable method. Different procedures have been tried. The total nitrogen content is not reliable, as the protein nitrogen in older extracts gradually changes to non-protein nitrogen. Protein nitrogen content is therefore a better standard to use, but even this is not sufficient because with different methods of precipitation it can be shown that not all of the reacting substance is found in one portion of the protein. Some patients seem to react to the fluid which is left over when all of the protein should be precipitated from it. Noon's pollen unit (23) is the amount of extract obtained from 0.001 mg. of pollen, but great discrepancies exist between the content of reacting allergen and the weight of the pollens. Coca (6) redefined the Noon unit as the quantity of pollen extract which contains 0.00001 mg. of total nitrogen, but here again the question of protein nitrogen and non-protein nitrogen comes into consideration, and so far no chemical standardization method has been fully acknowledged. A completely different method is the biological one in which intracutaneous reactions with the old known extracts are compared with those of a new production. The extracts may be tested in two corresponding areas on a patient or animal sensitive to the allergen concerned. The test material is, for example, made as shown on Table II, and after the pulverization has taken place, the extraction with buffer solution is carried out in the proportion 1:100 (weight per volume). From this solution dilutions are made and compared with similar ones of the old extract, and the new ones are diluted until they respond with an intradermal reaction identical to the one produced by the old extract.

Concentrated solutions of extracts preserved cool, in dark airtight bottles, under sterile conditions, keep about one year or more without losing their strength. However, weaker solutions will not last as long. Dry powder seems to keep its strength for years.

C) *Patch tests* are done in cases of contact allergy. If the suspected substance is solid, some of it is placed on a small piece of gauze,

TABLE 2

Preparation.

	Purified house-dust	Dust etc. from pts	Animal hair	Feather	Meat fish	Vegetables	Fruit	Nuts seeds	Cereals	Milk cream removed	Eggs	Pollen	Moulds	Tobacco
Grinding					+	+	+	+	+					
Squeezing						+	+							
Sifting	+											+		
Extraction with ether	+				+			+						
Extraction with aqua distillata	+				+	+	+	+	+		+			
Extraction with 14 % alcohol			+	+										
Vacuum-distillation			partly	+										
Precipitation with acetone			+		+	+	+	+	+	+	+			
Double fractioned	+													
Paper-filtration			+		+	+	+	+	+	+	+			
Washing with ether				+						+	+			+
Cultivation													+	
Washing with alcohol													+	+
Drying			+	+	+	+	+	+	+	+	+	+	+	+
Pulverizing			+	+	+	+	+	+	+	+	+		+	
Extraction with buffer solution	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Paper-filtration	+	+	+	+								+		+
Dialysis	+													+
Sterile-filtration	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Aseptic dilution	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Control of sterility	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Biological test	+		+	+	+	+	+	+	+	+	+	+	+	+

moistened with saline or one-tenth normal sodium hydroxide, and thus attached to the skin by means of an adhesive plaster. It is best to use plasters with a circular piece of plastic fastened to it, and in order to keep it *in situ* a small piece of foam rubber may be put between the gauze and the plastic. A liquid substance can be dripped directly on the gauze. The patch may be left in place for 2 or 3 days provided the reaction is not very strong or induces itching. It is considered positive when small red papules develop corresponding to the piece of gauze and not outside the plastic. Sometimes, however, the patient is allergic to the plaster so that the circular spot is normal but surrounded by a red and irritated square corresponding to the plaster.

D) *Prausnitz-Küstner* (26)–*de Besche* (2) tests (passive transfer tests) are done in patients with extensive eczema, a contageous skin disease, or when ordinary skin tests are difficult to interpret because of the presence of an ichthyosis, urticaria etc. They are also used when the patient is so ill that a direct test may aggravate the distress, in cases of fighting and struggling children, or in infants too small to do as many prick tests as required.

The test is made by taking blood from the patient and injecting 0.1 cc of this serum into the skin of a normal person, or at least a person not reacting to the substances which should be tested. The sites of injections are marked on the skin. The next day the test solution is injected in the same sites and, as a control, on a symmetrical place on the opposite side. If the reaction is positive on the serum site and negative on the other, the patient is sensitive to the tested substance.

This, of course, can also be used as control for an unexpected reaction obtained in the ordinary way, especially if the patient shows a whole series of positive reactions which are believed to be false, or to determine if a patient is sensitive to a serum which is intended to be given against tetanus or diphtheria.

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PROVOCATION TESTS

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1. BRONCHIAL TEST. CHANGES IN PULMONARY FUNCTION IN CONNECTION WITH THE INHALATION TEST

A positive skin reaction in an asthmatic patient does not necessarily prove, nor does a negative one exclude, that the antigen concerned is of etiological importance.

To determine the existence of a hypersensitivity in the small bronchi to a certain antigen, the latter can be brought into contact with the mucous membrane through inhalation of a nebulized solution. This is called a provocation test.

The sensitivity of the bronchial mucosa can also be evidenced by the so-called exposure test in which the patient is brought into contact with the suspected antigen under natural circumstances; for example, a patient who is suspected of being allergic to horse epithelium may be asked to remain in a stable an hour or so under close supervision.

A positive bronchial provocation or exposure test will result in asthmatic symptoms: shortness of breath and the appearance of sibilant rales, when no abnormal auscultatory signs were present before the test. In certain cases the changes are so evident that there can be no doubt that the antigen which has been tested is able to provoke asthma. In other cases an objective registration of the changes in respiratory function is necessary in order to judge the results of the provocation test. For this reason the variations in respiratory function in connection with asthma will be discussed first.

A. *Changes in Certain Pulmonary Functions in Asthma*

a. *Oxygen uptake, carbon dioxide elimination and body temperature.*

It has been shown (Colldahl) that pulmonary ventilation, oxygen uptake and carbon dioxide elimination are altered in a regular

way both in experimentally induced asthma in guinea pigs (1943) and in asthma in humans (1947). During very severe attacks ventilation of the lungs as well as oxygen uptake are lower than under basal conditions. The organism is compelled to carry out an increased breathing effort with participation of all the accessory respiratory muscles, but is nevertheless unable to take up even as much oxygen as is required when the organism is at rest. This brings about an oxygen debt and this deficit must be compensated for when the attack is over. Consequently the oxygen uptake is considerably increased when the attack has subsided. In a moderately severe attack of asthma, the arterial oxygen is lowered, as was demonstrated already in 1921 by Meakins. In a mild attack pulmonary ventilation and oxygen uptake are increased above normal values. No oxygen debt arises, the organism being able during the attack to take up the necessary amount of oxygen which may even exceed by 100% the requirements under basal conditions.

The alteration in gaseous tension occurring during an asthmatic attack produces disturbances in the intermediate metabolism which have been demonstrated experimentally in guinea pigs (Colldahl 1943 1947). There are reasons to believe that similar changes occur also in asthmatic patients during severe prolonged attacks. During severe asthma in guinea pigs the concentration of blood lactate was elevated, a finding in favour of the fact that a lack of oxygen has taken place in the tissues during the asthmatic breathing.

Furthermore, it has been shown both in guinea pigs and in humans that during severe prolonged attacks the body temperature is lowered while in mild asthma it is raised.

The results obtained by Colldahl regarding oxygen uptake, carbon dioxide elimination, respiratory quotient and body temperature in experimentally induced asthma in guinea pigs and in spontaneously occurring asthmatic attacks in man, are similar to those found in asthma provoked by inhalation of an antigen to which the patient is allergic.

This is apparent from Schleinzer's work (1949–1951). This author, however, interprets the registered changes in the ventilatory gas exchange as being secondary to a primary metabolic reaction (Stoffwechselreaktion) resulting from antigen-antibody reaction in various organs. It seems difficult, however, on the basis of the gas exchange to conclude in favour of a disturbed metabolism in the cells when the gas exchange in the lungs undergoes such great alterations as a result of the beginning asthmatic breathing.

The fact that the degree of pulmonary ventilation and oxygen uptake are directly dependent upon the degree of difficulty of the stenotic breathing clearly shows that the variations in gas exchange

are caused by the asthmatic breathing. During a severe attack oxygen uptake and lung ventilation per minute are lowered under normal levels but as soon as the asthma improves, oxygen uptake as well as lung ventilation increase. (Colldahl 1943–1947). (Further details are given under "d").

b. *Intrapulmonary air mixing.*

Several authors have shown that the intrapulmonary mixing of respiratory gases is lowered in asthma and emphysema. In 1952 it was shown by Colldahl and Lundin that in provoked asthma, changes in the intrapulmonary air mixing occur even before the patient feels a sensation of tightness in the chest or difficulty in breathing. At this stage no lowering of the arterial oxygen saturation could be evidenced.

The nitrogen content in the exhaled air during the oxygen breathing is registered continually; the method is simple and does not demand much cooperation on the part of the patient. It is most important that the patient breathes normally as forced breathing may aggravate the asthmatic state. In case an objective registration of a provocation test is necessary, the registration of the intrapulmonairy air mixing is probably one of the most sensitive and best methods.

As an example is quoted a provocation test with horse epithelium in a patient, 17 years old, in which contact with horses resulted in asthma. (Colldahl and Lundin 1952). The intracutaneous titration gave a positive reaction with an antigen dilution of 10^{-10}.

TABLE I

Inhalation	Washing-out time, min.
—	2.0
Coca's solution	2.0
Horse epithelium extr. 10^{-12}	2.3
„ „ „ 10^{-11}	2.3
„ „ „ 10^{-10}	2.3
„ „ „ 10^{-6}	2.0
„ „ „ 10^{-5}	2.5
„ „ „ 10^{-4}	7.1

Table I shows the results of the inhalation tests. As criterion of the ventilatory changes, the time required for the patient to wash out the nitrogen from the lungs on breathing at rest after the transition from air to oxygen breathing i.e. "washing-out time" has been

used. The nitrogen washing-out is recorded by continuously registering the nitrogen content of the alveolar air by means of a so-called nitrogen analyser.

The elimination of nitrogen during oxygen breathing depends on the alveolar ventilation (tidal volume, dead space, respiratory rate) and on the intrapulmonary air distribution.

c. *Vital capacity.*

Determinations of the vital capacity have frequently been performed in connection with provoked asthma (e.g. Lowell and Schiller). These authors have shown, by using a closed respiratory system, that in asthma there appears a temporary decrease in tidal volume, an increase in the functional residual capacity and a decrease in the expiratory reserve volume, inspiratory capacity and vital capacity.

In 1954 Ten Cate published an investigation on provocation tests in which the determination of the vital capacity was used to register objectively the results. The provocation test was only considered to be positive when repeated measurements of the vital capacity after the inhalation were lowered by at least 10 % in comparison with those prior to the test. It must be remembered, however, that in some patients repeated measurements of the vital capacity, especially when asthmatic symptoms are present or when made at short intervals, may lead to a progressive diminution in the vital capacity and eventually to the appearance or aggravation of respiratory symptoms (Schiller and Lowell, 1954).

d. *Oxygen saturation of the arterial blood.*

In normal individuals the inspired gases are distributed to the perfused alveoli in a very efficient manner. Their abnormal distribution in asthma may lead to an underventilation of well perfused alveoli and consequently the blood leaves these spaces without becoming fully saturated. This can only be compensated for if these spaces become better ventilated or less perfused (Schiller and Lowell).

As early as 1921 Meakins showed that severe asthma leads to a lowering of the oxygen saturation of the arterial blood. In asthma in guinea pigs severe enough to produce an insufficient gas exchange in the lungs, the arterial blood becomes unsaturated (Colldahl 1943). In mild provoked asthma in man, Colldahl and Lundin (1952) found no reduction in the oxygen saturation of the arterial blood in spite of the fact that an important alteration in the intrapulmonary air mixing could be shown.

Likewise, Lowell, Schiller and Lowell (1952) found a decrease in

the oxygen saturation of the arterial blood, as determined with an oximeter, in the more severe attacks of asthma but not in the milder ones which were nevertheless associated with definite changes in the respiratory pattern. Arner, Wiholm and Öhnell have also demonstrated a lowered arterial oxygen saturation in severe attacks of asthma.

Hansen and Schleinzer (1949–1956) have a divergent viewpoint on this question as they believe that in provoked asthma a decrease in oxygen saturation of the arterial blood takes place before any difficulty in breathing is experienced by the patient. These authors seem to base their opinion primarily on the fact that of the various changes in respiratory function which they had tested (i.e. lung ventilation, oxygen uptake, carbon dioxide elimination, arterial oxygen saturation and body temperature), the reduction in the arterial oxygen saturation appears first, which returns to normal as soon as the inhalation is stopped or aludrin is given. According to these investigators, the reduction in arterial oxygen saturation is an indication of a primary general metabolic reaction, the cause of which is still unknown (Hansen 1956). As opposed to this interpretation, it should be stressed that in any case where a reduction in oxygen saturation of the arterial blood can be shown in connection with provoked asthma or in other allergic reactions, the gas exchange in the lungs is evidently insufficient, whether resulting from pulmonary or cardiovascular causes or from both. In other cases the increased demand for oxygen could be compensated for rapidly by the lungs and by the circulation adapting themselves to the new requirement. At the onset of asthma, before it becomes severe, the oxygen uptake is raised. Later, when the severity increases, an adequate uptake of oxygen, corresponding to the actual requirement, becomes impossible, resulting in a lowered oxygen saturation of the blood. This is the reason why the blood can be unsaturated, in spite of an increased or unchanged oxygen uptake in comparison with that before the onset. Not until the asthma is aggravated still further, will the oxygen uptake be lowered under the initial amount. The fact that aludrin can cause their disappearance, also points out that the variations in the gas exchange are due, at least to a considerable extent, to pulmonary and cardiovascular changes.

For the registration of provoked asthma, the determination of intrapulmonary air mixing and vital capacity, are, according to present investigations, probably the most suitable methods. The former causes less strain to the patient and is less dependent upon his cooperation; the latter requires a simpler apparatus and can be performed more rapidly. The determination of the varia-

tions in the respiratory gas exchange is not suitable as these changes differ in mild and severe asthma. Likewise, determinations of the arterial oxygen saturation are probably not appropriate, since, according to several investigators, a lowered oxygen saturation will appear in severe asthma only and the provocation test should be interrupted in mild but definite asthma. The determination of the maximal breathing capacity cannot be used for this purpose as the method can induce asthma. Other methods of investigation such as pneumometry (Wyss-Hadorn), pneumotachygraphy (Fleich) and the determination of resistance and compliance can also be used advantageously for objective registration of provocation tests. Results on these investigations have recently been published (Colldahl, Nisell, Ripe and Svanborg; Nisell and Ehrner; Engström, Karlberg, Koch and Kraepelien).

B. *Technique of Provocation Tests.*

A good nebulizer should be used e.g. the model indicated by Barach or the De Vilbiss # 40. It is important that the nebulized solution does not contain large drops. This can easily be checked by holding a mirror before the nebulizer making certain that the mirror does not become wet. The nebulization is best performed with compressed air. The patient first inhales about 1 ml. of the pure solvent used for the extract, which lasts approximately 10 minutes. In most cases, a T-tube is inserted in the circuit of the rubber tube conveying the compressed air so that nebulization takes place only when the patient closes the opening with his thumb. Expiration can be made through the mouth or through the nose. If, after inhalation of the solvent, the patient does not feel any symptoms, he should inhale the antigen solutions. It is advisable to start with a weak concentration e.g. 1 : 100,000. After each inhalation of an antigen solution one must wait 10 minutes; if no symptoms arise during this period, the inhalation may be continued with stronger concentrations. The patient should be examined after each inhalation and the auscultatory findings as well at the subjective symptoms should be recorded.

If it is considered necessary or desirable, an objective registration determining e.g. the intrapulmonary gas mixing or vital capacity can be made between inhalations.

The provocation test will not be reliable if, at the onset of the test, the patient has any objective symptoms. It is not considered important, however, if the respiratory sounds before the test are somewhat impure on auscultation (Colldahl, 1952).

C. *Results of Provocation Tests*

Results of provocation tests of the bronchial mucosa have been published by several authors, among others: Peipers, Stevens, Harris, Lowell and Schiller, Christensen and Sonne, Nilsby, Juhlin-Dannfelt, Arner, Wiholm and Öhnell, Schleinzer, Colldahl and Ten Cate.

TABLE II

Antigen	Result of intracutaneous skin test	Result of provocation test, in % +	?	−	Total of performed provocation tests
All antigens employed ...	—	16	10	74	58
	+	43	15	42	111
	+ & —	34	13	53	169
Dust	+	72	14	14	29
Pollen	+	59	6	35	17
Animal epithelium	+	20	22	58	41

TABLE III

Lowest antigen concentration giving just a positive skin reaction (intracutaneous tests)	Positive provocation tests, in %	Total performed provocation tests
10^{-5}	62	13
10^{-4}	45	33
10^{-3}	32	57
$>10^{-3}$	16	58

Colldahl published in 1952 the results of 169 provocation tests in 44 asthmatic patients (Table II). From this table it appears that a positive skin reaction to house dust is of greater significance in regard to the patient's illness than a positive skin reaction with animal epithelium; pollens occupy an intermediate position.

From Table III it appears that the higher the percentage of positive tests, the higher also is the skin titer (Colldahl, 1952–1953).

Ten Cate found that out of 300 asthmatic patients, 165 or 55 % presented one or more positive inhalation tests with antigens producing a positive skin reaction.

The results obtained by different authors concerning provocation tests in asthmatics generally show that frequently positive skin reactions are found while no disturbances appear when the same antigen is inhaled. Some authors have also shown that occasionally

an inhalation test can be positive while the intracutaneous test remains negative (Stevens, Colldahl).

An allergic state with positive skin reactions having no etiologic significance with regard to the patient's disease, even after strong exposure, has been called "latent allergy" by Salén and Juhlin-Dannfelt (1932 1935) and "non-clinical allergy" by Tuft, in opposition to "manifest allergy" where the skin tests possess an etiological significance.

2. Nasal Test

The method of determining the etiologic factors in nasal allergy by bringing the suspected allergens into contact with the nasal mucosa was introduced many years ago. In this connection it will only be necessary to mention the elucidation of the etiology of hay fever in the 19th century when it was discovered that pollen, when kept until winter, could provoke hay fever symptoms when inhaled by patients hypersensitive to the same pollen. Efron and Penfound (1930) are of the opinion that the nasal reaction with pollens permits a more reliable diagnosis of hay fever than skin tests.

According to Juhlin-Dannfelt (1950) the best way of performing the test is as follows: the solvent is first dripped into one of the nostrils and if no reaction occurs, a weak antigen solution is used. A skin titration will provide some information as to how strong the chosen solution should be; it is advisable to start with a solution just producing a positive skin reaction. After each solution, one must wait for at least 10 minutes before administering the next one. If, however, after using the strongest antigen solution (1:10) no symptoms appear, the dry antigen should be tried e.g. by taking a very small quantity of the substance with a toothpick and letting the patient inhale it. It must be ascertained beforehand, however, that pulverized substances do not produce an aspecific irritation. For this reason the patient should first inhale talc or some other indifferent substance through the nose.

When the test is performed the patient should be free of nasal catarrah. A positive provocation test is indicated by a watery nasal discharge, nasal obstruction, asthma, urticaria, etc. In case of a very severe positive reaction, the nostril should be washed with a salt solution in order to remove the antigen as quickly as possible. If, in spite of this, severe symptoms continue, nose drops with adrenalin or ephedrine should be given. Occasionally the reaction does not appear until some hours later; therefore, only one substance should be tried within 24 hours.

3. Conjunctival Test

Blackley, as early as 1873, tested pollen sensitivity by introducing a small quantity of pollen into the conjunctival sac. This test is still used nowadays, particularly in examining hypersensitiveness to pollen and other inhalants. As is well known, certain forms of pollen rhinitis are accompanied by conjunctivitis, and in certain cases, the latter may even predominate over the nasal symptoms.

The test can be performed in the following manner: a drop of the solvent is dripped into the conjunctival sac by means of an eye-pipette. If no reaction occurs, the test is continued with antigen solutions of different strengths. It is advisable to start with the minimal dilution which gives rise to a positive skin reaction. If no reaction follows the introduction of the strongest antigen solution (1:10), a very small quantity of the dry testing substance is placed on the conjunctiva of the lower eyelid by means of a toothpick. After approximately 5 minutes, the testing substance may be removed with a small swab dipped into a salt solution. In case of a positive reaction, there appears a redness of the conjunctiva; a chemosis may be seen in very severe reactions. As severe reactions are to be avoided, stronger antigen solutions than actually needed should not be used. As soon as a reaction becomes evidently positive, the eye should be washed and occasionally drops of boric acid and adrenalin should be administered. This test has been studied especially by Peshkin (1926–1931).

4. Provocation Test of the Digestive Tract

Skin tests with food extracts are not as reliable as those with inhalants. Rowe and Hansen, however, found around 50 % accuracy with food tests.

When a food allergy is suspected and skin tests with foodstuffs remain negative, Rowe's elimination diets may be helpful when the symptoms are of daily occurrence; a food diary may be of value when they occur rather infrequently.

The symptoms of a positive provocation test with foods are manifested in the digestive tract by cheilitis, herpes labialis, aphthae, nausea, vomiting, diarrhea, spastic constipation etc.

a. If a certain food antigen is suspected, it must be excluded from the diet until the patient becomes symptom free. It is then reintroduced into the diet and the clinical symptoms are observed. Sufficient quantities of the food should be given e.g. 100 gr. of milk, 10 or 20 gr. of egg etc. In case of a negative result, the provocation test may be repeated with larger amounts.

It is sometimes of interest to make radiologic studies of the digestive tract after mixing the suspected antigen with the barium meal. Before the provocation test the patient should be free of symptoms. First he should be given an ordinary contrast medium whereby the mucosa, the secretion, the peristalsis and the evacuation can be studied. Half an hour later the contrast medium in which the antigen has been mixed should be given. The quantity of antigen which is added must be chosen with caution. In case of a moderate hypersentivity to egg, e.g. 1/10 of the white or the yolk can be tried. If no changes occur the quantity should be increased. Malaise and vomiting may follow the ingestion. The X-ray will show thick folds of the mucosa and the passage through the pylorus is delayed or obstructed. It is advisable after a few days to make another X-ray examination with an ordinary contrast meal. The changes on which the radiologic findings are based consist in an oedema of the mucosa and moreover, a change in tonus may occur (Weltz, 1940).

During symptom-free periods, 80 % of the patients with food allergy have normal amounts of gastric juice (Rowe, 1931). In connection with the ingestion of the antigen, Gay (1936) demonstrated a reduction in the quantity of acid up to anacidity.

b. If no particular antigen is suspected, the patient should be kept on a very restricted diet. As soon as he becomes sufficiently free of symptoms so as to make it possible to recognize an exacerbation, one foodstuff after another is gradually added to the regime. Food additions must not be made too rapidly, a 2 to 4 day interval is required and in some cases even more.

Rowe and others have described different elimination diets. The physician should start with the one which is most adaptable to the patient's needs. If no improvement occurs after a few weeks with a certain diet, another should be tried. As soon as a definite improvement is noted, a new food may be added every three days. The aggravation of the symptoms subsequent to the addition of a new food is the best evidence of an allergy to that particular food. To test the result, the offending food should be removed from the diet for several days and then given again. A daily supplement of vitamins is desirable but not until some therapeutic response has been obtained.

According to several investigators (Vaughan, Squier and Madison), a change in the blood picture possessing a diagnostic significance often occurs after ingestion of the offending food, i.e. leukopenia and increase of the eosinophils. The "leukopenic index", according to Vaughan, should be performed in the morning. Two fasting leukocyte counts are made at a thirty minute interval, whereafter the patient is asked to ingest the food to be tested. Leucocyte

counts are made again sixty and ninety minutes later. If either of the last two counts drop 1000 or more below the fasting counts the test is considered to be positive, indicating an allergy to the tested food. Similar changes in the thrombocytes have been described. Not all investigators have been able to confirm the results and consider these tests of no proven value.

Conclusion

There is no doubt that the possibility of an effective treatment in allergic manifestations is considerably greater when the etiologic factors are known. The history of the patient, the skin test as well as the exposure and provocation tests, represent the most important steps in the diagnosis of allergy. A positive skin reaction means that a hypersensitiveness is present in the skin which can possibly, but not necessarily, correspond to a hypersensitiveness in the diseased organ of the patient. If history and skin test are not in accordance, it may be necessary to test the reaction of the diseased organ against a certain antigen and it will then become evident that several positive skin reactions do not possess any etiological importance, but are merely a manifestation of a so-called latent allergy. A hyposensitization treatment with such an antigen cannot lead to the recovery of the patient. Part of the confusion concerning the value of specific hyposensitization is the result of a lack of consideration as to the existence of latent or non-clinical allergy.

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ALLERGY OF THE UPPER RESPIRATORY TRACT

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The two main functions of the upper respiratory tract involve olfaction and respiration. The air passages heat and conduct the atmospheric gasses towards the lungs, protecting them against any foreign particles (dusts, microbes) which might have been inhaled.

Histology shows that the essential structures of the entire respiratory tract, from the paranasal sinuses to the end of the bronchi, consist of the surface epithelium, basement membrane and tunica propria. The normal epithelium is comprised of three types of cells: ciliated cells, goblet cells and undifferentiated cells, the latter having the capacity to evolve into ciliated cells. The number of cellular strata and consequently the thickness of the epithelium varies according to the caliber of the bronchus. The question arises whether in reality there is more than one layer of cells whose nuclei, located at different levels, contribute to assume the appearance of a pseudostratification (1). But, at whatever level it is considered, the mucosa is essentially the same and this unicity calls for similarity in reaction towards pathological aggression.

This normal epithelium undergoes certain changes in its adaptation to environmental circumstances (age of the individual, frequency of acute infections, irritations due to allergy, or to contact with occupational dusts etc.) (2). The most important role is played by the vibratil cilia which ensure disposal of the atmospheric impurities and adequate drainage of the nasal cavities and of the air-cells of the head.

Pathology of that region is dominated by the deficiency or the impairment of this particular function. It is therefore understandable that inflammation of the respiratory mucosa, particularly when chronic as in extrinsic allergy or in bacterial allergy, is one of the main elements of the diseases of the upper respiratory tract.

It is true that, contrarily to asthmatic patients, those suffering

from blocking of the nose very often delay seeking early medical advice. Although the same causes may be operative on the nasal mucosa and on the bronchi, in the latter case, bronchial spasm and oedema of the smaller tubes interfere violently with normal respiration. When only the nose is involved, conscious breathing through the mouth may alleviate the respiratory difficulties for a certain length of time, at least during the day, but the patient will become more and more conscious of his impairment in respiratory function during his sleep, and only then will he seek professional advice.

Classification of Rhinitis.

Rhinitis may be classified in three categories according to their etiology.

1. *Allergic rhinitis.*

a) *Pollinosis* (seasonal rhinitis) which has a typical seasonal incidence corresponding to the pollination of the causative plant or the outpouring of fungi spores into the air.

b) *Perennial allergic rhinitis* (non seasonal rhinitis) due to a variety of specific allergens other than pollen or fungi such as house dust, animal epidermals, orris root powder, occupational dusts (and sometimes, but rarely, ingestants such as foods or drugs) or, especially in children, bacterial sensitization.

2. *Vasomotor rhinitis* due to non-allergic irritants or to undetermined causes.

3. *Infective rhinitis* (i.e. the common cold) due to the toxins of microbes or viruses.

Secondary infection may complicate allergic or vasomotor rhinitis thereby making a correct diagnosis most difficult.

Pathology of Allergic Rhinitis.

During the acute stage, the membrane is moderately swollen and red because of the engorgement of the blood vessels. As the case tends towards chronicity, the oedema is often more marked, the hyperemia is less pronounced and the color becomes grayish red or pearly gray in appearance. Nasal polyps are sometimes present and are often associated with chronic sinusitis, chronic infection or bacterial allergy (3). Goblet cells and mucous glands are hypertrophied and secrete actively. The mucosa is infiltrated with lymphoid and eosinophil cells, the later passing into the mucoid secretions. They may be evidenced on appropriate slides and constitute an important element in the diagnosis.

Physiology of the Allergic Rhinitis.

What changes take place when an allergen (e.g. a pollen granule) comes in contact with the sensitized nasal mucosa?

Firstly there is a considerable slowing down of the ciliary movement and a formation of oedematous blisters in the layer of the ciliated cells, which undergo a very rapid change either to ordinary epithelial cells, or perhaps, to secretory ones.

Later, the submucosal structures are distended by oedema arising from the submucosal capillaries which infiltrates the cells of the lower layer without impairing their vitality.

Of these successive changes, the first one, i.e. the impairment of the movements of the ciliae, is the most important because it conditions the tissular and the humoral development of the attack by suppressing the physiological barrier which normally prevents penetration of all foreign particles, whether solid or liquid, which might come in contact with the walls of the nasal fossa (4).

Differential diagnosis.

The diagnosis is made from the symptomatology, clinical history and the skin reactions.

In *pollinosis,* the onset of the symptoms is clearly marked. There is a watery discharge, the eyes are red and swollen with constant itching of the nose and, in some cases, of the throat, the palate and the external auditory canal.

But one or more of these symptoms may predominate exclusively and many factors (specific or non specific) exert their influence upon them. These are discussed later (see Pollen).

For instance, in a few cases we have seen as only evident symptom a vascular congestion of the conjunctiva; in others, the symptoms consisted almost exclusively in a constant itching of the cheeks and lower palpebral region.

Fortunately, as skin tests are positive in a great majority of cases, the correct diagnosis, eventually to be confirmed by the results of specific desensitization, is easier to reach than in the case of perennial rhinitis.

In *rhinitis due to allergens other than pollens or seasonal fungi,* skin tests are not as reliable but the history most of the time, is self explanatory. As, in the majority of cases, the symptoms are produced by contact with domestic or occupational dusts, they will be relieved whenever the patient spends a few days away from home or his place of work.

Although, according to most allergists, ingestants do not play a major role in allergy of the respiratory tract, a divergent opinion

has been upheld by *Rowe* (5) and *Pisani* (6) who assign great importance to the various food allergens, the inhalants constituting only a secondary, aggravating factor.

Many cases of perennial rhinitis show concomittant sensitization to pollens and experience exacerbations of their symptoms during the pollen season.

In Europe at least, sensitization to pollen alone is far less frequent than sensitization to both pollen and house dust. According to our statistics on 1275 cases of respiratory allergy (asthma and/or rhinitis), 62 % were sensitized to house dust, 25 % to house dust and pollen and only 13 % to pollen alone.

Patients experiencing symptoms all the year round are apt to develop allergy to drugs, especially to nose drops of which they often make excessive use, (antihistamine sprays, local vasoconstrictors, antibiotic aerosols).

Infective rhinitis. Infection exerts its action in two different ways:

1. as a *toxic* agent: either as the only cause of the disease (common cold) or as a complication of a pre-existing allergic or vasomotor rhinitis;

2. as an *allergen:* the bacteria in this case are endogenous and act as allergens. Bacterial allergy may be a disease in its own right or a complication of an extrinsic allergy. In typical cases, infective rhinitis is easy to differentiate from allergic rhinitis. Fever, sore throat, malaise, the simultaneous occurrence of the same symptoms in other non-allergic members of the family as well as the preponderance of neutrophils in the nasal secretions are the main points in the diagnosis. Unfortunately, in practice, it is not so easy as the two conditions often occur together. In this case, the symptoms due to the infection are the most conspicuous and they tend to mask the underlying allergic condition.

In bacterial allergy, the patients present local symptoms which are due to the allergic inflammation of the mucosa (nasal blocking, sneezing, watery discharge, postnasal drip) and often, but not always, generalized symptoms due to the absorption of bacterial toxins (malaise, depression, lack of appetite, generalized neuralgia, insomnia). Allergy due to bacteria displays a tendency to periodic exacerbations, often precipitated by chilling, fatigue, overwork, worries or menstruation. According to *Surber,* staphylococcus aureus is the main causative organism, the next important being streptococcus viridans, streptococcus hemolyticus and pneumococcus type 3 (7).

Skin tests with bacterial allergens are not of a great help in rhinitis due to bacterial allergy. Foci of infection in the tonsils or adenoids in young children, in the paranasal sinuses in adults and older children are significant and anti-infectious therapy may help

to clear the way for a more precise unveiling of the basic cause. As Sherman and Kessler rightly state: "While the absence of reactions to extrinsic allergens obviously directs attention to infective factors, the coexistence of factors of both types is very common and the suspicion of infective factors should be based on positive evidence rather than exclusion of extrinsic factors" (3).

Vasomotor or *reflex-type rhinitis* is the "no man's land" of rhinitis. It is unfortunately a kind of wastepaper basket apt to welcome all of those cases in which a complete examination has not been able to reveal the cause.

It apparently afflicts more frequently patients over forty, possesses undoubtedly an emotional basis and may be due (in part) to nervous or hormonal unbalance.

Blocking of the nose passages can be induced by a variety of causes, cold, heat, ultraviolet light, local irritants or even by normal physiological functions like digestion or by changes in position etc. All these stimuli are immuno-biologically neutral and do not cause formation of antibodies. In normal individuals, they hardly produce any symptoms. For some unknown reason, in vasomotor rhinitis, the reaction threshold is lowered and the nasal mucosa is therefore abnormally irritable (8).

The allergic history as well as the skin reactions are usually negative although border cases do exist and it is often very difficult to separate the allergic from the reflex type.

Vasomotor rhinitis holds about the same place, in the pathology of the uper respiratory tract, as non-allergic asthma in the lower.

Complications.

1. *Hyperplastic sinusitis.* In allergic rhinitis, the nasal mucosa, chronically inflamed by contact with the allergens offers poor resistance against bacterial invaders. In the paranasal sinuses, the oedema of the mucosa impairs efficient drainage and infection will thus develop in a closed vessel, evolving towards a stage of chronicity interrupted by occasional flare-ups. After a few months, even when the focus has undergone more or less complete auto-sterilization, the mucosa of the sinuses will most of the time acquire some degree of sensitivity towards the bacterial proteins. This will result in chronic hyperplastic sinusitis with a thickening of the lining membrane of the sinuses which very often can only be evidenced by X-ray examination. There is little or no exudate except during the acute stage. Most authors agree with Sherman and Kessler that chronic hyperplastic sinusitis is at least partly due to bacterial allergy.

Unlike acute, chronic sinusitis is resistant to most therapeutic

measures. Antibiotics are of little avail against foci of infection deeply imbedded in the mucosa. Treatment should endeavour to restore proper drainage of the cavities, to impede further progress of the infection and to remove all known causative allergens from the environment of the patient. During acute flare-ups, sinus lavages and antibiotics are indicated; later, when quiescence has been obtained, desensitization with stock or autogenous bacterial vaccines or with vaccines prepared by the more rational "pathogen-selective" method (9) may be tried but results are in most cases questionable.

The only drug of choice is *prednisone* as it is of special value against the effects of bacterial allergy. Recurrent respiratory infections or local flare-ups should be treated with prednisone and antibiotics, but prednisone alone can be used in hyperplastic sinusitis at least until the allergy has been brought under control.

2. *Nasal polyps.* Examination with a nose speculum often reveals mucous polyps in the nasal cavity or arising from the antra and ethmoid cells. They are the result of the same changes in the mucosa of the nose as those undergone by the membrane of the sinuses in hyperplastic chronic sinusitis.

They are irreversible, due to bacterial allergy and therefore inaccessible to treatment directed exclusively against extrinsic allergens.

When polyps cause obstruction of the air passages, surgical removal is indicated but recurrence is frequent.

Here, as in hyperplastic sinusitis, bacterial vaccines, avoidance of irritants (inhalant allergens, drugs administered locally, respiratory infections) and more reliably, peroral prednisone are indicated.

Treatment of allergic rhinitis.

Successful treatment of allergic rhinitis depends on whether or not diagnostic measures have been able to evidence if not all at least the most important causes of the disease. History taking, skin testing, thorough examination of the nose and sinuses (with X-rays), eventually specific provocation tests, are the fundamental steps which cannot be avoided or abridged. Special attention should be paid to acute or chronic infection, a complication which is more frequent in the upper than in the lower respiratory tract.

In clear cases, specific desensitization and avoidance of the allergens will bring lasting results. However, in complicated cases and in those where food allergy is involved or where complete removal of the cause, even when specific, is unattainable (as in occupational allergy), both the sagacity of the doctor and the endurance of the patient may be severely taxed.

POLLEN

The term "pollinosis" comprises all the pathological manifestations occurring when pollen grains enter into contact with a specifically sensitized mucous membrane.

Among the thousands of pollen-producing species, only about a hundred are suspected of being responsible for all the cases of pollinosis. Even among these, there are at the most a dozen, the influence of which must be considered predominant within a particular region.

Their importance depends upon their manner of pollination and, for this reason, they may be classified into three groups:

1. The *entomophilous* plants, pollinated by insects. These species, the flowers of which display attractive colours, are fragrant or produce nectar. The pollen is thick, sticky and scanty. Example: the fruit trees.

2. The *anemophilous* plants, the pollen of which is exclusively carried by the wind. Their flowers are unobtrusive, non-fragrant, without nectar and mostly unisexual. Their pollen is very abundant, dry and dusty. Example: the *Grasses, Plantago, Rumex.*

3. The *amphiphilous* plants, which combine the characteristics of the two preceding groups. They have visible and fragrant flowers with abundant and light pollen. Example: *Salix.*

A certain number of species, in which the entomophilous pollination is imperfectly carried out, may be classified among the last mentioned. Their pollen is often dispersed in the atmosphere by insects which have gathered it on the flowers or it has been propagated by gusts of wind, as demonstrated by the frequency with which it is found on the slides of the pollen-surveys. Example: *Dahlia, Helianthus, Solidago.*

The Thommen Postulates.

In order that a plant may be suspected of provoking epidemic pollinosis, the following five conditions (called "the Thommen postulates") must be fulfilled:

1. *Its pollen must contain an excitant for hay-fever.*

The pollen of pine is inoffensive because, although widely dispersed in the atmosphere during certain periods of the year, it does not contain the active principle which induces hay-fever.

2. *Its mode of pollination must be wind-borne.*

This principle applies to the great majority of plants which provoke pollinosis. However, the pollen of the species classed as amphiphilous may be found in the atmosphere when the pollen is very

abundant (*Tilia, Olea,* certain *Compositae* etc.), or when coming from a large area devoted to the cultivation of a single species (*Helianthus* fields in Eastern Europe). Gardeners, florists, hothouse cultivators etc., who often handle entomophilous flowers and regularly inhale the pollen, may become sensitized more or less rapidly.

3. *Its pollen must be produced in a sufficiently large quantity.*

This is a characteristic of anemophilous plants and explains why pollinosis is caused essentially by these species.

4. *Its pollen must be sufficiently buoyant to be carried considerable distances.*

The pollen corresponding best to this specification is composed of small grains (less than 35 microns), is dry, light and spherical. Certain pollens, as for instance that of *Zea Mays,* although fulfilling all the other conditions of the Thommen postulates, are inoffensive because their grains are large and sticky.

5. *Its pollen must be produced by an abundant, widely distributed plant.*

This fact is of primary importance. Certain species, extremely noxious in certain regions of the world where they are plentiful, are of no importance in other parts, due to insufficient distribution, e.g. *Ambrosia,* the principal cause of pollinosis in America. Although rare specimens of this plant are found scattered here and there in Europe, it must be considered as inoffensive outside of the Americas. The same applies to *Parietaria,* the growth zone of which does not extend beyond the Mediterranean Basin. *Cynodon dactylon* is abundant south of the 34th parallel in America because it is cultivated as pasture and lawn grass, where it causes the majority of cases of pollinosis due to grasses. It extends into the Northern and Eastern regions, but in insufficient quantity to provoke clinical symptoms.

Furthermore, certain species may be abundant in one locality or even in a section of one locality as is the case especially with trees. This explains why the symptoms experienced by patients may disappear completely after a change of residence.

Factors which may influence the Concentration of Pollen in the Atmosphere.

Generally, the floral anthers release their pollen during the early hours of the morning (between 4 and 8 A.M.) and the symptoms experienced by patients are strongest during this period. The dispersion of the pollen, however, is subject to numerous meteorological factors, the investigation of which encounters serious difficulties as they may exercice their influence on vast regions or only on localized areas.

The vigor of plants is conditioned by the quantity of water at their disposal during growth. If the months of April and May have been rainy, it can be anticipated that the pollen season for grasses will be severe. The rain influences not only the abundance of pollen but also its antigenic property. This explains why vaccines, prepared under the same conditions, may differ in antigenic power from one year to another according to the harvest, even if it comes from the same region.

Clear, sunny weather favours the opening of the anthers and the scattering of the pollen in the atmosphere. It must be noted, however, that the majority of patients are mostly troubled when an early morning mist covers the ground, even making them believe that the mist is the only cause of their complaints. Ordinary steam from a boiler or an inhaler is, nevertheless, well tolerated by these same patients and even helps them. The divergency arises from the fact, as demonstrated by Heise and Heise (1), that the presence of the ground mist is the consequence of an inversion of the temperature of different air layers, the coldest being in contact with the ground and thus imprison the granules of pollen which have been emitted.

The pollen is propagated by the turbulence of the atmosphere and it is easy to understand that a violent wind can transport it enormous distances. This explains the occurrence of "pollen showers" during which considerable quantities of pollen, falling from the upper atmospheric levels, can be collected on the slides even though the local conditions at the ground level (clouds, rain) are completely unfavourable to the unfolding of the anthers.

Differences of opinion on this point exist between European investigations and those carried out in the U.S.A. The pollen-surveys in the latter country, especially those carried out by Wiseman et al. (2) in the harbour of New York, show an obvious correlation between the quantity of pollen gathered at various stations and the direction and force of the wind. Sack (3), utilizing stations on board vessels and aeroplanes, demonstrated the presence of pollen grains in the atmosphere at a distance of more than 300 km from the coast. Contrarily, van Dishoeck and van Horn (4) concluded, from the results of surveys carried out in Holland and compared with data furnished through meteorological observations, that the quantity of pollen in the air depends exclusively on the maturity of the floral organs of the plants and has nothing to do with the humidity of the atmosphere or the precipitations of rain. The release of the pollen diminishes when the temperature of the air falls below 15° C, or when the barometric pressure rises.

These divergencies may be explained, up to a certain point, by the fact that the experiments in the U.S.A. were made with *Ambrosia* pollen and that in Europe the experiments could be carried out only with grass pollen, considerably more heavy (20 to 100 microns Ø) than the first named (17 to 24 microns Ø). Moreover each *Ambrosia* plant pours out into the atmosphere twice as many pollen grains as a *Graminea*, and three times as many as *Plantago*. *Ambrosia* pollen will thus be dispersed over extensive areas and will be recovered much further away from its source than the pollen of grasses.

Factors beside Pollen which may influence the Symptoms.

Other factors than pollen may aggravate the symptoms. Alone, they are, of course, inoperative and cannot manifest their influence unless the patient is sensitized to pollen. Therefore, they are difficult to analyze as it is impossible to separate exactly what is due to the specific action of the pollen from what must be considered due to the aggravating factors.

1) *Meteorological Factors.*

Wind, humidity, rapid fluctuations in the barometric pressure, stormy weather and especially the sun's rays all influence unfavourably the comfort of the patient. Most of hay-fever sufferers cannot stand bright sunlight and protect themselves instinctively by wearing tinted glasses. Itching and watering of the eyes increase during the bright and sunny days. As these meteorological conditions, however, are exactly the ones which favour the diffusion of pollen in the atmosphere, the tendency has been to consider these only.

Special climatic circumstances have enabled us to provide proof of the action of sunlight on some patients outside the pollen-season. In Brussels, three days, the 11th, 12th and 13th of March 1957, were extremely hot and sunny, with a maximum temperature of 20° C. Five of our patients, then under desensitizing treatment, presented minor but typical symptoms of pollinosis at this time. All were sensitized to grasses only and no pollen-grains from species belonging to this family exist in the atmosphere in Belgium during the month of March. Furthermore, pollen-survey slides had collected only a few grains of Ulmus during the days mentioned.

2) *Food Factors.*

By subjecting systematically 540 pollen-patients in Belgium to skin tests with cereal allergens, we have been able to show that 43 per cent of them had positive reactions to wheat flour and 6 per cent to rye flour. This must be due to cross reactions, and it seems probable that a common antigen is present in the pollen and in the grain of the *Gramineae*. The predominance of the reactions to wheat may be explained by the feeding habits of the local population which does not eat rye bread. However, in 11 of these 540 cases we have been able to demonstrate by alimentary provocation tests, the existence of a clinical sensitization to wheat, the symptoms of which (mostly of a gastro-intestinal nature) did not appear until the period of pollination of the grasses. These troubles disappeared rapidly after substituting rye in the diet for wheat. As the symptoms existed only during the months of May-June, it must be concluded that they were provoked by the simultaneous action of the wheat and grass-

pollen allergens. When each of these two allergens is absorbed separately, no reaction takes place because the threshold of tolerance of the organism has not been reached. But, this is not the case when both allergens gain entrance into the organism at the same time and the antigenic effect of each will be increased by the antigenicity of the other. A clinically apparent reaction will then occur (5).

Pisani (12a) believes that the cross sensitivity between foods and pollens extends farther than merely an antigenic similarity between the cereals and the grass pollens. Using the Ovary technique, he showed in guinea-pigs that a great number of pollen antibodies evidence reactive capacity to extracts of a series of semi-digested foods having no botanical relation such as cottonseed, hazel nuts, figs, cabbage, turnips, beans and soya. The author claims that treatment on these lines i.e. by eliminating from the patient's diet all of those foods who have cross reacted with the pollen antibodies, has been successful in the majority of his hay fever cases.

The importance of the food factor in pollinosis has been stressed previously by Feinberg (12b) and there is no doubt that there is a great deal of truth in this theory, but much experimental and clinical work will have to be done before it is definitively proven that alimentary allergens play the major role in the production of the pollen syndrome.

Specificity of Skin Tests.

It cannot be denied that a tendency exists towards cross reactions among plants belonging to the same genus, but this cross sensitization is never complete, even between the grasses.

1. *Cross Reactions between the Grasses.*

In testing 900 cases of pollinosis with 27 different kinds of grass pollens, we did not find a single case which reacted to all the pollens. If *Dactylis glomerata,* the most widely spread graminea in the temperate zone of Europe, has given 75 per cent of positive scratch tests, more uncommon species, such as *Oplismenus crus-galli,* or even species completely unknown in the vicinity, such as *Cynodon dactylon* have given respectively 32 and 27 per cent positive skin reactions. The species, whose pollen lacks buoyancy because the grains are large and heavy (*Secale cereale, Zea Mays*) or which are fertilized by autopollination (*Triticum sativum*) only produced 39, 40 and 38 per cent of positive reactions. It can therefore be admitted that roughly between 10 and 30 per cent of the patients sensitized to grasses will react to pollen of grasses with which they have never had the opportunity to come into contact with. Table I sums up the

TABLE I

Comparison of the percentage of positive reactions in grass sensitive patients tested with seven different grass pollens in the USA, Italy and Belgium.

Botanic names	U.S.A. (Virginia) Grubb & Vaughan (6) 218 cases	Italy Serafini (7) 872 cases	Belgium Duchaine (8) 900 cases
Dactylis glomerata .	48.1	52.6	75
Phleum pratense ...	45.4	35.6	63
Agrostis alba	65.6	56.2	59
Poa pratensis	51.4	50.2	60
Bromus spp.	39.4	44.3	55
Sorghum halepense	44.5	32.5	40
Cynodon dactylon .	35.1	12.2	27

work carried out in the U.S.A., Italy and Belgium, and shows that the phenomenon of cross sensitivity to grasses exists all over the world.

That grass pollens have a common main protein component has been established immunologically by Augustin and Hayward (8a) using precipitation tests, Ouchterlony's diffusion tests, skin tests and chemical and electrophoretical isolation.

A differing opinion has recently been upheld by Feinberg (8b) who, using an original modification of agar gel immuno,-analysis, has found "striking individualities among the common grass pollens".

Contrarily to the opinion of Freeman and his school who advocate the use of only one or two grass pollens for hyposensitization against grass hay fever, Feinberg favors treatment with as wide a range of pollens as practicable.

2. *Cross Reactions between the Compositae.*

Many studies have been made in the U.S.A. on this subject but the results have been difficult to appraise because of the ubiquitous presence of *Ambrosia* pollen in the air during most of the pollination period of the other Compositae. In Europe, where *Ambrosia* is unknown, the problem has been studied, but no definite conclusions have as yet been reached.

Even if autumn hay fever, in our opinion, is a very rare affliction in Europe, we have been rather surprised to find that about 15 per cent of our patients showed positive skin reaction to different anemophilous or amphiphilous Compositae pollens. All of these patients were sensitized to grasses, but only 4 of them (0.44 per cent) presented clinical symptoms during the flowering period of the *Compositae,* which follows that of the grasses (August-September). Pro-

vocation tests after inhalation of different *Compositae* pollens were positive in 38 per cent of these cases. The absence of clinical symptoms suggests *latent allergy,* which never has the opportunity of developing into *clinical allergy* because the amount of pollen dispersed in the atmosphere by the *Compositae,* as attested by what is gathered on the slides, never appears to be sufficient to provoke manifest clinical symptoms (9).

It is because of cross-sensitization between the *Compositae* that a certain number of cases of sensitization to *Ambrosia* (with positive skin and inhalation tests) can be explained in patients who have never lived outside of Europe. It is probable that the sensitizing allergen here is the pollen of dahlias and asters used to decorate rooms during summer-time and which, mixed with the house dust, may sooner or later provoke sensitization of the respiratory system to all the pollens of the *Compositae* family. Pyrethrum powder, manufactured from flowers of *Chrysanthemum coccineum,* may play the same role.

The active Agent in Pollen.

Much work has been done with the aim of extracting and purifying the antigenic component contained in the pollen grain. Pollen extracts have been submitted to chemical analysis, electrophoretic separation, ultracentrifugation, ager gel analysis etc.

Although no unanimity of agreement has yet been reached, most of the authors are of the opinion that there is more than one antigenic substance and that no single grouping represents the whole antigenicity of the pollen grain. The active component is probably a polypeptide (Rockwell (9a)), a denatured protein of the albumin type (Harley (9b)) or a non dializable protein of low molecular weight: 14,000 (Augustin (9c)), 5,000 (Abramson (9d)), less than 10,000 (Silver and Bookman (9e)).

Until the question: why is a pollen grain antigenic ? has been satisfactorily answered and the substance responsible for its antigenicity isolated, all methods of standardization of extracts must necessarily be empirical and the extracts will vary according to the technique used for their preparation, to their keeping qualities, and to divers factors which have exerted their influence on the plants before and during pollination.

Field and Pollen Surveys.

In each region, the severity of pollinosis depends on the abundance of anemophilous plants, the quantity of pollen which they disperse in the atmosphere and the duration of their pollination. Hence

the necessity of establishing field surveys to identify the regional species, and of pollen surveys to detect what pollens may be found in the air and their relative atmospheric incidence.

1 *Field Surveys.*

These are carried out with maximum efficacy by professional or amateur botanists. Hundreds of interested allergists and botanists have thus covered most of the European and of the North American regions. The result of their work is summarized in tables II and III. The pollination data mentioned are approximate ones. They depend on local conditions, meteorological factors and the temperature of the air, which determine the changes in the seasons. These are brief and well-defined in the temperate zone. Pollen season will be severe but of short duration because most of the anemophilous species release their pollen all at the same time. Contrarily, in the regions near the equator, there will be only two seasons, poorly demarcated, the dry and the rainy seasons. The period of pollination may last several months and the quantity of pollen released each day in the atmosphere will be correspondingly reduced.

To facilitate matters, from the point of view of pollinosis, the earth may be divided into three regions: Europe (excepting the Mediterranean Basin), the Mediterranean Basin (South of France, Italy, Spain, Portugal, Turkey, Israël, North Africa) and the Americas. As far as Asia, Australia, Oceania and the major part of Africa are concerned, details are either completely lacking or are too fragmentary.

A. *Europe,* excepting the Mediterranean Basin.

Grasses predominate almost exclusively because they are cultivated for hay and pastures. Denseness of population is very high in most regions and nearly all of the land, even the most arid, is under cultivation. This explains the relative scarceness of species like *Artemisia, Chenopodium, Rumex* and the complete absence of *Ambrosia* and *Franseria* which have never been able to gain foothold in Europe, notwithstanding favorable climatic and soil conditions, because they are promptly eradicated by the farmers.

Pollinosis from trees is uncommon and autumn hay fever is extremely rare, although it exists.

B. *The Mediterranean Basin.*

This region embraces a varied flora comprising most of the species of the temperate regions in addition to others which are only to be found in the warmer regions (*Cynodon dactylon, Parietaria, Olea europea, Acacia* etc.).

TABLE II

Relative Allergenic Significance of Plants
(with their English, French and German common names).

Key to Symbols: ○ according to most authors, this plant is of very little importance, except as cross reactive; ± may be important, at least locally; + locally important; ++ important over widespread areas; +++ very important; ? influence unknown.

Botanic Names	Common English and American Names	Common French Names	Common German Names	Allergenic significance
		1. Trees		
Aceraceae				
Acer spp.	Maple Box-elder	Erable	Ahorn	±
Anacardiaceae				
Schinus molle	Pepper-tree			○
Arecaceae				
Chamaerops humilis	Dwarf palm	Palmier	Palme	?
Betulaceae				
Alnus spp.	Alder	Aune	Erle	±
Betula spp.	Birch	Bouleau	Bircke	±
Carpinus spp.	Hornbeam Ironwood	Charme	Weissbuche	±
Ostrya virginiana	Hop-hornbeam Leverwood Ironwood			±
Corylus spp.	Hazel Filbert	Coudrier-Noisetier	Haselnuss	○
Caprifoliaceae				
Sambucus spp.	Elderberry	Sureau	Holunder	±
Casuarinaceae				
Casuarina equisetifolia	Casuarinatree Australian pine Beefwood			±
Coniferae				
Cupressus fragrans	Lawson cypress			±
Juniperus spp.	Juniper Mountain cedar Redberry	Genévrier	Wacholder	±
Picea spp.	Spruce	Epicéa	Rottanne	○
Pinus spp.	Pine	Pin	Kiefer	○

TABLE II (cont.)

Fagaceae				
Castanea spp.	Sweet chestnut Chinquapin	Châtaîgnier	Kastanie	( )
Fagus spp.	Beech	Hêtre	Buche	( )
Quercus spp.	Oak	Chêne	Eiche	-|-
suber	Cork-oak	Chêne liège	Korkbaum	-|
Juglandaceae				
Juglands spp.	Walnut Butter nut	Noyer	Walnuss	( )
Carya Pecan	Hickory	Noix Hickory	Hickorynuss	-|
Mimosaceae				
Acacia	Opopanax Popinack	Mimosa	Akazie	?
Prosopis juliflora	Honey mesquite Algaroba			:|:
Mirtaceae				
Eucalyptus spp.	Gumtree	Eucalyptus	Eukalyptus	( )
Moraceae				
Morus alba	White mulberry	Mûrier	Maulbeere	-|
Broussonetia papyrifera	Paper mulberry	Mûrier du Japon	Japanische Maulbere	-|-
Oleaceae				
Olea europaea	Olive-tree	Olivier	Olivenbaum	-|
Ligustrum spp.	Privet	Troëne	Rainweide	:|
Fraxinus spp.	Ash	Frêne	Eschenholz	:|:
Phyllirea angustiflora		Philaria		±:
Palmaceae				
Cocos nucifera	Coconut palm	Cocotier	Kokospalme	?
Phoenix dactylifera	Date palm	Palmier dattier	Dattel Palme	?
Platanaceae				
Platanus spp.	Plane Sycamore	Platane	Platane	-|-
Salicaceae				
Salix spp.	Willow	Saule	Weide	( )
Populus spp.	Poplar Cottonwood Aspen	Peuplier	Pappel	-|-
Simarubaceae				
Ailanthus altissima	Tree-of-Heaven	Vernis du Japon		±

TABLE II (cont.)

Taxineae				
Taxus spp.	Yew Ground hemlock	If	Eibe	?
Tiliaceae				
Tilia spp.	Lime Basswood	Tilleul	Linde	+
Ulmaceae				
Ulmus spp.	Elm	Orme	Ulme	+
Celtis occidentalis	Hackberry Sugarberry False elm	Micocoulier	Falsche Ulme	+
		2. Grasses		
Cyperaceae				
Carex paniculata	Tussock sedge	Carex paniculé	Riedgras	±
Cyperus esculentus	Nutgrass Galingale	Soucher	Zypergras	±
Scirpus lacustris	Bulrush	Jonc des tonneliers		±
Gramineae				
Aegilops ovata	Goat grass	Egilope	Geissauge	○
Agropyrum repens	Dog's grass Couchgrass Quackgrass	Escourgeon Chiendent	Ackerquecke Hundsgras	○
Agrostis alba	Common bent Red top	Traîne	Straussgras	++
Aira media (= Deschampsia)	Hair-grass	Canche	Rocksbart	±
Alopecurus pratensis	Meadow foxtail	Vulpin	Wiesenfuchsswanz	○
Ammophila spp. (= Psamma)	Marram grass European beach-grass	Oyat	Strandhafer	±
Andropogon ischaemum	Wooly Beard grass	Pied de poule	Bartgras	○
Anthoxanthum odoratum	Sweet vernalgrass	Flouve odorante	Ruchgras	++
Arundo Donax	Bamboo-Reed Giant reed	Cannevelle	Bambusrohr	±
Avena bromoïdes	Perennial oat grass	Avenette	Wiesenhafer	±
– elatior (= arrhenaterum elatius)	Tall oat grass False oat grass	Fromental Fenasse	Glatthafer	+
– fatua	Wild oat	Folle avoine	Wildhafer	++
– sativa	Common oat	Avoine	Hafer	○

TABLE II (cont.)

Bouteloua gracilis	Mesquite Buffalo grass Grama			+
Brachypodium pinnatum	Tor-grass	Palêne	Fiederzwenke	+
Briza media	Quacking grass Totter-grass	Tremblote	Zittergras	+
Bromus mollis	Soft brome Lop grass	Brome mollet	Weiche Trespe	+
rigidus	Ripgut grass	Brome très grand		+
sterilis	Barren brome Hungarian brome grass	Averon	Taube Trespe	+
Cympogon spp.	Turpentine grass			+ +
Cynodon dactylon	Bermuda grass Dog's tooth grass	Herbe des Bermudes	Bermudagras Hundszahn	+ + +
(Capriola dactylon)	Scutchgrass	Chiendent pied de poule Patte de perdrix		
Cynosorus cristatus	Crested dog's tail	Crételle	Kammgras	?
Dactylis glomerata	Cocksfoot Orchard grass	Pied de poule	Knauelgras Hahnenfuss	+ + +
Digitaria sanguinalis	Hairy fingergrass Crabgrass	Sanguinette	Blutfennich	+ +
Elymus spp.	Lyme grass Giant rye	Oyat	Seehafer	+
Eragrostis spp.	Love grass	Amourette	Liebesgras	+ +
Festuca elatior	Tall fescue Dover grass	Grande fétuque	Hoch-Schwingel	+
ovina	Sheep's fescue Black twitch-grass	Coquiole	Schafgras	+
pratensis	Meadow fescue	Fétuque des prés	Wiesenschwingel	+
rubra	Red fescue	Fétuque rouge	Rotschwingel	+
Holcus lanatus	Yorkshire fog Tufted grass Velvet grass Wooly soft grass	Houque laineuse	Wolliges Honiggras	+ +
vulgare	Indian Millet Guinea corn	Millet d'Inde	Mohrenbartgras	+
Hordeum murinum	Wall barley Mouse barley	Orge des rats	Mausegerste	+ +
vulgare	Cultivated barley	Orge cultivée	Gerste	+ +
Hyparrhenia spp.	Tambookie grass			+ + +
Imperata spp.	Blady grass Lalong grass	Impérata	Silberhaargras	+ + +
Koeleria cristata	Crested hair-grass Western June grass	Koeleria à crête	Kammschmiele	+

TABLE II (cont.)

Lagurus ovatus	Hare's tail grass	Queue de lièvre	Hasenschwanz	○
Lolium perenne	Rye-grass Ray-grass Eavers	Ivraie Raygrass anglais	Lolch Englisches Raigras	+++
Loudetia arundinacea				?
Melinis minutiflora	Molasses grass			+
Melica ciliata	Nodding melick	Mélique	Perlgras	±
Molinia caerulea	Purple moor-grass	Molinia	Besenried	±
Oplismenus crus-galli (=Echinochloa)	Cockspur grass Barnyard grass	Pied de coq	Hühnerfennich	±
Panicum miliaceum	Common millet Red millet Para grass	Panic faux millet Mil d'Inde	Hirse	+
Paspalum dilatatum	Dallis grass Water grass			±
Phalaris arundinacea (=Baldingera)	Reed grass	Alpiste roseau	Rohrglanzgras	±
– canariensis	Canary grass	Alpiste des serins	Kanarienglanzgras	○
Phleum pratense	Timothy Cattail Herd's grass	Fléole des prés Timothée	Wiesenlieschgras Timotheegras	+++
Poa annua	Annual meadow grass Annual blue grass Low spear grass	Paturin annuel	Jähriges Rispengras	○
– compressa	Canada bluegrass English bluegrass			++
– pratensis	English meadow grass Kentucky bluegrass June grass	Paturin des prés	Wiesenrispengras	+++
– trivialis	Rough meadow grass Rough bluegrass	Gazon d'Angleterre	Rauhes Rispengras	○
Polypogon monspellienses	Beard grass Rabbitfoot grass	Polypogon de Montpellier	Vielbart	○
Saccharum officinarum	Sugar cane	Canne à sucre	Zuckerrohr	±
Scleropoda rigida (=Catapodium)	Fern grass Hard meadow grass	Poil de loup	Steifes Viehgras	±
Secale cereale	Rye	Seigle	Roggen	±

TABLE II (cont.)

Sesleria caerulea	Blue moor-grass	Seslérie bleue	Elfengras	( )
Setaria spp.	Bristle grass	Sétaire Panic	Borstengras	+
Sorghum halepense	Johnson grass Sorghum Egyptian millet	Sorgho d'Alep	Aleppobartgras	+
vulgare var. sudanensis	Sudan grass	Millet à balai	Mohrenhirse Negerkorn	+
Sporobolus pungens	Drop-seed grass	Sporobole	Samenwerfer	+
Stenotaphrum americanum	St Augustine grass Short grass Buffalo grass	Chiendent de boeuf	Buffalo gras	?
Stipa juncea	Rush-feather grass Needle grass	Stipa faux-jonc	Pfriemgras	( )
Themeda triandra	Rooigrass			+
Tricholaena rosea	Natal grass			±
Trisetum flavescens	Yellow oat grass Golden oat grass	Trisète jaunâtre Avoine dorée	Goldhafer	±
Triticum sativum	Cultivated wheat Corn	Blé	Weizen	( )
Vulpia ciliata	Rat's tail	Queue de rat	Kammschwingel	±
Zea Mays	Maize Indian corn	Maïs	Mais	( )
Juncaceae				
Luzula campestris	Common wood rush Good Friday grass	Luzule des champs	Binse	±
Typhaceae				
Typha latifolia	Cattail	Massette	Sumpfpflanze	±
		3. Weeds		
Amaranthaceae				
Amaranthus spp.	Pigweed Carelessweed Tumbleweed	Amarante	Amaranthe	+
Acnida tamariscinia	Western Water-hemp			±
Cannabinaceae				
Cannabis sativa	Hemp	Chanvre	Hanf	±
Humulus lupulus	Hop	Houblon	Hopfen	( )

TABLE II (cont.)

Chenopodiaceae				
Atriplex spp.	Saltbush Orache Shadscale Quaibrush All scale	Arroche	Melde	+
Beta vulgaris	Sugarbeet	Betterave sucrière	Runkelrübe	○
Chenopodium spp.	Lambsquarter Goosefoot Mexican tea	Chénopode	Gänsefuss	±
Kochia scoparia	Burning bush Summer cypress Fire bush			+
Salicornia spp.	Glasswort	Salicorne	Meerfenchel	±
Salsola pestifer	Russian thistle Saltwort Tumbleweed	Salsola	Salzkraut	++
Sacrobatus vermiculatus	Greasewood Chico			±
Compositae				
Achillea millifolium	Yarrow Milfoil	Mille-feuilles	Schafgarbe	○
Ambrosia spp.	Ragweed Hogweed Bitterweed	Herbe-à-poux Sarriette	Traubenkraut	+++
Anthemis cotula	Chamomille Dogfennel	Camomille des chiens	Kamille	○
Artemisia spp.	Wormwood Mugwort Sagebrush	Armoise	Beifuss	++
Aster spp.	Aster	Aster	Aster	○
Baccharis spp.	Groundsel bush Desert bush			±
Bidens spp.	Bur-marigold	Bident Chanvre d'eau		±
Chrysanthemum Leucanthemum	Dog-daisy Oxeye-daisy	Marguerite	Margerite Gänseblümchen	○
Cyclachaena xanthifolia	Prairie ragweed Carelessweed Burweed marshelder			++
Franseria spp. (= Gaertneria)	False ragweed Rabbit bush			±
Helianthus annuus	Sunflower	Tournesol	Sonnenblum	±
Hymenoclea salsola	Burrow weed			±
Iva spp.	Marshelder Poverty-weed			+

TABLE II (cont.)

Solidago virgaurea	Goldenrod	Solidage	Goldrute	( )
Taraxacum officinale	Dandelion	Pissenlit	Löwenzahn	( )
Xanthium spp.	Clotweed Burweed Cocklebur Clotbur	Lampourde	Spitzklette	( )
Euphorbiaceae				
Mercurialis perennis	Dog's mercury	Mercuriale vivante Chou du chien	Bingelkraut	( )
Ricinus communis	Castor oil plant Palma Christi	Ricin	Rizinus	( )
Papilionaceae				
Ceratonia Siliqua	Caro-bean tree	Caroubier	Johannisbrot-baum	( )
Medicago sativa	Alfalfa Lucerne	Luzerne	Schneckenklee	( )
Melilotus spp.	Sweet clover	Mélilot	Honigklee	( )
Robinia pseudacacia	Locust	Robinier	Robinie Falche Akazie	( )
Trifolium spp.	Clover	Trèfle	Klee	( )
Plantaginaceae				
Plantago lanceolata	English Plantain Ribgrass Ribwort	Plantain	Spitewegerich	( )
Polygonaceae				
Rumex spp.	Dock Sheepsorrel Mexican tea	Oseille Surette	Ampfer	( )
Urticaceae				
Parietaria officinalis	Pellitory	Pariétaire	Mauerkraut	( )
Urtica spp.	Nettle	Ortie	Nessel	( )

C. *The Americas.*

The flora is characterized by the abundance and the variety of noxious species. This fact must be ascribed to the vastness of the territory, to the variety of climatic conditions as well as to the local agricultural technique, adapted to the cultivation of extensive areas, with the tendency to let less profitable soils lie fallow. The anemophilous *Compositae* (*Ambrosia, Franseria, Kochia*), which cannot be found in any other regions of the world, constitute the most allergenic element.

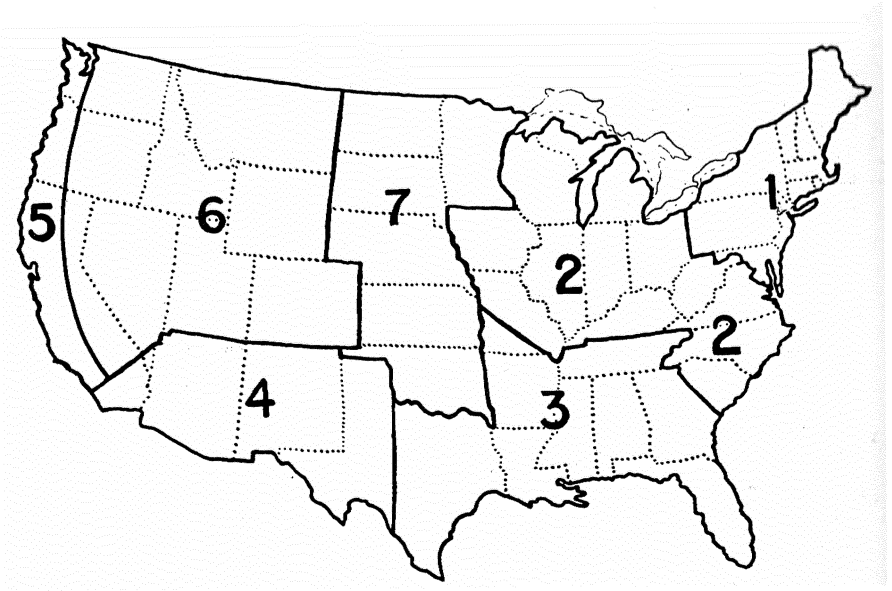

Fig. 1. The United States divided into hay fever zones (19).

The U.S.A. can be divided into seven pollination zones (fig. 1), but the shortcomings of this procedure have been exemplified by G. E. and E. M. Rockwell (10). "That the flora of the United States is not such that the country can be divided into zones with well defined boundaries is exemplified by the fact that writers have divided the country into a varying number of sections with widely differing boundaries. Since each section covers a wide territory, many interesting local situations are missed. In Zone 4 particularly, widely varying types of flora may be encountered within relatively short distances, owing to differences in elevation and conditions of irrigation. Also, there are year to year variations in the flora, pollen count, and days of pollination in a specific locality."

2. *Pollen Surveys.*

It is important that surveys should be conducted according to definite procedures so that data from all over the world could be compared.

These procedures have been standardized by the National Pollen Survey Committee of the American Academy of Allergy.

Essential Equipment.

"Standard air sampling device consisting of two parallel planes of polished stainless steel, 23 cm. in diameter, with the slide holder raised 25 mm. above the lower plane. It is supported by a 76 cm. metal rod on a tripod laboratory stand. Screw holes are provided in the base so that it may be fastened securely to any wooden floor. This apparatus can be purchased from Wilkens-Anderson Com-

pany, 4525 West Division Street, Chicago 51, U.S.A. If the worker prefers to build his own instrument, a working drawing will be furnished without charge by writing to Oren C. Durham, Abbott Laboratories, North Chicago, Illinois, U.S.A.

Compound microscope (preferably binocular) with mechanical stage (preferably with graduated scales and verniers).

Glass slides, 25 by 75 mm. If slides with frosted ends are used, no paper labels will be necessary.

Cover glasses, 22 by 22 mm.

Soft petrolatum jelly: 75 per cent petrolatum, 25 per cent mineral oil.

Dissecting needle.

Calberta's solution, made up of 5 cc. of glycerin, 10 cc.of 95 per cent alcohol, 15 cc. of distilled water, and 2 drops of saturated aqueous solution of fuchsin.

Specimen reference slides, photomicrographs, drawing of pollen grains.

Place and time of exposure.

The ideal location for the sampling apparatus is the centre of an unobstructed roof of a tall, flat-topped building near the geographic centre of a given community. The building chosen should not be immediately flanked by taller structures. If the roof is equipped with a parapet, the top of the exposure apparatus should be 75 cm. above the parapet. Porches and window ledges are not satisfactory sites for pollen sampling.

Slides should be exposed, with label under the clip, for periods of twenty four hours, starting preferably in the morning and at approximately the same hour each day.

Identification technique.

Slides should be prepared with a very thin film of petrolatum jelly (rubbed out not flowed on with heat). Preparation of slides should be carried out in a room free from air currents and dust particles.

Examination of slides and identification of allergenic particles may be carried out most effectively by staining with Calberta's solution. The larger dirt particles, soot and sand should first be removed with a dissecting needle with the aid of a hand lens. A few drops of the stain are then placed directly on the slide. The amount used should be just sufficient to fill the space between the irregular oiled surface of the slide and the cover slip and will vary according to the quality of debris on the slide. If the cover glass actually floats free, the excess stain may be removed with a blotter. The slide may usually be examined within three to five minutes after application of the stain.

Identification and counting may be carried on without stain. Even when stain is used, only about one-half of the slide surface will be disturbed, leaving the remainder for observation of unstained granules.

Counting.

For routine counting, low power should be used—usually a 10 × objective with a 10 × or 15 × eyepiece ... The whole area (4.84 square centimeters) under cover should be counted by systematic sweeping of the cover glass area. Dividing by 4.84 gives the average number of pollen granules per square centimeter[1].

[1] This method of counting is undoubtedly time consuming. To those allergists who do not dispose of sufficient technical help, we would suggest that they use a 10 mm. × 10 mm. cover slip which corresponds exactly to one square centimeter. Results may not be quite as accurate as those obtained with the larger cover slip but they are adequate for daily routine work. Nevertheless, if the data are published, details on the technique used should be given. (Author's note).

TABL

Pollination Times of Plants Causing or Suspect

Key to Symbols: numbers in squares represent pollinating months. Plus sign indi little allergenic importance; ++ the plant may be locally important; +++ the pl its abundance, the amount of pollen shed and the clinical reactivity in the patients, ing its importance are lacking. Pollinating times for South America and Africa ar to fig. 1 (see p. 176). (This chart has been partly compiled from a similar one draw countries. For sources, please refer to the bibliography (13)).

Botanic Names	Canada		U.S.A.			
	British Columbia Alberta Saskatchewan	Manitoba Ontario Quebec	1	2	3	
1. *Trees*						
Acer	4–5 +	4–5 ++	4–5 +	3–5 +	3–4 +	1
Acacia						2
Ailanthus			5–6 +	5–6 +	4–5 +	5
Alnus	3–4 +	3–4 +	3–4 +	3–4 +	1–2 +	1
Betula	4–5 +	4–6 +	4–5 ++	3–4 ++	4–6 +	3
Broussonetia			4–5 +	5 +	3–4 +	
Calluna vulgaris						
Castanea sativa			7 +	6–7 +		
Carpinus			2–4 +	3–4 +	3–4 +	
Carrya		6 +		3–5 ++	3–5 ++	4
Casuarina				3–11 +		3
Celtis		5 +	4–5 +	4–5 +	3–4 +	2
Ceratonia						
Chamaerops humilis						
Cocos nucifera					+ +	
Corylus	3–4 +	4–5 +	3–4 +	3–4 +	2–3 +	
Cupressus						

[illegible] III

[illegible]ing Pollinosis in the Different Regions of the Earth.

[illegible] importance: | the plant grows in the region but its pollen is of no or of very [illegible]tant over all the region concerned; | | | the plant is very important because of [illegible] indicates either that the plant does not grow in the region or that data concern- [illegible]mmed because they vary considerably according to latitude. U.S.A. regions according [illegible]nsito U.S. cities by Harris and Shure (12) and from data published in the different

	U.S.A.						Africa	
	6	7	West Indies	Central and South America	Temperate Europe	Mediterranean Basin	Forest	Savanah
[illegible]			2–3			2		
[illegible]			+	+		++		
[illegible]	4 5	4–5			4–5	4		
[illegible]	|	++		+	+	++		
[illegible]	6 7	5–6				5–8		
[illegible]	|	+				+		
[illegible]	2 4	3–4			3–4	3–4		
[illegible]	|	+			+	+		
[illegible]	4 5	4–5			4–5	4–5		
[illegible]	| |-	+		+	+	+		
						4–5		
						+++		
					7–9			
					+			
[illegible] /	7	6–7			7	6–7		
[illegible]	+	+			+	+		
	3 4					3–5		
	+					+		
			3–6					
			+					
[illegible]	4–5	4–5				4		
[illegible]	++	+		+		+++		
						8–10		
						+		
						5–7		
						+		
			+++	+			+	
[illegible]		4–5			2–3	2–3		
[illegible]		+		+	+	+		
[illegible]					3–5			5 10
[illegible]					+			+

TABLE III (c

Botanic Names	Canada		U.S.A.			
	British Columbia Alberta Saskatchewan	Manitoba Ontario Quebec	1	2	3	
Eucalyptus						
Fagus		5 +	4–5 +	4–5 +	3–4 +	
Fraxinus		5–6 ++	4–5 +	4–5 ++	4–5 +	
Juglans		5–6 +	4–5 +	4–6 ++	4–5 ++	
Juniperus		4 ++			2–3 +	
Ligustrum				5–7 +		
Morus		5 +	4–5 +	4–5 +	3–4 +	
Olea						
Ostrya		5 +	5 +			
Phoenix						
Phyllirea						
Picea		5–6 +	5–6 +	5–6 +		
Pinus		5–6 +	5 +	5 +		
Platanus			4–5 +	4–5 +	3–5 +	
Populus	4 +	4–5 ++	4–5 +	3–5 +	2–4 +	
Prosopis				4–6 +	4–6 +	
Quercus	4 +	5–6 +	4–5 +++	3–5 +++	3–4 ++	
Robinia						
Salix	2–4 ++	4–5 +	4–5 +	3–5 +	3–5 +	
Sambucus						
Schinus molle						
Taxus		4–5 +				

TABLE III (cont.)

	U.S.A.						Africa	
	6	7	West Indies	Central and South America	Temperate Europe	Mediterranean Basin	Forest	Savanah
				+				
	4–5				4–5			
	|				+			
	4–5	4–6		12–2	4–5	4		
	|	+		+	++	+		
	3–5	4–5				3–4		
	|	+		+		+		
						5–6		
						++		
	4–6	4–5				4–5		
	|	+		+		++		
						4–6		
				+		++		
			+	+				
						6		
						++		
	5–6	5–6						
	|	+						
	5	5			5			
	|	+			++			
	4–5	4–5			4–5	4–5		
	|	+		+	++	++		
	2–5	4–5			2–5	3–4		
	|	+		+	+	++		
				+				
	4–5	4–5			4–5	4–5		
	+	+		+	++	+++		
					5	5		
				+	+	++		
	4–5	3–5			3–4	3–4		
	+	+		+	+	++		
					5–6	5–6		
					+	+++		
								10–2
				+				+
					4–5			
					+			

TABLE III (co

Botanic Names	Canada		U.S.A.			
	British Columbia Alberta Saskatchewan	Manitoba Ontario Quebec	1	2	3	4
Tilia		6–7 +	4–5 +	4–5 +	4–5 +	4
Ulmus	4 +	4 ++	3–4 +	3–4 ++	8–10 +	2 +
2. *Grasses*						
Aegilops ovata						
Agropyrum repens	6–8 ++	6–7 +	6–8 +	6–8 +	5–7 +	5 +
Agrostis alba	6–7 +	6–7 +	6–7 +	6–8 ++		
Aira spp.						
Alopecurus pratensis			5–6 +			6 +
Ammophila						
Andropogon spp.						
Anthoxanthum odoratum	4–5 +		5–7 +	6–7 +	5–7 +	
Arundo Donax						
Arrhenaterum elatius	5–6 ++					
Avena spp.					4–5 +	
Bouteloua gracilis					5–7 +	6 +
Brachypodium						
Briza						
Buchloe dactyloïdes						5–7 +
Bromus spp.	6–8 ++		5–7 +	6–7 +	5–6 ++	4–6 +
Carex spp.		5–6 +	4–5 +	4–5 +		
Cympogon Afronardus						
Cynodon dactylon				3–11 ++	4–11 +++	3–1 ++

TABLE III (cont.)

	U.S.A.		West Indies	Central and South America	Temperate Europe	Mediterranean Basin	Africa	
	6	7					Forest	Savanah
	4–5	4–5			6–7	6		
	+	+			++	++		
	3–5	3–5			2–4	3–4		
	+	+		+	++	+		
						5–6		
						++		
	6–8	6–7			7–8	6–9		
	+	+			+	+		
	6–8	6–8			6–8	5–7		
	++	+		++	++	+		
					6–7	6		
				+	+	+		
					4–6	5–7		
					+	+		
					6–8	6–8		
					+	+		
						8–10		
				+		+		+ + +
		5–7			4–6	4–6		
		++			+	+		
					8–10	9–10		
					+	++		
			6		6–9	6–9		
		+			++	++		
	5–6		6–7		6–8	5–8		
	+		+	+	++	+++		
		5–7						
		+		+				
					6–8	6–8		
					+	++		
					6–8	6–8		
				+	++	+		
		5–7						
		+						
	5–6	5–7			5–7	5–7		
	++	+		+	++	+++		+ +
						4–6		
				+		+		
								+
		7–9	1–12	5–9		8–9		
		+	+++	++++		+++	+	+ +

TABLE III (co

Botanic Names	Canada		U.S.A.			
	British Columbia Alberta Saskatchewan	Manitoba Ontario Quebec	1	2	3	4
Cynosurus cristatus						
Cyperus esculentus				6–8 +	6–8 +	6
Dactylis glomerata	5–7 ++	6 ++	5–6 ++	5–7 ++	5–8 +	6
Digitaria spp.				8–9 +	8–9 +	8
Distichlis spp.					6–8 +	
Echinochloa crus galli			6–8 +	7–9 +	7–9 +	5
(Oplismenus)						
Elymus					5–6 +	5
Eragrostis spp.						
Festuca spp.	5–6 +		5–6 +	6–8 +	6–8 +	4
Holcus lanatus	5–7 ++		6–7 +	2 +		
Hordeum vulgare						
Hyperhania spp.						
Imperata cylindrica						
Koeleria cristata	6–8 ++		5–6 +	5–6 +	5–6 +	6
Lagurus ovatus						
Lolium spp.	5–7 ++		5–7 +	6–8 +	4–6 ++	3
Loudetia arundinacea						
Melinis minutiflora						
Melica spp.						
Molinia caerulea						
Panicum						
Paspalum spp.					4–10 +	6–9

TABLE III (cont.)

	U.S.A.		West Indies	Central and South America	Temperate Europe	Mediterranean Basin	Africa	
	6	7					Forest	Savanah
					6–8	5–7		
					++	+		
						6–8		
						+		
	6–7	5–6			5–6	5–6		
	++	++		++	+++	+++		
		8–9						
		+					+	
	6–8							
	+							
	6–9	6–8				8–9		
	+	+		+		+	+	+
	5–7	5–6			6–8			
	++	+			+			
						6–7		
				+		+		+ + +
	6–7	6–7			6–7	5–6		
	+	+			++	++		
					5–6	5–6		
				++	++	+++		
					6–7	5–7		
				+	+	++		
								+ + +
								+ + +
	5–6	6–7			6–7	5–6		
	+	++			++	+		
						5–7		
						+		
	6–7	4–6			5–8	6		
	+	+		++	+++	+++		
								+ + +
			11–2					
			+	+				+ + +
					5–7	5–6		
					+	++		
					7–8	7		
					+	+		
			11–2			7–9		
			+	++		+	++	+ + +
	7–9	7–8				8–10		
	+	+		++		++	++	+ + +

TABLE III (co

Botanic Names	Canada		U.S.A.			
	British Columbia Alberta Saskatchewan	Manitoba Ontario Quebec	1	2	3	4
Phalaris canariensis			6–7 +	6–7 +	4–6 +	
Phleum pratense	6–7 +	6–7 +++	5–6 ++	6–8 ++	4–7 +	
Poa pratensis	6–8 +++	5–6 +++	5–6 +++	5–7 +++	5–9 +	
Polypogon monspelliensis ...						
Saccharum officinarum						
Scleropoda rigida						
Secale cereale				6–7 +		
Sesleria caerulea						
Setaria						
Sorghum halepense				6–8 +	5–11 +++	
Sporobolus spp.						
Stenotaphrum americanum					1–12 +	
Stipa spp.						
Themeda triandra						
Tricholaena rosea					7–9 ++	
Trisetum flavescens						
Triticum sativum	6–7 +	6–7 +	6–7 +	6–7 +	6–7 +	
Vulpia ciliata						
Zea Mays		7–8 +	7–8 +	7–9 +	7–9 +	
3. *Weeds*						
Achillea						
Acnida				7–9 +	6–9 +	

TABLE III (cont.)

	U.S.A.		West Indies	Central and South America	Temperate Europe	Mediterranean Basin	Africa	
	6	7					Forest	Savanah
	5 6	6 7				4 5		
	6 7	6 7			6–8	6–7		
	5 10	5 7			5–6	4–5		
					6–8	3 8		
			11–2					
					5–6	5–6		
		6–7			5–6			
					4–6	4–6		
					8–10	7–10		
		5–10						
						8–9		
						7–8		
					6–7	6–7		
	6 7	6–7			6–7	5–7		
						5–6		
	7	7–8			6–9			
					6–9			
		7–9						

TABLE III (c

Botanic Names	Canada		U.S.A.			
	British Columbia Alberta Saskatchewan	Manitoba Ontario Quebec	1	2	3	4
Amaranthus spp.	7–9 ++	6–8 ++	4–8 ++	7–9 ++	5–11 +++	8 +
Ambrosia spp.		7–9 +++	8–10 +++	8–9 ++++	8–12 ++++	+
Anthemis						
Artemisia	8–9 ++	7–9 ++	7–9 +	8–9 +	7–11 ++	4 +
Aster						
Atriplex	8–9 +	7–8 +	7–8 +	5–9 +		5
Baccharis						
Beta vulgaris						
Bidens						
Cannabis sativa				7–9 +		
Chenopodium	7–9 +	7–8 ++	6–10 ++	5–10 ++	6–9 ++	5 +
Chrysanthemum leucanthem.						
Cyclachaenia spp.	7–8 ++					7 ++
Franseria spp.	7–9 +				5–9 ++	3 +
Helianthus						
Humulus lupulus						
Hymenoclea						5 +
Iva spp.	7–9 +		7–9 +	7–9 +	7–9 ++	5 +
Kochia spp.	8–9 +	7–8 +			6–8 +	6 ++
Luzula campestris	4–5 +	4–5 +	4–5 +	4–5 +	4–5 +	4 +
Medicago			5–7 +	5–7 +	5–8 +	5 +
Mercurialis						

TABLE III (cont.)

	U.S.A.		West Indies	Central and South America	Temperate Europe	Mediterranean Basin	Africa	
							Forrest	Savanah
	7 8	6–8	1–12			7–10		
	1 1	+ +	+ +	+ +		+ +		
	8 9	7–9						
	1 1	+ + + +	+	+ +				
					6–9	7–10		
					+	+		
	8 9	7–9			7–9	9–10		
	1 1 + +	+			+	+ +		
					7–9			
					+			
	5 9	6–8			7–9	8–9		
	1 +	+			+	+ +		
				+				
	7 8		5–10		7–8			
	1 +		+		+			
					7–9			
				+ +	+			
		7–9				6–7		
		+				+		
	5 10	6–9	5–10		8–9	8–10		
	1 +	+	+	+ +	+	+ +		
					5–8	6–9		
					+	+		
	7–8	7–8						
	1 + +	+ + +						
	8–9	8–9						
	1 + +	+		+ +				
					8–9	8–9		
					+	+		
					7–9	6–9		
					+	+		
	6–9	8–9						
	+ +	+						
	7–8	7–9						
	+	+ + +						
	4–5	4–5			4–5			
	+	+			+			
	6–8	5–7			6–8			
	+	+		+	+			
					3–5	4–8		
					+	+		

TABLE III (co

Botanic Names	Canada		U.S.A.			
	Britisk Columbia Alberta Saskatchewan	Manitoba Ontario Quebec	1	2	3	4
Melilotus						
Parietaria spp.						
Plantago spp.	5–9 ++	5–9 ++	5–8 +	6–8 +	4–9 +	4- +
Ricinus communis						
Rumex spp.	+ 8–9	+ 6–8	+ 5–8	+ 5–8	3–11 +	4- +
Salicornia						
Sarcolatus vermiculata						
Salsola	7–9 ++	7–8 +			7–11 ++	7- +
Solidago		7–8 ++				
Taraxacum officinale	5–9 ++					
Trifolium spp.						
Typha						
Urtica	7–8 ++	6–7 ++				
Xanthium spp.			8–9 +	8–10 +	6–8 +	7– +

For the sake of uniformity, it is advisable that counts be computed and reported on the basis of the number of pollen grains (or spores) of each type or species found on one square centimeter of slide area." (11)

Conclusion

There is no doubt that skin testing in pollinosis constitutes only one of the elements in the diagnosis. Not only must the allergist have a thorough knowledge of the anemophilous flora in his region and data about their periods pollination, but he must also subject each individual patient to a detailed anamnesis with the object of studying, and later eliminating or at least neutralizing, all the specific factors (flowers in the house, insecticides, mattress dust, air-

TABLE III (cont.)

	U.S.A.		West Indies	Central and South America	Temperate Europe	Mediterranean Basin	Africa	
							Forest	Savanah
					6 9	6 9		
					+	+		
					6–9	3–10		
					+	+++		
	5 8	5 9			5–9	4–7		
		+		+	+++	+		
						5–10		
				+		+		
	4 9	5–9			5–8	6–9		
		+		+	++	++		
					8–9			
					+			
	8 10							
	7 9	7–9				7–8		
		+++				++		
					7–9			
					+			
					4–5			
				+	++			
					5–9	5–9		
					+	+		
					6–8	6–8		
				+	++	+		
					6–8	6–8		
					++	++		
	5 9	7–9			9–10	7–9		
	+	+		+	+	+		

borne fungi spores, foods etc.) or non-specific ones (irritating odours, alcoholic drinks, fatigue, overwork etc.) which he may have been able to uncover.

The care needed by a hay-fever sufferer thus exceeds by far the ordinary limits of pollen allergy.

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FUNGI AND MISCELLANEOUS INHALANT ALLERGENS

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As long as the primary cause to which the allergic constitution is due continues to be obscure, in spite of the immense number of studies concerned with allergic diseases, we shall have to do the best we can with what has so far been brought to light pertaining to the precipitating factors which may give rise to allergic symptoms. First of all, we must not forget that the patient should be regarded as a whole; it is the patient who is ill, not an area of the skin or a portion of the mucous membrane of the respiratory tract.

In certain conditions, the examination may appear to be a simple matter, e.g. when a patient with hay fever has his attack in the spring; however, even in these cases other factors beside pollen, such as fungi, foods and secondary infections of the paranasal sinuses as well as emotional factors may play an important role.

As a rule, an allergic manifestation is due to a number of determining factors, though one or two will frequently be predominant. These determining factors may be of the somatic, psychological, and/or social type.

Somatic factors may be classified into:

(1) true *physical* allergy,

(2) *broncho-bacterial* factors and focal infections (sinusitis),

(2a) *endogenous parasites,* e.g., worms in the digestive tract, fungus diseases of the skin associated with mycids in other areas,

(3) *endocrine factors,*

(4) *allergic factors* including:

  (a) *food and drug allergens*;

  (b) *inhalant allergens* such as house dust, fungi occurring in the in- and outdoor air, in factories and workshops; industrial dust, especially of organic origin, the dust of mites and

moths, epidermal materials of domestic animals and, possibly, human dandruff;

(c) a wide variety of substances causing *specific contact allergy of the skin.*

Although there is little doubt that meteorological conditions as such influence the allergic state in many patients, genuine climatic allergens are very likely to be inhalant allergens, regardless as to whether they are gaseous emanations of the soil or substances of vegetable or animal origin (air-borne bacteria, fungus spores and disintegration products of fungi on their natural substrate).

Accordingly, it is essential to study these factors in detail, particularly as the differential diagnosis is of utmost importance in view of specific treatment and as the great majority of patients with so-called allergic disorders show a polyvalent rather than a monovalent type of allergy, at least if there is any (demonstrable) allergy involved at all.

The great majority of patients developing symptoms in a particular area or during a particular season, probably do so because of the fact that a large number of allergens harmful to them are present in that district or during that period, which alone or in conjunction with other factors, are just sufficient to induce an attack.

Of primary importance is the correct recording of the patient's history. Pollinosis mostly occurs during one of the specific pollen seasons; many patients with fungus allergy observe a particular increase in the severity of their condition in late summer and autumn, the severity showing marked seasonal variations in several districts, though pronounced symptoms may also persist throughout the rest of the year. These seasonal influences will depend mainly on the species of fungus involved. Some patients, whether or not affected by fungus allergy, continue to show symptoms all the year round, except when snow has fallen; other patients with bronchobacterial infections or substantial pulmonary emphysema, possibly associated with an allergic condition, are liable to present attacks of bronchospasm in the event of a dry north or east wind, while at other times, attacks may be due to emotional causes or to a combined action with other allergens (food or house allergens). The range of possibilities is enumerable and each patient confronts us with new problems.

Fungus Allergy

In comparison with the vegetable kingdom, *fungi* rank slightly above bacteria. They are found almost everywhere, chiefly in humid and moderately warm places, though certain fungi are known to

grow in refrigerators or on snow. In addition, there exist markedly xerophilic and thermophilic fungi such as those of the genus *Aspergillus,* which are frequently found in citrus-fruit plantations; this genus also includes a number of species able to live in the bodies of human subjects and birds.

This is sufficient to show that their mode of life is cosmopolitan. They live as parasites or saprophytes, mainly upon the living and dead parts of higher plants. They occur on every kind of material of vegetable or animal nature, in damp houses, closed spaces under staircases, cellars, upholstered furniture, in flour, on leather, vegetables and fruit; they may cause decay of food, etc. Fungi preferably grow in a moderately acid and moist environment where bacteria are less liable to multiply; there they may accumulate in enormous quantities.

So far, thousands of species and saltants have been described and though most fungi live as saprophytes in nature, others may occasionally act as pathogenic agents in plants and human subjects, as endogenous parasites in the lungs (e.g. the notorious Aspergillus fumigatus Fres), or as inhalant allergens.

Diaspores of moulds and yeasts are found both in- and out-of-doors as well as in factories and workshops, though the number and species vary as a result of several factors. Fungus spores still capable of germinating have even been found at times in severe cold and in the higher layers of the air.

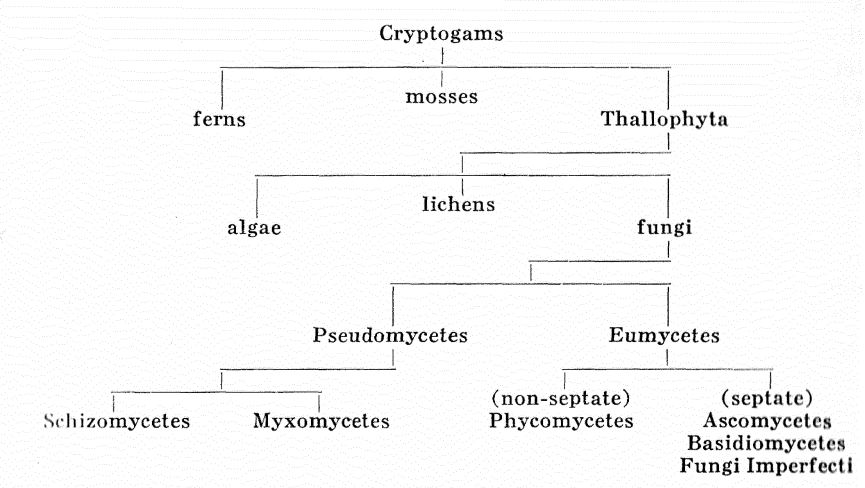
As such spores consist of small, very light particles, characterized by great buoyancy, they are readily displaced by horizontal and vertical wind currents and are present in the surrounding atmosphere for prolonged periods. They are particularly abundant in the lower marshy coastal areas. The incidence of fungus diaspores in the surrounding atmosphere gradually diminishes above sea level and when higher air layers are reached, although layers containing high concentrations may also be observed at higher altitudes, e.g. just below clouds or in the lower cloud strata.

Storm van Leeuwen, who actually rediscovered the significance of fungi as inhalant allergens, simultaneously with *Cadham* in the U.S.A., was the first to identify, in conjunction with *Kremer,* circulating reagins and blocking antibodies. Later, the distribution of air-borne fungus diaspores at various levels and over large areas was chiefly studied by *Durham, Nilsby* and *Heise.* Data on the presence of fungi in damp houses have also been available for a long time. To-day it is a well-established fact that cases of occupational asthma are also frequently caused by fungi and their products.

The above shows that allergy to fungi is a very likely contingency which has been underrated for many years, and as the significance

of fungi as causative organisms is still widely ignored, we believe we are justified in paying particular attention to this section on inhalant allergens especially those which are of paramount importance in general practice and in the treatment of allergic conditions.

Mycetes are subdivided into *Pseudomycetes,* including *Schizomycetes* (bacteria) and *Myxomycetes* (slime moulds), and *Eumycetes,* the true fungi, which in turn are subdivided into those having unicellular (non-septate) mycelia, *Phycomycetes,* and those having multicellular (septate) mycelia, *Ascomycetes, Basidiomycetes* and *Fungi Imperfecti.* Actinomycetes are intermediate organisms between true fungi and bacteria; they are classified today as bacteria.



Almost all *Eumycetes* consist of a network of filaments, hyphae, collectively termed the mycelium. Phycomycetes have no septa and are therefore unicellular, with the possible exception of the hyphae bearing fruit-bodies of asexual spores. The other fungi possess a septate mycelium.

The *spores* of the various fungi are highly specific and are characterized by a constant structure, shape, size, colour and arrangement, which makes classification possible. Two types of spores may be differentiated, the sexual and asexual spores.

Phycomycetes, Ascomycetes and *Basidiomycetes* have been classified in a natural system, as these three classes are capable of sexual propagation and are therefore complete forms of the species.

The moulds coming under the heading of *Fungi Imperfecti* do not produce sexual spores, with a few exceptions, e.g. some species of Aspergillus and Penicillium, which have complete forms. For the

sake of convenience, however, these are all classified as Fungi Imperfecti, subdivided into form genera. *Mason* has attempted to classify fungi, and especially Fungi Imperfecti, according to their biological and physiological characteristics, with particular reference to the possible distribution of the spores. This has been elaborated in greater detail by *Ingold* and *Gregory*. Spores may be distributed by passive liberation or active discharge. In the event of passive liberation, the spores may remain at the same site until conditions of growth, which have temporarily been unfavourable, show an improvement; they may then be distributed by water, birds, etc., and especially by air currents. The spores in this case may be so-called "dry" spores which are immediately detached from the sporophores by the wind during dry spells, whereas the so-called "slimy" spores which are embedded in a slimy substance, are only detached during wet periods, when, according to *Gregory,* they are diffusely dispersed by splashing droplets of rain, so that they become air-borne. However, even this classification cannot always be adopted in view of intermediate stages in certain fungi and the presence of both dry and slimy spores in some species. Actively discharged spores are, for example, the sexual spores of Ascomycetes, which are forcibly ejected from the ascus in fungi having a complete perithecium. This concept is of special importance with regard to allergy.

Reduction, division and nuclear fusion occur in sexual spores, whereas asexual spores are vegetative and are detached from more or less specialized hyphae, i.e. without previous nuclear fusion.
Phycomycetes, are classifiable into two groups:

(a) Oomycetes and
(b) Zygomycetes.

The former are probably of no importance as allergens, as they mainly live in water, the latter are found on land. The Zygomycetes include two genera which are also frequently found indoors, *Mucor* and *Rhizopus*. These Mucorales predominate in several types of factories, especially in the flour-using industries and in textile mills.

Ascomycetes: Of this group, the most important for our purpose are the manure fungi *Sordaria* and *Chaetomium,* which are found occasionally in upholstered furniture. In addition, Saccharomycetales may play a role in food allergy.

Of the *Basidiomycetes, Merulius,* or house fungus, deserves special mention.

The *Fungi Imperfecti* include most fungi liable to cause allergic reactions. Amongst them *Cladosporium,* in view of its high incidence and ubiquity, ranks first. It is the most widely distributed seasonal

climatic fungus in the Netherlands; it is not confined to this country, however, but is cosmopolitan. In addition, it is one of the fungi most commonly found in houses, on wall-paper, blotting paper, beneath carpeting and in weather-stained cotton and linen. *Alternaria*, considered one of the predominant fungi in the U.S.A. is of little importance in this country as an outdoor fungus, except in corn-growing districts. This is also the case of *Stemphylium*. Alternaria, however, is a very important house fungus in some cases.

Though very common in northwest Europe, *Pullularia* is hardly ever reported as occurring in other parts of the world. The same can be said for *Fusarium* which is a fungus highly selective in regard to its substrate and, when not cultured correctly, it will often be classified as *mycelium sterilium*. This form genus also shows marked seasonal variations, its peak occurring late in July as well as in August and September. *Botrytis*, predominant both indoors and out, shows peak incidences somewhat later, viz. in September and October. *Penicillia* are observed both indoors and outdoors all the year round, especially when there is a high degree of humidity. Curiously enough, it is found to occur conjointly with *Aspergillus* in Spain and apparently it has a preference for towns rather than for rural districts, contrary to *Cladosporium*.

For differentiation, etc., the reader is referred to Smith's Introduction to Technical Mycology and to the recently published monograph by one of the present authors, which provides some reading matter for those who have received no previous mycological training, as a preliminary guide to the cumbersome mycological textbooks.

With regard to the yeasts, some are species of *Saccharomyces*, the others, of which there are various classifications, belong to the Fungi Imperfecti. Of the latter, the most important in regard to allergy are *Candida* and *Rhodotorula*, the spores of which are air-borne. In addition, the *Torulopsis* species should be mentioned which also occur endogenously as commensals or parasites. This might possibly be the case with a few other fungi which, besides being capable of inducing inflammatory reactions, may act as endogenous allergens as well, e.g. certain *Aspergelli*.

Identification of species of yeasts requires entirely different methods of culturing and differentiation. Yeasts, however, should be taken into serious account as allergens. *Feinberg et al.* (1935), studying 600 patients with respiratory allergy, observed a positive response to yeasts, including responses to cross tests using yeasts, in 10.8 per cent of the cases.

History.

Even the older literature contains reports on a number of cases in which fungi must undoubtedly have played an important part, especially in inducing attacks of bronchial asthma or vasomotor rhinitis. *Floyer* (1726–1782) cited *Bonetus* who reported the case of an asthmatic patient who developed dyspena when entering his wine cellar where must was fermenting. *Tersáncky* (1848–1849) and *Hirt* (1871) reported fungi as having a pathogenic action in workers in the tinder industry. *Michel* (1863) described the "mal de canne de Provence" in osier workers and reed cutters who developed symptoms, which to-day may be classified as allergic, within 12 to 24 hours after working in hot and windy weather. *Kuttner* (1928) observed allergic symptoms in a cavalry officer on inspection of the stables; this author had previously reported two cases of house dust and house fungus allergy respectively. The great impetus to the study of fungus allergy was given by *Storm van Leeuwen,* although it may have been *Blackley* (1873) in his book on hay fever and before him, *Salisbury* (1861–1862) who made the first tests using fungus spores without sufficiently realizing the significance of these studies.

About 1924, *Storm van Leeuwen* reached the conclusion that there must be a still unknown asthmogenic substance, in view of the local occurrence of asthma in the rural Dutch province of Zeeland. In conjunction with *Bien, Varekamp* and *Kremer,* he called these soil effluvia, consisting of disintegration products of vegetable and animal origin, miasmata. These patients showed a particularly rapid improvement in his allergen-free rooms.

Prior to *Storm van Leeuwen, Jack* (1924) had believed attacks in asthmatic patients to be due to noxious "hemolytic" gases produced by decaying organisms in the soil, so that he proceeded to construct gas filters and built air-conditioned rooms which had beneficial effects.

Later, *Varekamp* studied a large number of allergic patients in the Netherlands, and found that the somewhat higher, dry sandy areas were usually more favourable than low marshy humid districts.

Like others after him, *Storm van Leeuwen* not only had observed that mountain regions had a favourable effect on these patients, but in conjunction with *d'Hérelle,* he provided evidence showing that when an asthmatic patient is brought into contact with his noxious allergen at high altitudes, he will then also develop his hypersensitivity reaction.

These studies were well-planned, as all measures had been taken

to eliminate any psychological effects. Others having obtained similar results in Spain and France, *Storm van Leeuwen* decided to introduce his "miasma theory". Although at that time he had not as yet encountered fungi as such, continued investigation showed the fungi to be a highly important group of causative organisms acting as inhalant allergens. At the same time, he examined the air in a number of hospitals and homes, finding *Penicillium, Cladosporium, Mucor* and *Aspergillus* in nearly every case. His mycological studies of the outdoor air, which were rather casual at the time, mainly revealed the presence of *Penicillium, Cladosporium, Mucor* and *Phoma*. As skin tests with extracts of these fungi were positive in approximately 30 per cent of the cases, and as 90 per cent of his patients showed a positive response to house dust, he did not believe fungi to be very harmful at the beginning. Shortly later his opinion changed upon finding an *Aspergillus* in the kapok of a mattress and pillow of a female patient with asthma and eczema. When a sister of this patient used the same bed, she suddenly developed an eczema of the face.

The next few years, working in conjunction with *Kremer, Tissot van Patot, Varekamp, Bien, van Niekerk, von Bánszky, de Lind van Wijngaarden* and *van Dishoeck,* were epoch-making ones in this field.

Cadham (1924), independently of these authors, reported 3 cases of asthma in Canada due to a fungus causing rust in wheat. From that time on, the study of fungi as allergens rapidly advanced all over the world; in Germany, the first author concerned with the study of fungi was *Grimm* (1925–1928), subsequently followed by *Hansen*; in Spain, *Jiménez Díaz* (1932) and in the U.S.A., inter al. *Prince, Vaughan* and *Feinberg. Hansen,* who was especially interested in skin tests, found 15 per cent of his asthmatic patients to be hypersensitive to one or several *Aspergilli* and *Penicillia.*

In subsequent studies, the results obtained by inhalation tests using fungi were also found to be positive (inter al. *Nilsby* 1949, *ten Cate,* 1954). *Blackley* (1873), who actually had been the first to make inhalation tests, failed to recognize the significance of fungi as non-pollen factors in hay fever. After *Storm van Leeuwen* in 1925, it was chiefly *Rackemann* and his associates who stressed the importance, not only of the fungi themselves, but also of the disintegration products formed by fungi on their natural substrate. Investigations on this subject, however, are still in the initial stage. The data reported by *Cohen* are not in concordance with the above. It is beyond the scope of this book to mention all of the names of investigators in this field.

Attention should briefly be drawn to the fact that these studies

have shown that the coastal areas of Europe from Norway to Spain, are of particular importance as to the prevalence of fungus allergens. This was reported by *Jiménez Diaz* (1932) in Spain; *Frânkel* obtained positive skin test with fungi in about 57 per cent of the cases in England, while the number of positive tests was only 10 per cent in Germany.

It is essential, especially in the case of asthmatic patients, that the surrounding air which they breathe daily be free of harmful types of dust which frequently contain fungi. Owing to the humid condition of floors and walls, many homes, especially those in the lowlands, contain fungi, the spores of which are scattered in the atmosphere of living-rooms and bedrooms and may even spread rapidly all over the house, as was shown by *Christensen.*

The fungi concealed behind cupboards, in store-rooms containing old furniture, in attics or cellars, in carpets, behind decorative wallcloths and in floor seams, as well as those found in factories using material of vegetable or animal origin, are mainly various species of *Stemphyllium* and yeasts, *Penicillium, Aspergillus, Cladosporium, Rhizopus, Mucor, Fusarium, Botrytis, Alternaria, Trichoderma* and the dreaded house fungi of the genus *Merulius.* They may be found anywhere, in worn clothing, cupboards, old shoes or slippers (leather), in kapok and feathers of mattresses and pillows, on the covers of books, etc. Henceforth, almost every asthmatic patient shows considerable improvement after his home has been cleaned.

The important part played by fungi in the pathogenesis of asthma explains some of the favourable effects of open-air schools and the moving to drier districts (sandy soil).

Like the symptoms caused by pollen in hay fever, typical "fungus symptoms" tend to occur in seasons particularly marked by the appearance of certain fungi, especially *Cladosporium, Fusarium, Botrytis* and *Pullularia,* when patients stay for some time in damp houses, cabins, in a circus, etc.

Not taking into account a pre-existent latent allergy due to a hereditary predisposition, anyone may become sensitized to fungi (occupational asthma), although this will also depend on the degree of personal susceptibility. The spores are the main source of allergens, the mycelium being considerably less active; asthma is particularly liable to be induced by mould spores, as these are so finely divided (smaller than 12 μ) that, unlike the much coarser pollen, they are readily able to penetrate into the lower respiratory tract. *Kremer* (1940) reports that at least 1 per cent of the population in the Netherlands has been allergized by fungi, though this need not mean that the patient shows symptoms, e.g. vasomotor rhinitis or asthma which induce him to see a physician.

According to *Feinberg* (1937) patients with fungus allergy may be of any age and of either sex. He found 20 per cent of his allergic patients to be sensitive to fungi. Several investigators in this field observed markedly varying percentages of mould allergens, apart from mycological technical errors in culturing, preparation of extracts, omissions and inadequate taking of fungus inventories resulting in too small a number of test series. Regional, seasonal and annual variations undoubtedly play a part in this.

Symptoms vary with the degree of pollution of the atmosphere; in addition to marked seasonal variations (May-November), there are also changes in the fungus flora during the day. Towards dawn, slimy fungus spores are abundant, especially when dew has fallen; rainy weather is marked by the presence of yeasts, *Fusarium, Phoma* and parasitic species of the form genus *Botrytis.* In the daytime, fungi bearing dry spores such as *Cladosporium* may often be collected in large numbers. They frequently disappear almost completely during and immediately after rain showers, suddenly appearing in increasing numbers on the dry days following these wet spells.

Wind is their important carrier and, hence, the spores become widely distributed; they have even been found to be present in the stratosphere and occasionally large numbers may be found in conjunction with autochthonous fungus spores.

Cladosporium, Fusarium, Pullularia and *Botrytis* are typical seasonal fungi. Occasionally, *Rhodotorula* is very common on certain days in November and December, especially in foggy weather; fungi such as *Candida* and *Penicillium* distribute their spores all the year round. Therefore, all statistics relating to the lowlands show marked peaks in late summer and autumn.

Not only do the fungi vary in quality and quantity from one place, district or country to another where they are naturally found in conjunction with ubiquitous fungi, but annual variations are observed as well. A striking feature, however, is the fact that there are relatively constant combinations or associations, as have long been known to occur in the higher plants. The same holds true in regard to houses, various factories and workshops. Accordingly, the investigator concerned in making a more detailed examination in the case of a patient who has a history suggesting respiratory allergy and especially fungus allergy, should study the fungus flora characteristic of the district as well as the fungus flora in the home and place of work of the patient.

As previously stated, the possibility of fungus allergy should also be borne in mind in the case of a patient affected with so-called pollinosis; otherwise, specific desensitization might be apt to fail. This

does not apply only to vasomotor rhinitis, but seasonal dermatitis and conjunctivitis may be caused by specific fungi as well, e.g. *Cladosporium* and *Alternaria* (*Simon*, 1938).

Maunsell (1954) has drawn particular attention to the marked specificity of fungi. In this author's opinion, only those fungi which elicit an immediate positive skin reaction are allergenic (mainly saprophytes); those eliciting a delayed response belong to the so-called pathogenic fungi.

Treatment.

In the therapy of fungus allergy three factors should be borne in mind, beside the fact that not only the fungus itself, but also the products developed by the fungus on its substrate, may act as an allergen, viz.:

(1) Fungus allergy is hardly ever the only factor involved, but fungi can be one of the causes inducing an attack in the patient.
(2) Sanitation of the patient's environment is a highly important factor in fungus allergy.
(3) Fungus allergy may be desensitized satisfactorily.

On a whole, the method used in desensitization is similar to that used in pollinosis. As a rule, injections are administered twice weekly in the beginning or sometimes only once a week, depending on the time when the patient is first seen by the attending physician. If the patient is seen for the first time shortly prior to the peak of the fungus season, injections should be made as often as possible in order to still afford at least some protection. As a rule, desensitization should be started as soon as the diagnosis has been established, as this treatment will have to be continued over a long period of time, (from 1½ to 2½ years).

The initial concentration of the injected fluid should be tested accurately depending on the highest dilution which still produces a wheal in skin tests; the initial solution employed may sometimes even be as high as 1: 10,000 per cent. Usually, 1 ml. of a 1 per cent solution will be sufficiently strong to start administration of the maintenance dose; in some cases, a 5 per cent solution will be necessary, especially when the injected fluid has not been prepared from a single fungus or allergen.

Which fungi should be used in desensitization? This will undoubtedly depend upon the symptoms shown by the patient and the results obtained by specific tests (intracutaneous, inhalation and provocation). Subsequently, the composition of the fluid may be determined from the results of these tests.

It should be remembered, however, that the intensity of the skin reaction does not afford a true measure of the severity of the allergy; moreover, it may well be possible that the combination of several antigens in the desensitizing fluid will either potentiate or weaken the action of one (or several) of these antigens.

In carrying out investigations, it is essential to know which fungi should be studied. Prolonged studies have shown that the findings in the Netherlands bear a marked qualitative and quantitative resemblance to those in other countries. Differences, in this respect exist however, not only from one country to another, but also in the Netherlands from one district to another. In regard to houses, the variety of species is larger in damp homes than in dry ones (7 to 3), the spore counts being higher as well. In addition, the fungus flora in some houses varies markedly from the usual flora. This is even more apparent in factories and workshops, especially those using substances of a vegetable or animal nature. *Westerdijk* assumed that there are relatively constant fungus associations which are characteristic of the various, very particular, substrates. A mycological study by one of the present authors, involving a large number of factories and workshops, provided conclusive evidence showing that this theory of fungus associations is correct. This is a fortunate circumstance, as it means that of the thousands of known fungi, there remain only about 120 which are not observed sporadically, only 30 being actually common in the Netherlands and therefore of possible importance in the case of allergic patients. There are exceptions to this rule, e.g. we once found a fungus causing the so-called pineapple disease of sugar cane in a home. The housewife showed a markedly positive response to this fungus both in the skin and provocation tests, and little if any response to other common allergens (other inhalants, foods).

Formerly (and these attempts are still being continued to-day in other countries) every effort was made (in vain) to obtain a satisfactory uniform culture medium. As when growing in nature, fungi have a special preference for a particular substrate *in vitro*. Many fungi such as true mildew, which causes rust and blight, and many species of toadstool do not grow at all or only yeast-like in cultures; a small number of ubiquitous fungi will readily grow on any medium, provided it is slightly acid; the majority, however, require a slightly acid, not too rich nor too dry, natural and therefore biological substrate such as tomatoes, cherries, malt, sausage, plums, potatoes, rice, oatmeal, slices of carrot or lupin stalks (Lupinus polyphyllus Lindl).

When, therefore, the common error is made of preparing the medium too rich (particularly in carbohydrates) or using media

having a neutral or even alkaline reaction, this will result either in a rapid growth of a large number of hyphae and hardly any spore formation or in no growth whatsoever. This also occurs in the case of most fungi cultured at incubator temperature. The optimum temperature to store stock cultures is 10° C., the optimum temperature for growth being 20° C. in the majority of cases. In a manner of speaking, the fungi have to wage a struggle for life prior to bearing fruit, and this is just what is essential for the preparation of extracts. In addition, if we wish to preserve a culture, it should be transferred from time to time to another medium, as otherwise the species will be bound to degenerate and thereby lose its allergenic properties. Accordingly, most families, form-groups and species require special diets with varying menus for collection and identification, culturing, storage of the collection, or for cultivation with the view of preparing fungus extracts.

If any break-down products of natural liquid substrates should adhere to the mould pellicle, these products may have a non-specific irritant effect in the skin test. Therefore, in preparing extracts of readily growing fungi, transfers may be made from the stock culture to a liquid synthetic medium such as Czapek's medium or one of its many variations. For the remaining large group of fungi a direct inoculation may be made on a solid natural medium from which, after or without desiccation, the spores may be removed by shaking off, scrapping or washing off with alcohol or ether. Another method consists in placing a cellophane paper on the solid culture medium, on which the fungus is then to be inoculated. Later, the entire mycelium can be removed very quickly. When the fluid underneath the pellicle or the oxalic acid, gallic acid, oil drops, citromycetin, etc., lying on top of the mould film have been aspirated, and after defatting and drying have taken place, the dried material may then be preserved for years. When a liquid extract is required, we use a hypertonic saline solution, thereafter the fluid is passed through a Seitz filter and a 0.5 per cent solution of crystalline phenol is added. The allergen extract prepared by this method will remain stable for about 4 months whereafter it is bound to be unreliable. Any assay solely based on determination of the dry weight volume and the determination of nitrogen or protein nitrogen units will be useless in measuring allergenic potency.

So far, bio-assay is the only reliable method. Therefore, if a liquid fungus extract of long-lasting potency is to be made available, it will be necessary to use other fluids in preparing and preserving the extract, especially glycerin containing fluids. These, however, have other disadvantages such as inducing a non-specific irritation in skin tests when used in the undiluted state and of causing

pain to the patient. The mycological data relating to conditions in the Netherlands, culturing methods used for continued cultivation, identification, preparation of extracts and maintenance of stock cultures, the required temperatures, degree of humidity and of light exposure, briefly all of the measures essential to obtain a series of satisfactory fungus extracts have been reported in a monograph by one of the present authors.

One problem has not as yet been approached, viz. that of strains and mutations.

(1) Thus, the colour of *Aspergillus versicolor* (Vuill.) Tiraboschi varies from yellow to orange, pink and even red and every monosporular culture shows similar variations in colour. Accordingly, this is and remains a single strain of a single species.

(2) *Penicillium expansum* (Link) Thom is marked by a smooth velvety growth, but develops on certain culture media, tree-like structures (coremia), a bundle of erect hyphae crowned by spores. This form of growth will disappear on another medium, to return again on the initial medium. This also is species-specific and not a mutation, or more correctly, to use the mycological term, a saltation.

(3) Nor can we speak of saltation when a colony degenerates as a result of errors in cultivation, losing its colour and capacity for fructification.

(4) The growth of *Alternaria tenuis* Nees varies markedly with the different culture media. Occasionally, the growth suggests a large number of strains and in some cases may change in such a way as to convey the transient impression of an entirely different species. In this case also, morphological and possibly morphological-biological saltations, i.e. permanent variations of the species, are again out of the question.

(5) Species of *Fusarium,* which are difficult to identify and cultivate, are often recorded as *Mycelia Sterilia.* Rice, acid oatmeal and lupin stalks are essential for fructification in this species. The microconidia of the various species of the genus *Fusarium* are all more or less identical in form and size; the macroconidia of a single colony of a certain species may be composed of 3 to 7 cells. These spores also bear a marked resemblance to one another, so that 2 species may be mistaken for 2 saltations of a single species.

On the other hand, there are also a number of fungi which are known to have different strains:

(a) There are strains which can be differentiated by the morphological characteristics, either macroscopic, e.g. a strain of *Aleurisma* is characterized by a velvety growth, while another develops a coremia; or by their microscopic characteristics, the spores and

the mycelium showing various sizes and colours which remain a constant feature. There is e.g. a certain species of *Cladosporium*, the main strain of which varies from light to dark brown and of which there are 3 saltations, 1 green, 1 white and 1 dark; the first two produce spores which are characteristic of each type as well as of the main strain; the dark saltation remains sterile.

(b) In addition, it may also be that the physiological properties differ despite an identical morphological structure, but little if anything is known about the subject from the mycological-physiological point of view. Hereby, the strains or saltations might be morphologically identical, but differ as to their physiological characteristics.

So far, no method has been developed by which it can be determined whether the allergenic fractions do differ from one strain to another. Cross neutralization tests do not provide a true solution, for, in making these tests, there is the primary difficulty that a very marked response in the passively sensitized sites may occasionally rule out any subsequent reactions to entirely different allergens. These simply do not get a chance.

The other objection is even more important: when cross neutralization tests are made, using allergens of two fungi, if the second allergen fails to induce a response subsequent to one or several injections of the first allergen at the site of transfer, antigen A will be said to contain B.

Now the process is reversed: initially, the second antigen is injected one or several times, inducing a slight doubtful response; subsequently, antigen A is injected at this site. In this case, a reaction results and it is concluded that there is a third allergen as well. Consequently, antigen A contains antigen B plus a third antigen. This conclusion is not justified, however, as B may merely be a 1:100, 1:1,000 or even a 1:10,000 dilution of A. Henceforth, a reaction must necessarily also result when the high concentration of this antigen is injected. In a number of species, some indication may be afforded by testing ten different strains of one species in ten different patients, provided entirely different results are obtained. However, when certain patients show a strongly positive response to two or more strains, this test again will not be any more conclusive than the others. Thus, it is still undecided whether only a single generic allergen is involved, as is assumed by *Feinberg*, or whether several generic allergens, species-linked or strain-linked allergens are involved, assuming the genus in question to be a natural genus and not a so-called form genus.

Finally, a solution has to be found to the problem as to which asthmogenic substances, if any, are produced by the various fungi, each from its own natural substrate. Here a vast field is still open

for investigations on a subject, the knowledge of which is far from complete.

Desensitizing vaccines should also be tested individually. Accordingly, a desensitizing fluid may, for instance, be composed as follows:

Alternaria tenuis Nees	1 %	2 ml.
Aspergillus versicolor Tiraboschi	1 %	2 ml.
Penicillium expansum Thom	1 %	1 ml.
House dust	1 %	4 ml.
Feathers	1 %	1 ml.

The above formula was intended for a particular patient with polyvalent respiratory allergy, whose symptoms did not typically appear during the summer. The more simple the composition of a desensitizing fluid, the more likely the clinical success will be. *Feinberg* (1946) obtained satisfactory results in 80–90 per cent of patients with fungus allergy alone.

Which measures may be adopted to prevent allergic patients from inhaling fungi? The fact that the allergen-free rooms (*Storm van Leeuwen, Kremer*) have been successful, certainly was not only due to the change of the patient in a different environment; *van Genns* (1956) recently provided conclusive evidence of this. The dry room which contains little dust and is free of allergens, causes improvement, as any allergens injurious to the patient have been eliminated. This is the primary object to be attained in the home of the patient (cf. *Dekker*).

Moving to a dry house on sandy soil would appear ideal but this is frequently not sufficient. In moving, the patient carries various spores to his new home, along with his furniture, clothes, curtains and shoes. Therefore, before changing, the older home should be made rid of fungi. Favorable results can be obtained if *Kremer*'s measures, recommended as early as 1940, are adopted:

(1) there should be no decaying floors;

(2) walls should not absorb moisture; therefore, plastered and painted walls are to be preferred to wall-paper;

(3) ventilation under the floors should be adequate, as fungi detest draughts (wall-grids in winter should never be closed);

(4) heating facilities should be provided for in every room (i.e. either central heating or stoves);

(5) all rooms should be provided with an effective system of ventilation;

(6) all measures should be adopted in the control of other inhalant allergens.

What else should be advised to patients in whom the constant contact with industrial dust causes frequent disease and disability? These patients include bakers, weavers, those employed in the pharmaceutical industry, etc.

(1) they should work in well ventilated rooms, or,
(2) an attempt should be made to transfer them to other departments where the allergens to which the patients are sensitive, are absent or less common.

In extreme cases, a change in occupation should be indicated. It would even be better to be able to give preventive advice to the patient in choosing an occupation, so that possible causes of sensitization may be taken into account in the event of allergy.

House Dust

History.

Van Helmont (1644) observed changes in the clinical picture of asthma when the patient moved to another house or town. He also reported the appearance of status asthmaticus in a subject who inhaled large quantities of dust during work. *Trousseau* (1861) observed dyspnea in several patients following inhalation of house or industrial dust. *Kern* (1921) was the first to obtain positive tests using an extract of house dust; he recommended to make skin tests with this extract in all asthmatic patients. *Cooke* (1922) found the dust of certain houses to be capable of inducing asthmatic attacks in 33 per cent of 327 patients. In 1922, *Storm van Leeuwen* initiated the systematic examination of asthmatic and other allergic patients. Using allergenic extracts as recommended by Cooke et al., Walker and Coca, he obtained positive skin tests in 5 out of his first 18 patients, positive results being also obtained with animal dandruff, foods, drugs and bacterial products.

Composition.

House dust allergy is very common. However, the question remains: what is house dust allergy? Is it an allergy to the constituents of house dust, does the dust merely act as a physical stimulus affecting the mucous membranes, thus having the secondary effect of preparing the field for other allergens, or is there a house dust allergen occurring as a kind of aeroplankton?

This problem may be readily solved when house dust allergen exposure tests are made and both house dust and a number of other

substances (fungi, etc.) give positive results. However, how can house dust show a positive reaction when tests with all other inhalants have been repeatedly negative? There are patients whose symptoms show a marked increase in winter and during the annual spring cleaning. As a rule, most patients show a much stronger reaction to an extract of dust from their own home than they do to a universal house dust extract. Personal studies have shown that dilutions up to 1:1,000 are required to produce a similar skin reaction. The *house dust antigen* is composed of various substances, some of which may have an allergenic action. In addition to the still unknown substance X which may be called aeroplankton or true house dust allergen, it consists of house refuse particles, epidermal materials from domestic animals, fungus spores adhering to their hair, animal and human hair, substances from mites, moths, flies and other insects and bacteria, squamae from human skin, fungus spores, mildew of plants, pollens, camel hair, wool of carpets and drapes, dust from clothes, beds and pillows, street refuse, factory dust or other types of industrial dust, atmospheric dust. In addition, it contains all these dust particles from other houses and airborne particles from the outdoor air. Besides about 50 per cent of it is comprised of non-organic constituents.

Not all these particles are inhaled, however. One of the present authors provided conclusive evidence showing that so-called *coarse* house dust is not inhaled, only the smallest dust particles are; henceforth, only these are of importance as allergens in asthma and other forms of allergic diseases. Besides ubiquitous fungi, the coarse rough house dust from vacuum cleaners contains a large number of "dirt" fungi which are definitely not air-borne. In addition, this dust undoubtedly contains substances having a secondary irritating effect. Fine house dust is the air-borne dust in the atmosphere of rooms, the particles seen to float about in a sunbeam. It may be collected e.g. with a postcard after settling visibly on smooth surfaces, mantelpieces, pianos, cupboards and other furniture when a room has not been dusted for a few days. Only this dust should be used in the preparation of extracts.

Rimington et al. found the allergen of house dust to contain a polysaccharide complex and a peptide-bound amino-acid bearing a resemblance to substances present in the specific human blood groups. The same substances were also found to be secreted by certain species of *Penicillium* (*Rimington, Stillwell, Maunsell* 1947, 1951, 1954, 1955). *Maunsell* observed a marked increase in the incidence of house dust allergy in the immediate vicinity (about 100–150 m.) of open water, i.e. in a humid locality. This is not the only report on this subject.

Epidermal Allergens

Next to house dust, these are the most important allergens which do not depend on seasonal factors; next to pollen and house dust, they are also the most common allergens. As a rule, this form of allergy is more common in adolescents and adults than it is in children, as this group includes various types of occupational allergy.

Blackley reported his first experiences in cases of rabbit hair allergy well over 70 years ago; later, this report was followed by several others. *Storm van Leeuwen* and *van Niekerk* had observed that an extract of the squamae of human skin produced marked skin reactions in subjects hypersensitive to it, and though *Storm van Leeuwen* had previously found that 95 per cent of all individuals showed more or less positive responses to this type of extract, a long time elapsed before the clinical significance was recognized as to its true value.

In this connection, the question of human subjects reacting or failing to react to human squamae and human hair offers somewhat of a problem. How many epithelial squamae are pure, containing no admixture of toilet soap, perfumes or the like? Hair from hairdressing-saloons, can certainly not be utilized for this purpose.

Caution is also indicated in the evaluation of data concerning the animal epidermal allergens, as all these statistical data will depend on the district where tests have been made, the local flora, the habits of the population, the hygiene of the people etc., briefly, all these data are merely regional. In addition, the fact should be borne in mind that the patient need not necessarily be allergic to the animal epithelium concerned, but that the animal itself may have a diseased skin to which the patient is allergic.

Not only highly developed animals, but also *mites* may produce an allergic reaction, as was reported by *Frugoni* and *Ancona, Storm van Leeuwen, Varekamp* and *Kremer.*

As a rule, allergy to animal epidermal substances is only of importance when the patient lives in close contact with the animal concerned. When someone shows marked allergy to a certain kind of animal epithelium, this will be bound to occur in his environment; cow hair and hide are comprised in the fabrication of various articles (carpets), hog hair is used in making brushes (it is doubtful, however, whether this allergen is of much importance, even in rural districts), camel hair is used in brushes also and in woolens, goat hair is contained sometimes in shawls. Mouse and rat epithelium are only of importance in the case of laboratory assistants, physicians and pharmacists, although a few cases of allergy resulting from the

presence of rats in homes have been reported. Guinea pigs may also cause asthma, vasomotor rhinitis and urticaria in laboratory assistants.

Horses may be the cause of allergy in farmers, jockeys, horseback riders etc.; members of their family may occasionally show symptoms due to contact with their clothes.

Horse hair is a common element in the stuffing of furniture, mattresses and clothing. An important disclosure was the fact that 22 per cent of those showing a positive reaction to horse dander, also showed a positive reaction to horse serum antigen. Therefore, these subjects are very liable to present a shock following the first injection of serum.

Cats and dogs are particularly likely to sensitize human subjects. The allergen is highly specific in some cases, as was shown by *de Besche*'s experiment: (without knowing, a patient with cat hair sensitivity seated himself on a chair on which a cat had been lying shortly before; an attack of asthma followed immediately). *Walker* found patients with cat hair allergy to respond to cat serum in 70 per cent of the cases.

Rabbit hair sensitivity mainly occurs in dealers and laboratory assistants, though it is occasionally encountered by allergists, depending on the customs of the population. Rabbit hair is used for a variety of purposes, such as the manufacture of felt hats and many furs (red fox, leopard, seal, etc.) consist of dyed rabbit skin. Hunters may occasionally show allergic reactions to their game (deer epithelium, hare).

Sheep wool acts as an allergen only in the raw state, prepared wool has become unimportant to the allergist; on the other hand, wool may have a pronounced irritating effect. Owing to constant exposure, sheep wool may at times give rise to asthma in workers in the spinning industry; as a contact allergen, it may cause urticaria or eczema. Wool is a common product with which everyone comes into daily contact.

Feathers are used in large quantities in many homes, not only as fillings for cushions and pillows in living-rooms and bedrooms, but also in all sorts of household articles. The patients usually develop symptoms shortly after exposure, e.g. after making beds or during sleep. Feather allergy usually is not very species-specific, as a rule it is a group allergy, so that the various species (chicken, goose, etc.) need not be differentiated. Old feathers are more allergenic, probably owing to the addition of fungi or mites.

As an occupational disease, this form of allergy usually is due to the handling of uncleaned feathers containing moths, mites, bacillus subtilis, etc. The diagnosis is established on the history of the pa-

tient, skin tests and exposure. A positive skin test may frequently be associated with a negative reaction to the meat of the same species of bird; in that case, it may be consumed by the patient, provided the skin is removed prior to cooking.

Various Inhalant Allergens

Cottonseed: Diseases due to the seed of *Gossypium* are not very frequent in Europe. In America, there is a disease very common in certain districts, which is known by the name of "Byssinosis". This is an occupational disease mainly observed amongst cotton-mill workers.

In this case, the seed is the chief allergen and several tests show that this form of allergy is typically species-specific. The allergenic action is frequently increased by admixtures of fungi or mites. There would be no point in discussing Byssinosis, if the so-called first stage was not marked by several symptoms identical to those observed in all other spinning-mills. The course of the disease is characterized by 3 stages, of which only the first two are of some importance from the point of view of differential diagnosis.

The patients complain of coughing and a feeling of oppression during the first stage, especially on returning to the factory after an absence of one or two days. For this reason, the disease has been termed "Monday fever".

In the second stage, which does not occur until a few months later, the patient shows typical symptoms of chronic asthmatic bronchitis.

From cottonseeds, oil is obtained which is used as a substitute for olive oil in all sorts of foodstuffs such as salad oil, in the fish preserving industry, the margarine industry , etc. Cotton itself is often used in the manufacture of clothes, etc.

A fairly large number of allergic patients show positive tests to this substance. *Feinberg* reports positive tests in 4 per cent of his cases. It usually causes asthma or rhinitis, though contact dermatitis or allergic gastro-enteritis is not uncommon. Cotton itself rarely behaves as an allergen, whereas the seed is an extremely potent allergen. Cotton is closely related to kapok and several investigators have naturally been engaged in studying the problem of the action of those allied allergens. As early as 1925, *Coca* and *Grove* found the reagins to differ only to a slight extent; they found cottonseed to contain 2 allergens, one of which was related to kapok. *Dale* found 3 allergens occurring in both cottonseed and kapok. This problem, however, has not as yet been entirely solved.

In addition to skin tests, inhalation tests may also be used to determine whether sensitivity is present in these cases; the majority

of investigators regard inhalation as the best exposure test for this allergen.

Kapok: Only well-worn kapok will act as an inhalant allergen. Java kapok has been found to be the kapok best fit for use, although this plant grows in several tropical regions. As the fibres are too short for manufacturing purposes, it is mainly used as a filling for cushions, mattresses and toys. Especially when sterilized, fresh kapok provides a poor medium for fungi; in damp houses, fungi are liable to lodge in kapok, in which case they often cause attacks in asthmatic patients at night (*Storm van Leeuwen*).

Flax: Flaxseed, like kapok and cottonseed, is a potent allergen. Flax is distributed all over the world. It was used by the ancient Egyptians and to-day it provides the raw material for the manufacture of articles ranging from Belgian linen and Brussels lace to boot polish, printing ink, lotions and shampoos. It is not only taken as a laxative, but also as a food in certain districts (Abyssinia); in Western Europe it is a common constituent of animal nurture. Therefore, it is not surprising that isolated cases of asthma, dermatitis or allergic abdominal symptoms occur whenever patients eat, inhale or come into contact with substances containing flaxseed.

Silk: Silk allergy is not uncommon. Until recently, the importance of silk allergy was greatly underrated, as practically the only cases reported were cases of contact allergy (dermatitis, neurodermatitis) in which no skin tests were made. *Sericin* is the substance containing the active reagin. So far, it is unknown to what extent the hair and squamae of the silkworm may act as allergen. It is a fact that the allergenic potency of the pupa is ten times higher than that of the cocoon (Milford, 1931). The silk thread itself is inactive.

Asthma, vasomotor rhinitis, conjunctivitis and dermatitis are very common amongst workers in the silkworm industry. Twenty-five per cent of them show positive skin reactions to extracts prepared from raw silk or from the cocoon. Allergic symptoms and positive skin tests are also observed in workers in silk factories who come into close contact with sericin. The skin tests usually are outstanding in cases of true allergy. Outside of the specific industries, the incidence of allergy to silk is very slight.

Reference might be made here as well to the caterpillars of the brown-tail moths which inhabit the dunes of Western Europe and cause asthma and vasomotor rhinitis in a number of patients. Yearly, during a 3 to 4 weeks period, we see in our out-patient department patients whose symptoms are caused by this allergen. The symptoms occur when walks are taken on the dunes at the time when the caterpillars lose their hair.

Orris root: Orris powder is derived from the dried orris root. In

view of its pleasant violet scent, it had at one time been employed to a great extent in oil, tinctures, perfumes and cosmetics. Although it may cause dermatitis, patients sensitive to it are more likely to develop asthma or vasomotor rhinitis. Skin tests using extracts of orris root are positive in a fairly large number of cases. Depending on the method used in preparing the extracts and the point of view adopted by the investigator, skin tests are positive in from 7 to 20 per cent of the allergic patients examined. Naturally, positive tests are more common in women than in men, although the latter can come into contact with this substance when using various soaps, shaving creams, tooth powders, etc.

The difficulty in regard to cosmetics is that they contain a wide variety of ingredients, a large number of which are secrets of the cosmetic industries, and the manufacturers usually refuse to disclose the nature of these substances to physicians.

Pyrethrum is related to the chrysanthemum and belongs to a group of compositae, of which ragweed is a member. It is used in the manufacture of insecticides (Flit). Accordingly, elimination of the allergen is a fairly simple matter in the home, but these insecticides are often used in public places.

Chemicals are often capable of inducing attacks, frequently of the asthmatoid type. *Wood,* for instance, may have a chemical toxic action due to certain poisons and/or a sensitizing action caused by its resins, wood dust, the spores of *Merulius* or *Coniophora* and similar *Basidiomycetes,* by other fungi such as *Trichoderma, Absidia, Penicillium* etc. or by the metabolic breakdown products of these moulds.

Of the *bacteria,* we shall only name the hay bacillus, B. subtilis, which is very common in old bedding material (especially when the latter consists of straw, hay, seaweed etc.). *Mites* may also be of importance, as they are found in this type of material and also in the flour-using industries, grain silos and farms. The same is true of remnants of moths and flies in homes.

Accessory Factors which may Disturb the Allergic Balance

The severity of allergic symptoms may be influenced by various factors such as the level of atmospheric pressure, degree of humidity of the air, the temperature, rapid variations in temperature of the outdoor atmosphere, passing from the warm indoor air into the cold outdoors and vice versa, the mist, fog, rain, snow, direction and force of the wind, in brief, the entire complex of meteorological conditions which collectively might be called climatic allergy as such. These factors should be sharply differentiated from evanescent aller-

gens such as airborne particles of chemicals, all sorts of gases produced by putrefaction such as emanations from the soil, and also from chemical-irritant, chemical-toxic or chemical-toxic-allergic vapours and purely mechanical irritants which may give rise to disturbances such as bronchial spasms.

Atmospheric pressure: Floyer (1698) already had observed that frost in conjunction with a high atmospheric pressure had a favourable effect on asthmatic patients. A marked fall in atmospheric pressure exerted an opposite effect, even at high altitudes (*Avellis*, 1904; *Burckhardt*, 1932). There is positive evidence showing that changes in meteorological conditions bear an influence on some allergic patients.

In addition to atmospheric pressure, the *humidity* of the climate also plays a very important part, especially in connection with the temperature. *Floyer* found that his patients showed more symptoms in damp weather than during heavy rain storms; the symptoms were also seen to increase in patients living in damp chilly houses or in districts where the atmosphere was corrupted by vapours. *Hirsch* (1862) found the incidence of catarrhal conditions to be particularly high when the air was virtually saturated with steam and in districts where cold winds and changes in temperature result in rain, fog and dew. Certain individuals show a critical optimum in regard to humidity, both for high and, curiously enough, low levels. The fact, however, that a high degree of humidity promotes the growth of fungi might possibly be a secondary factor in bringing about this condition. *Evers* and *Schultz* (1934) observed that a fall in temperature, associated with relatively high humidity of the air, was followed by severe attacks of asthma in 25 patients in whom tests for inhalant allergens had been negative; the part played by other atmospheric disturbances in addition to the above factors is still open to question. According to *Kopaczewski* (1933), changes in the electricity of the atmosphere, frequently associated with a fall in temperature and increased humidity of the air, have a bad influence on bronchial asthma.

Landsman found inhalation of negatively ionized air to be successful in 64 out of 79 asthmatic patients and attributes the symptoms to changes in ionization of the air. *Haag* (1932–1933) observed that patients with hay fever mainly showed symptoms during or shortly after a lowering of barometric pressure. *Preuner* (1933) also found rapid changes of weather to have an unfavorable effect on asthma in guinea pigs. *Hansen* and *Michenfelder* (1930) gained the impression from skin tests in hay fever patients that a low degree of barometric pressure is associated with increased sensitivity of the skin and vice versa.

Heat, cold and sunlight may each give rise to allergic symptoms, especially when the patients have not yet become acclimatized to the sudden changes. These usually take the form of an urticaria or an eczema. Certain highly sensitized subjects develop their symptoms just after autumn, symptoms being absent during the cold winter period; others, however, show symptoms in severe cold only; in other words, some individuals are sensitive to abrupt transitions while others are sensitive to the cold itself. The former group even show symptoms in summer when swimming in cold water. Likewise, allergic patients may show reactions on the first warm days of spring or on entering a heated house during winter.

The above shows that *seasonal factors* obviously play a part in the outbreak of allergic symptoms. As early as 1644, *van Helmont* suggested that the variable weather in autumn (wind) might induce attacks of asthma; in particular, he claimed east winds to be responsible for these. *Bray* in 1934 concluded to same in England. *Salter* (1860) observed that low-lying humid districts with an abundant vegetation have an adverse effect on asthmatic patients. *Trousseau* (1861–1864) reported peaks of asthma to occur in Paris during the period from May to November. *Kuttner* (1904), *Avellis* (1904), *Siegel* (1912), *Grimm* (1928) and others observed that some patients with bronchial asthma were more liable to present symptoms in coastal districts, whereas others do so in the interior of the country. Asthma is also more common in foggy lake districts or humid forest areas.

Moving from these areas to dry districts or high mountains, frequently results in suppression of the attacks. In addition, several inhalant allergens are absent at high altitudes and mental factors undoubtedly play a part as well, (leaving the environment which causes distress, resting, fewer or no further worries concerning their work, marriage, children, etc.). There is the striking fact, however, that this improvement does not become noticeable until the patient has reached a certain altitude above sea level; in Switzerland above 800 m. (*Storm van Leeuwen,* 1924), in Norway above 300 m. *(Bruun* and *Kjems*). *Spoujitch* and *Danilovitch* (1950), observed that asthmatic patients failed to show any improvement in the humid mountain regions of Yugoslavia, whereas they gained rapid relief in mountains where the air is dry. It should be noted that fifty per cent of the patients develop symptoms again on returning to their previous environment (*Turban* and *Spengler,* 1906).

Despite migration to high mountains, patients continue to be sensitive to climatic variations, even at high altitudes, where occasional attacks were seen to occur following marked changes in atmospheric pressure, changes in wind direction, sudden falls in

temperature, wet spells of snow, rain or fog. In the above, reference has been made to a large number of publications concerning this subject. These are merely a few of them; from *Hippocrates* to the present time, a large number of diseases have been found to be influenced by seasonal changes and climatic variations.

With *Preuner* it may be concluded that a whole set of atmospheric conditions is essential to induce any changes in the sensitivity of the subject to inhalant allergens. Besides these climatic variations (humidity, sun, wind, temperature), the altitude above sea level, the emotional state, the specific inhalant allergens present in the air (which might be called aeroplankton), the amount of dust, the diet and the physical resistance of the individual all play their part in upsetting the unstable balance in allergic patients.

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PATHOPHYSIOLOGY OF BRONCHIAL ASTHMA

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The term "pathophysiology of bronchial asthma" requires definition. Bronchial asthma is a disease of the bronchial tree which interferes with ventilation, and, eventually, with the free exchange of oxygen and carbon dioxide. Prolonged interference and, perhaps even more, the compensatory efforts of the body, produce local and systemic changes. The systemic changes include cardiac stress and, conceivably, cardiac failure, secondary polycythemia, and anoxia in tissues; changes in the lung itself alter bronchi, and lead eventually to selective destruction of their components: mucous membranes, glands, smooth muscles, elastic fibers, vascular bed, and autonomic nerves. Since structure and function of the lung are profoundly altered in bronchial asthma, the term "pathophysiology of bronchial asthma" is often applied to disturbed ventilation and respiration rather than to the pathophysiology of the underlying disease. Yet, while dyspnea, cough, and wheezing are part of the asthmatic syndrome, non-asthmatic lesions in the chest can produce similar impairment of ventilation and respiration. Fox (1) has expressed the complexity of our efforts to define even the most common denominator of ventilatory and respiratory disorders, dyspnea:

"... Actually, the mechanism of dyspnea is difficult to establish, and is fraught with unknowns. Dyspnea is produced when unknown stimuli act on unknown receptors in the lung which stimulate unknown afferent pathways to act upon an unknown center in the brain.

Thus, no single test can evaluate respiratory function as entity. We have tests that measure ventilation (vital capacity, timed vital capacity, maximum breathing capacity), distribution of gases within the lung ('nitrogen washout'), diffusion of gases across the alveolar-capillary membrane (alveolar O_2 and CO_2 tensions), and circulation, i.e., the differential blood flow to the alveoli. 'Breathing' is work performed against compliance of the lung, nonelastic tissue resistance, and resistance to the flow of air within the bronchi. Each constitutes a variable and all our tests still cannot answer the fundamental question: 'What causes dyspnea?' "

Each of the changes in the factors enumerated by Fox may occur in bronchial asthma; none occurs in bronchial asthma alone. With deliberation, therefore, this review separates the factors which are an integral part of the etiology of bronchial asthma from the changes in ventilation and respiration which are only incidental to the primary lesion and might well be produced by a non-asthmatic disease.

One of the stumbling blocks in our progress in understanding the pathophysiology of bronchial asthma is, strangely enough, the fact that it is possible to reproduce, in experimental animals, conditions which resemble bronchial asthma. A review of papers which have been written during the past thirty years suggests that the interpretation of symptoms of bronchial asthma in man was patterned by the symptoms of the anaphylactic shock of the guinea pig; and that the sequence: injection of antigen—formation and distribution of antibodies—reinjection of antigen—release of histamine broncho-constriction and broncho-obstruction—dominated both investigative approach and clinical practice. Certainly, the sequence exists in man and needs further analysis; yet the clinical entity, bronchial asthma, differs so significantly in many of its aspects from the induced broncho-constriction of the guinea pig that it will be the objective of this outline to emphasize the differences rather than the similarities.

It is certain that Rackemann (2) in his classical review of 648 cases of bronchial asthma felt the need for a revision of these simple concepts when he assigned the terms "complicated", "reflex", and even "unclassified" bronchial asthma to those patients whose symptoms would not fit into any of the existing categories. He was careful indeed in stating that some of his suggestions were made on an empirical rather than scientific basis, but he recognized clearly that the term "bronchial asthma" was loose and ill defined; that there were at least two distinct groups of bronchial asthma: those sensitive to foreign protein and those apparently non-sensitive; and that the recognition and the differential classification might be complicated by what he called "the line of organic change", which included primary pulmonary emphysema, secondary pulmonary emphysema, and myocardial insufficiency.

It might be necessary to emphasize the difference between pathophysiology and clinical classification of bronchial asthma. Rackemann's efforts lead to the differentiation of "extrinsic—allergic bronchial asthma" and "intrinsic bronchial asthma": an illness of "mixed causes" (3, 4). Unfortunately, Rackemann's valid distinction has been adopted by many of his followers without Rackemann's ability to differentiate his patients by a set of rigid standards. As a result, "extrinsic bronchial asthma" has been used often synonym-

ously with "reversible bronchial asthma", "intrinsic" with irreversible bronchial asthma"—this of course does not contribute to our insight into the pathophysiology of the disease.

Histological evidence that bronchial asthma represents not one, but at least two, clinical entities was presented by Huber and Koessler (5), who described the autopsy findings on twenty-one patients who had died during acute episodes of bronchial asthma. The authors acknowledge the existence of the hypertrophy of smooth muscle fibers but feel that the significance of a narrowed lumen and of the folding of the mucosa (while present) is uncertain; and conclude:

"... In only one disease, bronchial asthma, does a blood, sputum and tissue eosinophilia occur simultaneously. The eosinophilic infiltration of the bronchial wall in asthma is a characteristic histologic criterion of bronchial asthma, but if absent it does not exclude asthma. Since eosinophilia is regarded as one of the chief clinical and pathologic symptoms of allergy, its constant absence in certain forms of bacterial asthma is regarded as one important part of evidence that there are types of asthma which may not be of allergic origin. This form may be regarded as due to an intoxication with peptones or amines, bronchospastic poisons, which are formed by the action of micro-organisms on tissues."

Since the publication of these early papers, investigators have, as a rule, accepted the existence of two types of bronchial asthma, but leaned, without much evidence, toward one type or toward the other. Authors who deal with experimental bronchial asthma tend to emphasize sensitization mechanisms.

Kallós and Pagel (6) induced bronchial asthma by nebulized antigen in guinea pigs; Herxheimer (7) in man; and Ratner (8), who reviewed the existing evidence in recent years, concluded that repeated inhalation of specific antigens produces chronic allergic respiratory states which are indistinguishable in the two species. Clinicians have been inclined to consider bronchial asthma, by definition, an allergic disease; Jiménez-Díaz (9), on the other hand, emphasizes that the "disreaction" which is responsible for the clinical symptoms is based in less than twenty-five percent of the patients on an antigen-antibody mechanism.

Jiménez-Díaz asks the obvious question: does this mean that we do not recognize the antigen-antibody mechanism in the remaining 75 percent? Or, does it mean that they are based on a mechanism other than sensitization?

It might be well to examine, first, the pathophysiology of clearly allergic bronchial asthma. The evidence which is now available makes it necessary to accept a number of premises, e.g. the existence of a distinct group of individuals who are able to develop, after exposure by natural routes, such as inhalation or ingestion, antibodies

to substances which are innocuous for the rest of the population. The mechanism of this peculiar ability is not known; but most authors agree that it represents an inherited Mendelian trait. It is confusing that this trait Coca's "atopy" (10) refers, in infancy, to complete antigens, such as egg or milk, which would be antigenic, if injected, even for non-atopic people; that during the years of childhood sensitization to food becomes less and less common; and that by the age of six years sensitization is, more often than not, limited to inhalants which are virtually non-antigenic for non-atopic persons; the antigenicity of ragweed pollen, for instance, is low except for ragweed-sensitive individuals. It is tempting to assume that these particular atopic antigens—"allergens"—are haptens, which require a tissue moiety to become full antigens, and that it is this hypothetical -tissue moiety which distinguishes the atopic from the non-atopic individual. It has been suggested that non-atopic individuals might be susceptible to "atopic" sensitization if severe nasal infection or nasal injury, during a season of maximal exposure, might furnish breakdown products of nasal mucous membrane capable of chemical conjugation with the inhalant—atopic—antigen: such a fortuitous factor would explain the occasional presence of "atopic disease" in non-atopic persons.

It seems likely that we have underestimated even in atopic individuals the role of the fortuitous factor in the etiology of allergic bronchial asthma. It has been assumed that atopic individuals will form antibodies if they are sufficiently exposed to an allergen. Actually, this is only partially true. Atopic patients may be quite selective in their sensitivity: we have wondered, previously, why in the United States "ragweed is probably the most potent of airborne allergens; yet, one observes many atopic patients who are sensitive to environmental inhalants or to airborne allergens other than ragweed, even if they have spent every hay fever season in this area and have had ample opportunity to develop a ragweed sensitivity" (11).

Hansen (12) expresses a similar thought when he states that "... Inherited traits become manifest only when postnatal physiological stimuli have produced the appropriate reactivity. Such stimuli differ in different patients and different diseases. Exposure to antigen is a condition *sine qua non* in allergic diseases. Massive onslaught of inhalants on the respiratory tract creates the organ specificity. Frequent exposure, large doses, strong antigens, and concomitant irritants which favor penetration of the antigen by mechanical or chemical means favor sensitization."

The presence of antibodies in so-called shock tissues is necessary before antigen-antibody reactions—and, accordingly, clinical symp-

toms of allergy—can occur. The presence of antibodies, on the other hand, produces "sensitized" tissues but not necessarily "shock tissues". Patients who are sensitive to seasonal inhalant allergens carry antibodies in the skin; yet, it is the exception rather than the rule to observe an adult skin that participates in seasonal allergies, e.g. a seasonal urticaria.

It is unlikely that the localization of tissue reactions in the inhalant-sensitive individual is proportional to the degree of exposure. Certain exquisitely sensitive allergic individuals will suffer none but nasal symptoms; while others of moderate sensitivity might suffer from severe bronchial asthma after comparatively mild exposure. In other words, sensitization and re-exposure alone is not sufficient to explain the clinical course of bronchial asthma. The allergic individual must be distinguished not by one, but by at least two inherited traits, the first trait which permits the formation of antibodies to atopic antigens; and a second trait which determines the tissue in which symptoms will occur. The first trait has been known and recognized for many years. Awareness of tissue specificity is of relatively recent origin. It is true that most allergic individuals have been shown to react, at times interchangeably, in more than one shock tissue; on the other hand, we have seen atopic patients who have not only a family history of atopy, but quite often a family history of allergic reactions in the same organ; in other words, we have eczema families, hay fever families, families prone to develop bronchial asthma.

In preceding paragraphs it has been stated that antibody-containing tissues are not necessarily shock tissues. Recent studies with isotope-labelled antibodies (Talmage) (13) suggest, in fact, that their distribution might be rather uniform, but that clinical symptoms are restricted to tissues which are able to liberate chemical mediators, e.g. histamine, subsequent to antigen-antibody union. If, as we have shown, certain tissues—despite their ability (1) to fix antibodies, and (2) to release histamine—fail to participate in allergic reactions after re-exposure to a specific antigen, one wonders how they are protected. Of several possible mechanisms, the capillary endothelium might be the most likely site of protection. The infrequent occurrence of seasonal urticaria, or, more strikingly, the relatively infrequent occurrence of urticaria as a complicating "constitutional reaction" after injection of extracts of seasonal allergens might be due to the fact that the extracts bypass the skin, or rather, circulate through it without establishing contact with the antibodies—reagins —which are fixed in the subepithelial layer. The capillaries of the respiratory tract, on the other hand, might lack such protection. Injected antigen will then readily pass through the capillary barrier

and induce almost immediate antigen-antibody union and potentially the same clinical symptoms which are otherwise the result of extrinsic exposure; in other words, the "constitutional" reaction is not a constitutional reaction but a focal reaction in tissues which represent the site of the allergic disease in any particular individual.

It might be well to analyze step by step the sequence which leads to bronchial asthma. It seems certain that antibodies are fixed in the bronchial mucous membrane although recent experiments by Germuth and McKinnan (14) indicate that fixation is not a prerequisite for allergic symptoms: injection of a soluble antigen-antibody complex into normal non-sensitized animals might, without previous fixation, produce instantaneous symptoms of broncho-constriction and broncho-obstruction. The antibody is exposed to the specific antigen—as a rule, by inhalation: the antigen -antibody complex activates a non-stable enzyme (Mongar and Schild) (15), which in turn releases histamine from an inactive form into an active state. Histamine then exerts its pharmacological action: constriction of smooth muscles, increase in capillary permeability, and stimulation of mucous secretion, i.e. experimental or clinical bronchial asthma. Until recently, the liberation of histamine which follows antigen-antibody union has been considered a fairly specific phenomenon. It has been known, of course, that physical stimuli, e.g. scratching, can induce Lewis' triple response; that this physical release can be exaggerated so that mild pressure produces rather large exudates and synovial reactions; that cold and heat are able to activate the enzyme in certain predisposed individuals. Only during the last decade, however, a variety of polymers, which include plasma substitutes, such as dextran, polyvinylpyrroline (PVP), and a condensation product of p-methoxyphenyl-ethylamine and formaldehyde, known as compound 48–80, were found to release histamine from its storage, not in every, but each in several species. Moreover, it has been shown by Halpern (16) that the store of available histamine can thus be exhausted; and that exhaustion will effectively prevent the subsequent release of histamine by an antigen-antibody complex. Schachter (17) suggested recently that reactions caused by certain offenders, e.g. strawberries, might "not involve an antigen-antibody reaction. The findings that many of the offending agents possess the property of releasing histamine indicate the existence of a pharmacological basis for a possible additional mechanism." This is an attractive proposal but requires the additional hypothesis that patients who respond to the ingestion of strawberries with increased capillary permeability must have some additional reasons for it, since only a small fraction of the population suffers from urticaria after eating strawberries. It is obvious then that the severity of an antigen-antibody reaction

does not only depend on the amount of antigen which is brought in contact with fixed antibody (although this correlation is surprisingly good in patients who suffer exclusively from seasonal bronchial asthma) but also on the amount of available histamine, which may vary and which, as studies on histamine releasers have shown, can conceivably be brought down to zero. Schayer's (18) interesting studies with C^{14} labelled histidine and histamine show that, in the species which he has used, rats, radioactive histamine is rapidly excreted in the urine; but that radioactive histidine is stored in tissues for many months and probably available for decarboxylation to histamine. In Schayer's opinion "all the histamine bound in the organism, arises from histidine. I do not believe that the exogenous histamine is picked up by tissues." Histidine, of course, is a readily available raw material: it is ingested as part of several proteins, and probably synthesized by the gastrointestinal flora. One might speculate that the severity of bronchial asthma in a patient who suffers from chronic perennial bronchial asthma could be proportional to his intake of histidine in his diet or to the production of histidine by his gastrointestinal flora—a possibility which deserves further investigation.

It is still a matter of debate (a) where antigen-antibody reaction takes place within the shock tissue, and (b) where histamine is stored and released. Examination of tissue sections prepared by Warren and Dixon (19), who sensitized and shocked guinea pigs with I^{131} labelled globulin, suggest that the connective tissue proper is the site of the antigen-antibody union and, as it were, of the release of histamine. If this is correct, the state of a connective tissue, which acts as carrier for both the antigen-antibody reaction and the histamine system, will be an important factor in the distribution of histamine after its release and in the ensuing response of mucous glands, smooth muscles, and capillaries, which are "indicator tissues" rather than shock tissues. The ground substance of the connective tissue represents an intricate system of highly aggregated water and alcohol-insoluble mucoproteins—negatively charged colloids, which function as exchange resins for cations (Catchpole) (20). Under certain conditions, which include antigen-antibody reactions, this matrix can become less aggregated and water soluble—this, of course, will alter profoundly its physiological properties, e.g. its ability to take up molecules by combination and ions by virtue of its ability to function as an exchange resin. "Normal" ground substance might prevent the distribution of histamine quite effectively, while water-soluble ground substance might encourage its diffusion. Non-allergic factors which act on the structure of ground substance, for instance, stress and hormonal stimulation, might explain the known increase in sus-

ceptibility of allergic individuals during periods of tension or during the pre-menstrual increase in the titer of circulating gonadotropin.

It has been known for many years that patients who suffer from bronchial asthma, not only release histamine from their bronchial mucous membrane, but that they have also a very low tolerance for minimal concentrations of histamine administered by aerosol. Concentrations of nebulized histamine which fail to produce any significant changes in the ventilatory function of normal individuals, produce severe changes in the patients who suffer from bronchial asthma. (Samter) (21).

Increased permeability of the connective tissue is only one of the possible explanations of its failure to control the diffusion of histamine after activation. Inactivation of histamine by diaminooxidase (DO) is rapid. A positive skin test in an allergic individual tends to disappear within thirty minutes. A deficiency in the enzyme might readily explain persistent activity of histamine. The effectiveness of diamino-oxidase is not readily measured, however, and its action more complex than previously suspected. Zeller's (22) studies, for instance, permit him to suspect "that the first step in the degradation of a diamine consists of a non-oxidative deamination, which is followed by the oxidation of the intermediary product."

Of the so-called chemical mediators (Feldberg (23)) histamine has received the lion's share of attention in the study of bronchial asthma. The exact mode of its release is still uncertain. Ungar (24) believes that the chemical mediators which are active in the etiology of the allergic syndrome are liberated by a series of reactions which involve the fibrinolytic system. "The allergic stimulus (antigen-antibody reaction or its equivalent) activates a kinase system which may be identical with or closely related to the complement. The activated kinase converts the enzyme-precursor, profibrinolysin, into the protease, fibrinolysin. This enzyme, in turn, liberates the active substance by breaking up certain proteins."

MacIntosh (25) has recently proposed an interesting theory. It has been known for some time that other tissue hormones, for instance heparin, are also released during certain antigen-antibody reactions. It seems possible that histamine, a small molecule, is held in place by the large acid mucopolysaccharide, heparin; that histamine liberators are, in truth, heparin liberators: ". . . they are accumulated by mast cells in consequence of their affinity for heparin; the heparin-liberator complex increases the permeability of the mast cell granule; free histamine contained within the granule then diffuses out." a concept which has gained a good deal of acceptance since it has been demonstrated that mast cells, prominent holders of heparin, are readily destroyed by exposure to histamine releasers. It is un-

likely that heparin plays a significant part in the pathophysiology of bronchial asthma; but another tissue hormone, 5-hydroxytryptamine, appears to have a considerable potential as a possible etiologic factor. 5-hydroxytryptamine—serotonin—has been known for many years, but until recently, little attention was paid to its potential effect on shock tissues. The mechanism of its action is not clear. Herxheimer (26) and later, Bhattacharya (27) presented convincing evidence that 5-hydroxytryptamine constricts smooth muscles, but their efforts to analyze biochemical pathways through the protective use of selective antagonists—including antihistamine drugs, anticholinergic drugs, dihydroergotamine, lysergic acid diethylamide, and inhibitors of adrenergic impulses—need further extension. Benditt, Bader and Lain (28) demonstrated—in another tissue, another species—that the edema-producing effect of one gamma of 5-hydroxytryptamine equals that of fifty gamma of histamine. In more recent experiments Weissbach, Waalkes, and Udenfriend (29) measured the content of serotonin and histamine in the lungs of various species, and found:

"... that guinea pig lung contains little if any serotonin, whereas mouse lung contains relatively large amounts. It is known that mouse lung contains little histamine, whereas the histamine content of guinea pig lung is relatively high. These findings may explain some interesting observations that have been made in the past. Thus, in guinea pigs, the pulmonary aspects of anaphylactic shock appear to be completely explained on the basis of histamine release, and antihistaminic agents can block the effects almost completely. On the other hand, antihistaminic agents have little influence on anaphylactic shock in the mouse."

It is interesting to speculate whether man, as a species, resembles, in his pulmonary serotonin pattern, mice, rabbits, or guinea pigs. The question remains to be solved; in our own studies we have been unable to block clinical bronchial asthma with any of the known serotonin antagonists.

It seems possible, even likely, that other, still unidentified, chemical mediators might participate in the etiology of bronchial asthma. Brocklehurst (33), for instance, extracted a "slow reacting substance"—SRS-A—from the lungs of sensitized guinea pigs, after reinjection of the specific antigen, which "develops as a result of the union of antigen with fixed antibody." In his conclusions Brocklehurst emphasizes the species specificity of SRS-A, which constricts human bronchioles at dose levels which fail to yield significant responses on isolated bronchial muscles of cat, dog, rabbit, and guinea pig. "From the facts presented, it would appear that SRS-A is of particular importance in human asthma, a condition in which the antihistamine drugs have proved to be relatively ineffective."

The existence of so many different chemical mediators raises a question. Bronchial tissue has a limited capacity to respond to sensitization and re-exposure, but the response is not uniform. Bronchial asthma, in fact, might represent a composite of several possible responses. The final, "clinical", injury, therefore - the readily reversible reaction of smooth muscles and mucous glands, on the one hand; on the other hand, the probably less reversible edema and the cellular pattern of the bronchial tissue—might reflect the nature of the antigen, the nature of the antibody, or certain qualities of the antigen-antibody complex, which might be more specific than we are now willing to assume.

The "indicator structures"–mucous glands, smooth muscles, and capillaries—which represent the final link in the chain which leads to the clinical entity of bronchial asthma, are subject to autonomic control. Parasympathetic impulses induce broncho-constriction and secretion of mucous. The effect of histamine on these structures is sufficiently similar to the effect of the parasympathetic mediator, acetylcholine, that it has been suggested that histamine might activate acetylcholine; and that acetylcholine is the final "etiologic" enzyme; this, however, has not been confirmed. Histamine, itself, has been classified as a transmitter substance of nervous impulses (Rothlin and Berdi) (30) but the existence of a "histaminergic" system is open to question. The relationship of the multitude of potential chemical mediators—a problem which Rocha e Silva (31) has labelled the "autopharmacological problem in anaphylaxis and allergy"—remains an investigative challenge, although advances have been impressive. In 1941 Dragstedt (32) outlined the task ahead of us: "The mechanism by which the antigen-antibody reaction leads to the rather special type of cell injury resulting in the discharge of the agents characteristic to the anaphylactic reaction brings the next challenge in the study of this interesting subject, but there is considerable satisfaction in being able to discard the various esoteric speculations regarding the pathogenesis of the symptoms." It is gratifying to ascertain how much has been discarded, how much has been added during the sixteen years which followed the publication of Dragstedt's review.

The autonomic state of the indicator structures at the instant at which they are exposed to a chemical mediator, e.g. to histamine, might well determine the extent of the clinical manifestations of bronchial asthma. Mucous glands and smooth muscles under strong parasympathetic influence might react readily to histamine, while indicator tissues under predominately adrenergic control might resist the "parasympathetic" effect of histamine, and require much larger doses of histamine before sympathetic resistance is overcome.

If so, a sudden shift in the direction of the autonomic trend from sympathetic to parasympathetic might have a profound effect on clinical manifestations: this seems to be the most logical explanation for the accepted experience that emotional conflicts Blackley's (34) "nervous diathesis"—might modify the clinical course of the disease.

The prevalence of autonomic—sympathetic versus parasympathetic—impulses which affect indicator structures varies from individual to individual, and, moreover, in the same individual, with the varying demands of the environment. Eppinger (35) felt so strongly about the importance of autonomic regulations in the allergic syndrome that he classified allergic individuals as vagotonic individuals, allergic diseases as vagotonic diseases; this, in our opinion, goes too far. It is rather well established, on the other hand, that the responsiveness to histamine of mucous glands, smooth muscles, and capillaries increases during periods of rapidly changing autonomic adjustment.

Year after year, allergists in practice are confronted with the practical significance of this concept. The height of the ragweed pollen season in the area in which the author lives—the American midwest— occurs, as a rule, around Labor Day; in other words, during the first three days of September. At this time, however, the incidence of bronchial asthma is not high. The incidence rises abruptly five or six days later—toward mid-September—when the pollen count is much lower, but the cold fronts begin to move from the northern plains toward Illinois.

The Japanese school in particular has emphasized the possible role of acetylcholine in the pathophysiology of bronchial asthma. Nakamuro and his co-workers (36) demonstrated that circulating acetylcholine rises in sensitized guinea pigs after injection of the specific antigen; and that the rate of anaphylactic death is enhanced by the administration of parathyion which prohibits the inactivation of acetylcholine by cholinesterase. Nakamuro concludes that allergy and anaphylaxis are the result of specific reactions between antigen and antibody; that anaphylaxis and allergy produce effects which are virtually identical with effects produced by the autonomic nervous system and that the evidence implicates acetylcholine as the mediator of the sequels of the antigen-antibody reaction.

Since acetylcholine can duplicate the effects of histamine, it is interesting to speculate whether bronchial asthma could not conceivably originate on the basis of a purely cholinergic mechanism. Strangely enough, the concept has met with considerable resistance. Hansen (12) for instance, states: "In non-allergic types of bronchial asthma sensitization would by definition not be part of the pathological mechanism; but it is difficult to prove that allergens do not

participate in 'asthmatization'. It is my own personal opinion that they can never be ruled out."

Discussions of the possible role of acetylcholine in the etiology of bronchial asthma—much more commonly, by the way, than discussions of so-called cholinergic urticaria—tend to raise the question why symptoms caused by the release of acetylcholine fail to respond to the administration of atropine sulfate. The argument is open to debate. Few physicians will muster sufficient courage to administer large doses of atropine sulfate during acute episodes of bronchial asthma. Moreover, acetylcholine might exert at least part of its action through its nicotinic rather than its muscarinic component. The effect of atropine on the vascular bed—including the anomalous vascular response to atropine sulfate mentioned by Goodman and Gilman (37)—is still largely a matter of conjecture.

The assumption that bronchial asthma may be produced by acetylcholine requires at least two auxiliary hypotheses. The first of these hypotheses localizes the impairment of the acetylcholine-cholinesterase system: since the cholinergic effect is limited to the respiratory mucous membranes while other tissue under parasympathetic control show normal physiological behavior, the disease must be a disease of the respiratory tissue proper, not of the entire parasympathetic system. This is in keeping with Feldberg's (38) emphasis on the fundamental difference between the sympathetic and parasympathetic systems. The so-called balance, the antagonism, of the two systems may not exist: the sympatho-adrenal system may act as an entity, but the action of the parasympathetic system is localized within each of the tissues which it supplies.

The second hypothesis must explain the nature of the impairment—either a release of an excess of acetylcholine or a failure of cholinesterase to neutralize physiological levels of acetylcholine which has been set free from its inactive state. Atropine sulfate should, and will, inhibit smooth muscle constriction and secretion of mucus induced by acetylcholine. Should the essential phase of cholinergic asthma, however, be due to vascular reactions and to a resulting edema of bronchial tissue there would be little reason, if any, to expect a reversal of such edematous changes by atropine sulfate. In other words, if acetylcholine-induced bronchial asthma does exist, tissue edema should be its most impressive manifestation.

Studies which we have carried out since 1951 on more than 240 patients suffering from "intrinsic bronchial asthma" have led us to believe that the characteristic triad—nasal polyps, bronchial asthma, and aspirin sensitivity—which develops, late in life, in non-allergic individuals, might be based on a cholinergic, rather than a histamine-releasing mechanism. It is our impression that this group of patients

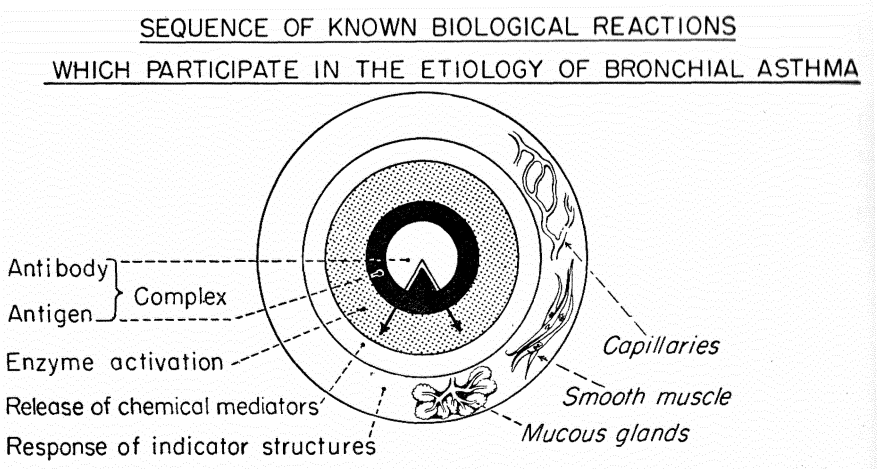

Fig. 1.

represents a separate entity which, although clinically similar to bronchial asthma of allergic origin, is a disease of different etiology and of a different course. If our reasoning is correct, this particular syndrome which originates at the receptor sites of the indicator tissues would be the only truly "intrinsic" bronchial asthma.

The pathophysiology of bronchial asthma is a complex process. It is perhaps only human to respond to its complexity by the attempt to simplify each of its phases, in anticipation of future experimental work. Talmage (39), for instance, who is aware of the large variety of allergic reactions, states, in his excellent review of the mechanism of allergic injury, that "the particular mechanism involved in any case probably depends largely on only three major components of the reaction: the allergen, the antibody, and the cell[1]." Similarly, Feldberg—in the lecture which I have previously cited—charts some of the vexing mysteries of the physiology of the autonomic nervous system; but he concludes his talk with Cannon's (40) reassuring interpretation that "the sympathetic is like the loud and soft pedals

[1] Talmage then proceeds, of course, to outline the potential of each of the three components:

"The allergen varies in physico-chemical property, affinity for cells and other tissue components, valence, distribution, rate of metabolism, toxicity of breakdown products, and ability to stimulate antibody production. The antibody varies in physico-chemical properties, valence, affinity for antigen, distribution in the body and rate of metabolism. Since the resulting antigen-antibody reactions vary in their secondary manifestation such as hemolysis or complement fixation, it is highly probably that they also vary in their ability to produce any type of cell injury. Cells, on the other hand, vary in the threshold of response to injury, and in the degree and quality of symptoms by which that response is manifest."

modulating all the tones together; the parasympathetic like the separate keys." With a feeling which must be akin to the feelings which have motivated Talmage and Feldberg, I have prepared a schematic drawing (Figure 1) which summarizes the areas of this discussion.

It has been the purpose of this review to define the questions which must be answered. It seems likely that we shall gain in the understanding of the pathophysiology of bronchial asthma more rapidly than before, particularly since biochemical contributions have made it possible for us to inhibit selectively more and more enzyme systems at will. Even so, we are in the dark about some of its outstanding features: we have yet to understand, for instance, the cause of eosinophilia. Eosinophils are formed in nasal and bronchial tissues after certain antigen-antibody reactions have taken place; but neither antigen nor antibody alone, neither histamine releasers nor histamine itself, nor antihistamine drugs, nor any other chemical mediators which are released during antigen-antibody reactions have induced eosinophilia in experimental animals. Function and fate of eosinophils are still unknown (Samter) (11, 12). In this area, as in most other areas which are linked with the pathophysiology of bronchial asthma, a great deal of investigative work is now in progress.

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CLINICAL ASPECTS OF BRONCHIAL ASTHMA

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The most frequent and disabling allergic manifestation is without doubt asthma. The term is derived from the Greek word ἀσθμα, meaning "gasping for breath". In literature, asthma is variably considered as a symptom, a symptom complex, a syndrome or a disease. There is, however, a general agreement in current literature that there exists a "type of illness" referred to as "asthma" or "bronchial asthma" which consists of recurrent attacks of dyspnea and wheezing due to a functional bronchial and especially bronchiolar obstruction, caused by edema, spasm and secretions; which develops spontaneously in those with a hereditary predisposition and is often accompanied by other naturally occurring allergic manifestations such as hay fever, urticaria, atopic dermatitis, migraine etc. (24).

THE ASTHMATIC ATTACK

a. *Precursor symptoms.*

During the hours or days preceding the dyspnea many patients suffer from rhinitis, particularly when inhalants are responsible for the attacks. They complain of frequent sneezing spells, accompanied by copious watery secretion and an itching of nose and eyes, while at other times the nose is so obstructed that nasal breathing becomes impossible. These symptoms are often accompanied by a dry, unproductive cough and an itching sensation in the throat.

Occasionally, when foods are the causative agents, the precursor symptoms involve the gastro-intestinal tract. Prior to the onset of the attack the patient may feel a flatulence, indigestion, or an epigastric or abdominal pain, at times accompanied by a burning feeling or a diarrhea.

Others experience during this period a general fatigue, irritability,

depression, headache, a burning sensation in the chest or an itching of the skin, particularly on the thorax.

Some patients are invariably aware of an oncoming attack, and parents can often predict the approach of one in their asthmatic child. In others, precursor symptoms may be entirely absent.

b. *Dyspnea.*

The shortness of breath rarely reaches its full severity at once. In the beginning the patient may feel a sensation of tightness or compression in the chest, lasting from a few minutes to a few hours. This sensation is felt throughout both lungs, although it may be confined to the retrosternal area. Gradually the breathing becomes more difficult until finally in severe cases the patient begins struggling for air.

When suffering his first attack he usually jumps out of bed and throws open the windows. By experience, however, he soon learns that the best way to combat his shortness of breath is to remain as quiet and motionless as possible. He then sits on the edge of bed or chair, often in a typical position with body bent forward, back rounded, shoulders squared, forehead resting on closed fists while the elbows are firmly fixed on his knees. If the dyspnea is very severe, he keeps his arms rigidly in extension, firmly clasping bed or chair in order to fix the shoulders and facilitate his respiration. The collar is opened and any tight-fitting clothing is loosened or removed. His expression is one of anxiety, the skin cold, pale, occasionally somewhat cyanotic with drops of perspiration appearing on the forehead. The neck veins are engorged and cervical, intercostal and abdominal muscles are contracted. He usually does not talk or responds only in broken phrases. The thorax moves rigidly up and down, is distended, and only slight expansion can be noted on respiration. The respiratory rate is accelerated, the expiratory phase prolonged, and the normally existing pause between in- and expiration is almost non-existent.

Either spontaneously or through the effect of medicaments he has taken in the meantime, the dyspnea diminishes progressively, and the patient once again experiences the comfortable feeling of the air passing effortlessly through his bronchi. During the night he can lie down again and endeavour to fall back to sleep.

c. *Wheezing.*

The wheezing consists of whistling and sibilant sounds audible during in- and expiration. Sometimes they are so discrete that they

can be heard only on auscultation of the chest, while at other times they are so accentuated that they are audible at some distance. Generally as the dyspnea increases, the wheezing is also more pronounced, although in very severe attacks, which involve a nearly complete bronchiolar obstruction, the wheezing may be less audible or even be absent.

The wheezing is produced by the passing of air through the narrowed bronchi and the vibration of the viscid bronchial mucus adhering to the walls.

d. *Cough.*

A dry unproductive cough precedes the acute paroxysm in many cases. In the beginning of the attack the cough tends to aggravate the shortness of breath, but when the severity diminishes, the cough may aid in bringing up plugs of tenacious sputum. For many patients this is the signal that the dyspneic symptoms will soon be over. When the coughing spells are of long duration and very severe, vomiting may follow, particularly in children.

e. *Expectoration.*

The sputum of uncomplicated asthma has a white or grayish gelatinous aspect; its consistency is sticky and tenacious. During the attack, only with great effort can the patient bring up little pellets of sputum. Towards the end he expectorates small, round, or cylindrical mucus plugs, having the shape of the bronchioles in which they have been compressed during the bronchiolar constriction. In attacks of long duration or in the case of a supervening infection, the sputum has a mucopurulent or purulent, yellowish or greenish aspect.

As a rule patients try to expectorate as much as they possibly can, as they have the feeling that this would relieve their shortness of breath. Sometimes various attempts are made to do so, including the inducement of long coughing spells which only result in aggravating still further their difficulty in breathing. They should be informed that these secretions act as ointment for their irritated mucous membranes and that the more sputum they expectorate, the more will be produced; only naturally-forthcoming sputum should be expectorated.

Evolution

The evolution of asthma, without adequate treatment, is difficult to predict as so many variations are possible. Indeed, asthma can appear, disappear, or aggravate at any age. In some cases the evolu-

tion is so rapid that in a few years the patient is completely disabled or crippled, while in other cases its course may remain stationary and the disease be limited to a few slight attacks of shortness of breath a year.

Asthma starts most commonly during childhood. In the months or even years preceding the first attack, the child often has a running nose, frequent sneezing spells, especially on awakening, or his nose may be blocked almost continuously. As time progresses the rhinitis symptoms become more severe and the copious watery discharge of the nose as well as the frequent sneezing spells become more troublesome. This is the period during which the allergic phenomenon takes place in the upper respiratory tract.

One night, usually on the occasion of a bronchial infection or an emotional upset, during the height of the pollen season or after a day of heavy exposure to dust, the mother observes that the child is somewhat restless and that his breathing is accompanied by an unusual noise. These symptoms are generally of short duration, and in the morning everything has returned to normal, until a few weeks or months later the same phenomenon recurs and the consulted physician speaks of "asthma".

If at this time no proper treatment is instituted, in most cases the attacks will return with shorter and shorter intervals and the symptoms become progressively more severe. The dyspnea, only slight in the beginning, increases in severity and the child now frequently has to sit up in bed part of the night. His barking cough becomes more troublesome and the wheezing more pronounced.

In some instances the asthma disappears spontaneously during childhood or fades out to reappear in full strength later in life. A change in his environment, in habits, or in the way of living sometimes provides an explanation for this spontaneous cure although in some instances no particular reason can be found.

During adult life, with the exception of the extremely severe cases with rapid evolution where the patient is already completely disabled, the attacks recur periodically with variable severity and frequency. The symptoms may return every night, once a week, month, or only a few times a year. They may be limited to a slight difficulty in breathing accompanied by wheezing, which the patient can readily relieve with the drugs he has at hand, or at times be so severe that his shortness of breath prevents him from moving for several days.

Almost invariably the symptoms begin and are more pronounced during the night-time; many a patient even experiences that they occur at approximately the same hour. As a rule the more severe the case, the earlier the symptoms appear; while in mild asthma

they usually appear before early dawn or upon awakening, in severe cases they start almost as soon as the patient lies down. The main reasons for the "nightly" occurrence of asthma are the breathing of the dusty atmosphere of the bedroom and the accumulation of secretions in the bronchial tubes. Some metabolic changes during sleep, such as the modified sympathetic-parasympathetic balance, may be of significance.

With age the course of asthma becomes more chronic; although the severity of the attacks tends to diminish, the symptom-free intervals grow shorter. In this chronic stage, a more or less pronounced dyspnea is almost continuously present. It is aggravated by exertion, coughing, laughing, a heavy meal, and influenced moreover by such non-specific stimuli as smoke, fog, wind, dampness, fatigue, exertion, anger or any other emotional upset.

On physical examination some wheezing is audible, especially on deep forceful expiration, even in those periods when the patient claims he feels well. Bronchial infections frequently supervene, further aggravating his distress.

In some patients the chronic respiratory discomfort becomes so pronounced that they are completely incapacitated and practically bedridden. A slight exertion, such as dressing or ascending the stairs, proves too effortful and exhausting and almost continuous medication is required. This condition may last for several years until finally an intercurrent sickness such as pneumonia, congestive heart failure or a violent status asthmaticus brings an end to his suffering.

Diagnosis

The diagnosis of asthma during an attack as a rule does not present any difficulties as some signs and symptoms are more or less characteristic of this condition. The general aspect of the patient, the labored respiration, the audible wheezing and the physical examination usually leave little doubt with regard to the diagnosis.

During the symptom-free intervals the diagnosis is based primarily on the history of recurrent attacks of dyspnea accompanied by wheezing, occurring most frequently during the night and promptly releived by aminophylline, epinephrine, ephedrine or responding to ACTH or adrenocorticosteroids. The presence of other allergic disorders, a family history of allergy, positive skin reactions with extrinsic proteins and the finding of a blood or sputum eosinophilia may afford convincing evidence.

a. *Physical examination.*

During the attack sibilant and sonorous râles are heard throughout both lung fields; although audible during in- and expiration, they are usually more pronounced during the latter phase.

Between attacks, if no complications such as emphysema, chronic bronchopulmonary infections etc. are present, these auscultatory findings disappear completely, particularly in the initial stages of the disease. When attacks occur frequently or when the disease has been of long duration, this complete return to normal is not further encountered and sibilant râles may be heard continually throughout the chest, particularly on forcible expiration.

The percussion note over the lungs during an attack is hyperresonant or tympanitic and the inferior borders of the lungs are generally one or two fingers below normal.

b. *Laboratory findings.*

The sputum examination is of particular interest in differentiating the types of asthma and recognizing associated diseases. In uncomplicated asthma the sputum is white or greyish and tenacious. Round or cylindrical opaque masses, resembling tapioca balls, may be present at times: the pearls of Laënnec. After standing for some time, the sputum may contain sharp-edged crystals, called the Charcot Leyden crystals. The reason for their formation is unknown; most observers attribute their presence to the disintegration of the eosinophil cells. These crystals are most numerously encountered in sputum brought up during an attack and the amount decreases when the attack subsides. Upon close examination of the plugs, threads of curly and twined mucus can at times be seen: the spirals of Curschmann. These represent casts of the finer bronchioles, their thickness is that of a needle and they are 1 to 2 mm in length.

The presence of pearls, crystals and spirals, however, does not have a diagnostic significance, as they may be found in other conditions as well.

During acute paroxysms and infectious episodes, eosinophil cells are almost invariably present; in between attacks they may or may not be found.

Bacteriologic studies, especially when infection is present, evidence large numbers of microorganisms: streptococci, micrococcus catarrhalis, pneumococci, staphylococci, H. influenzae, Friedlander's bacilli etc.

Routine white blood cell counts are normal and the differential count may or may not show an increase in eosinophil cells. Blood chemistry, sedimentation rate and urine analysis show no abnor-

malities. If the asthma is due to extrinsic proteins, positive skin reactions are usually obtained.

c. *Radiologic and bronchoscopic examination.*

The chest x-ray of an uncomplicated asthma does not show any characteristic features. In more advanced cases, signs of emphysema become visible: the lung fields are abnormally translucent while the hilar shadows and bronchial markings are more pronounced. On fluoroscopic examination during an attack, the diaphragms are lowered and their mobility decreased.

A bronchoscopic examination is indicated when doubts exist as to whether a cause other than asthma produces the wheezing, e.g. foreign bodies, a bronchial tumor etc. It may also be useful in obtaining uncontaminated specimens of secretions for cytologic or bacteriologic studies. During an attack the characteristic feature is an edema of the bronchial mucosa causing a narrowing of the lumen. The aspect of the mucosa is usually pale, sometimes reddish, particularly when infection is present, and may be covered with mucoid or purulent secretions. In the symptom-free intervals its aspect is fairly normal.

Pulmonary Function Tests

a. *Normal Ventilation.*

During normal breathing, approximately the same amount of air is in- and exhaled at each respiratory movement; this is called the *tidal volume.* This volume multiplied by the respiratory rate, normally between 10 and 16 times per minute, represents the volume which is in- and expired in one minute, the *minute volume.* In normal individuals under basic conditions a fairly constant relationship exists between the minute volume and the oxygen consumption: for a consumption of 100 ml of oxygen, between 2.2 and 3.4 litres of air have to be inhaled.

At the end of a normal expiration a considerable volume of gas can still further be exhaled when the expiration is extended to a maximum, the *expiratory reserve volume* (previously termed reserve or supplemental air). Likewise after a normal inspiration, a more or less large amount of air can still be inhaled by a maximal inspiration, the *inspiratory reserve volume* (also formerly known as complemental air). Tidal volume and inspiratory reserve volume form together the *inspiratory capacity.* The *vital capacity* is the total volume of gas which can be expelled from the lungs by a forceful expiration following a maximal inspiration and is equal to

the sum of inspiratory reserve volume, tidal volume and expiratory reserve volume. Sex, age, height and weight are the principal factors influencing the vital capacity in normal subjects. A formula often used for the calculation of the normal vital capacity is that of *Baldwin* (1), which takes into account the three principal factors. In men: V.C. $|27.63 - (0.112 \times \text{age in years})| \times$ height in cm. In women: V.C. $|21.78 - (0.101 \times \text{age in years})| \times$ height in cm. Owing to normal variation in the vital capacity, the results obtained can only be considered as pathological when they are more than 20 % below the predicted values (2).

After a maximal expiration not all of the air is expelled from the lungs, the remaining amount is called the *residual volume*. Most methods in use, however, actually determine the *functional residual capacity*, which is the volume of gas remaining in the lungs at the end of a normal expiration, the difference between normal and maximal expiration or the expiratory reserve volume being determined beforehand or later.

The sum of residual volume and vital capacity represents the *total lung capacity* which corresponds to the total amount of gas the lungs contain after a maximal inspiration. Its normal value for a normal young man is approximately 6 litres and 4.25 litres for a young woman (11).

Tidal volume, respiratory rate, oxygen consumption, vital capacity and its components can easily be determined by having the patient breathe in a spirograph; a more complex apparatus is needed for the measurement of the residual volume.

In a normal adult in lying position, the residual volume constitutes 20 to 25 % of the total lung volume, while 75 to 80 % is taken up by the vital capacity. Of the latter, 50 to 55 % consists of inspiratory reserve volume, about 10 % of tidal volume, and 10 to 20 % of expiratory reserve volume. As example, for a normal male subject, 20 years old, 1.70 m in height, and weighing 70 kg., the following figures are obtained:

Vital capacity	4,300 cc.
Tidal volume	575 cc.
Expiratory reserve volume	860 cc.
Inspiratory reserve volume	2,865 cc.
Residual volume	1,430 cc.
Total lung capacity	5,730 cc.

On growing older the residual volume gradually increases, whereas the vital capacity diminishes; above 50 years of age, the normal residual volume may reach 40 % of the total lung volume (8).

In the assessment of the ventilatory capacity of a patient, of

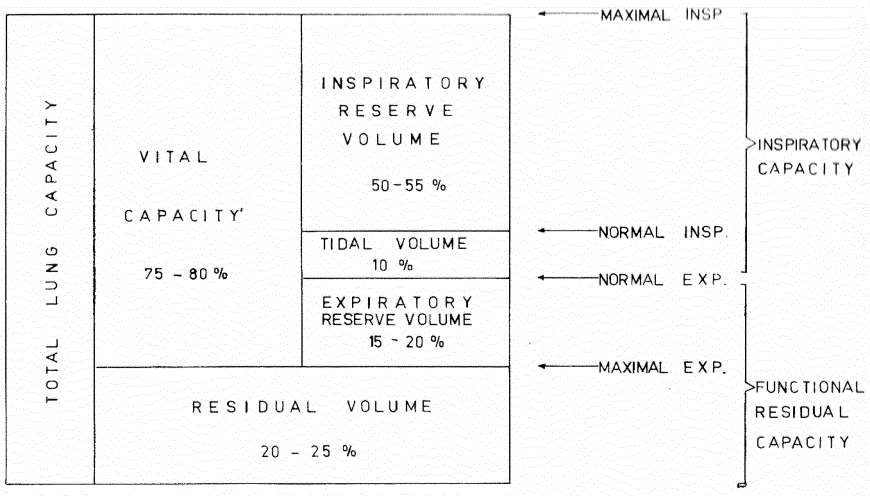


Fig. 1.
Normal lung volumes.

greater importance than the absolute value of the various lung volumes and their respective proportions (the static aspect of ventilation) are those which express the ventilatory capacity per unit of time (the dynamic aspect of ventilation). For the *maximal breathing capacity* the patient is asked to breathe as quickly and deeply as possible for a short time, usually 15 to 30 seconds; the expired volume, calculated in litres per minute, is compared with the theoretical normal values as given for instance by *Baldwin* (1). In man: [86.5—(0.522 × age)] × body surface. In women: [71.3—(0.474 × age)] × body surface. In the above mentioned example, the normal value would be 147 litres. These tests require great effort on the part of the patient; moreover, the results are not entirely comparable because they are influenced by the frequency chosen by the patient.

The *timed vital capacity* is less exerting and well reproducible. Here the volume is measured which can be exhaled during the first second of a forceful expiration following a maximal inspiration (the volume expired during the second and third seconds are eventually measured as well). The one-second value corresponds approximately to the tidal volume which the patient reaches during a maximal voluntary hyperventilation with a respiratory rate of 30 to 35 per minute. Its normal value expressed in percent of the vital capacity has to be at least 70 % of the latter. Lower percentages indicate either an increased bronchial resistance due to spasms, edema, secretion or anatomical narrowing of the bronchi, or a lessened retractile property of the lungs caused by loss of elastic tissue (21, 5).

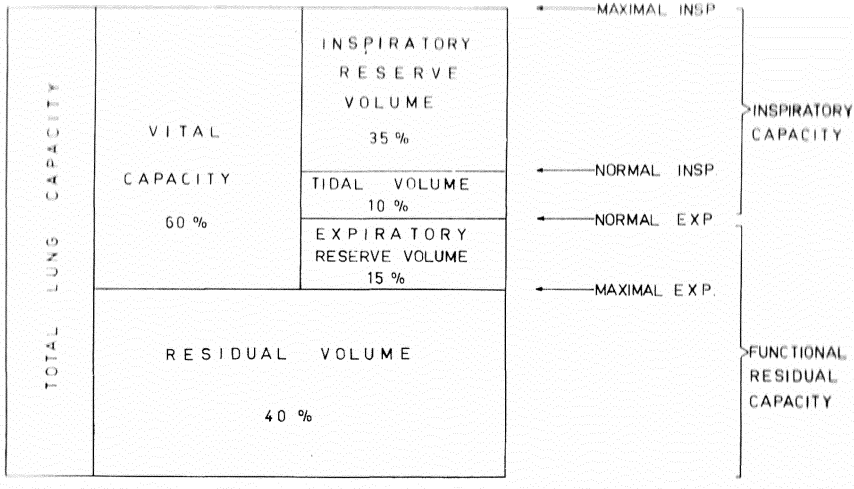


Fig. 2.
Lung volumes during a moderately severe attack of asthma.

b. *Ventilatory changes during an acute asthmatic attack.*

The changes in ventilatory values during an asthmatic attack are determined to a great extent by the narrowing of the lumen of the smaller bronchi and bronchioli. The first signs of slight asthma are shown by a diminution in maximum breathing capacity and timed vital capacity tests, both very sensitive to even a slight increase in bronchial resistance. After administration of bronchodilating drugs, both values are seen to improve and may even return to normal levels. The decrease in maximum breathing capacity and timed vital capacity are fairly proportional to the severity of the attack, they are the ventilatory tests which best express the degree of respiratory insufficiency in these patients (6, 20). *Herschfuss* et al. (9) also found a clear relation between the MBC and the auscultatory chest findings. In severe asthma the MBC may fall under 30 litres and the timed vital capacity to less than 40 % of the vital capacity.

Likewise, the vital capacity is mostly lowered when the patient experiences asthmatic dyspnea; however, proportionally to a less degree than the maximum breathing capacity and timed vital capacity.

In spite of the fact that the accessory muscles of respiration are called into play, difficulty in breathing is more pronounced during the expiratory than during the inspiratory phase. Consequently, at the onset of an acute attack, the amount of exhaled air will be lower at each respiratory movement than the inhaled volume; as a

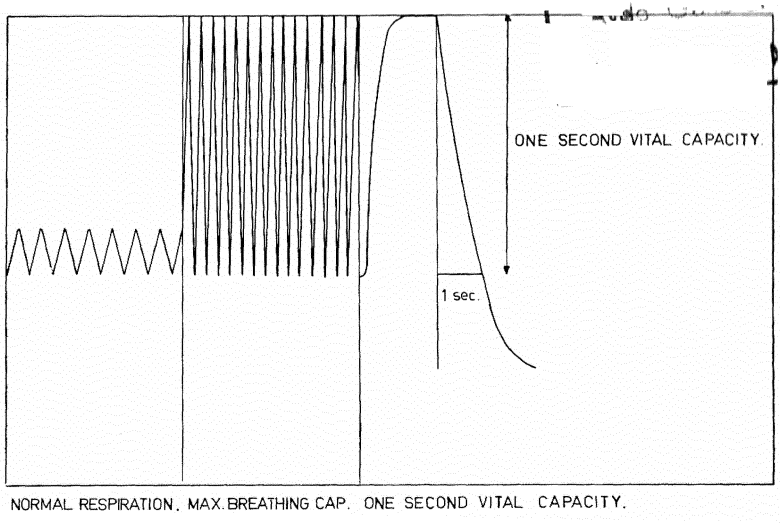


Fig. 3.
M.B.C. and timed V.C. in a normal individual.

result there is a shift of the resting expiratory level towards the inspiratory side, and the lungs become more inflated. During this process of inflation, the stretching of the elastic framework of the lungs widens somewhat the opening of the bronchioli and the elastic recoil of the lungs increases. These two factors are of benefit to the expiration, the volume of which now reaches the same value as the inspiratory one, and breathing then merely occurs at a higher expiratory level.

The vital capacity diminishes because the inspiratory reserve volume decreases due to the shift of respiration towards the inspiratory side. Moreover, during a severe attack the organism does not have the strength nor the time to exhale all of the air excepting the initial residual volume, whereby a lowering of the expiratory reserve volume is also produced.

When the determination of the vital capacity is made by a rapid, forceful, maximal expiration, the obtained value is often seen to be less than if the patient exhales quietly but completely. During a rapid forceful expiration against a raised bronchial resistance, a positive intrapleural pressure arises, as a result of which a certain number of bronchioli completely collapse. This "check valve mechanism" causes "air trapping", the air cannot escape from these shut-off bronchioli as long as the positive intrapleural pressure persists.

Although less sensitive in the detection of bronchial obstruction than the timed vital capacity and maximum breathing capacity,

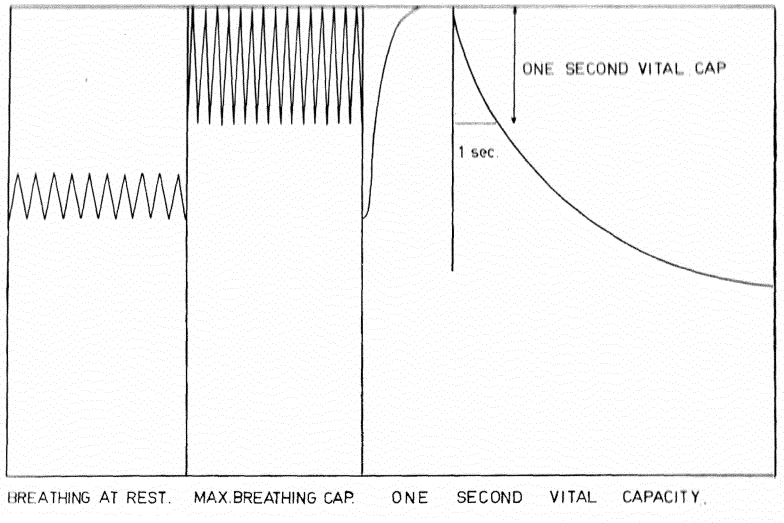


Fig. 4.
M.B.C. and timed V.C. during a moderately severe attack of asthma.

the vital capacity is of great aid in the follow-up of asthmatic patients.

An asthmatic attack is also accompanied by an increase in functional residual capacity because of the shift of the respiratory level towards the inspiratory side. When the expiration is hindered to such an extent that the expiratory reserve volume cannot increase sufficiently or is even lowered, the residual volume is increased as well.

The changes in minute volume in asthma have been studied especially by *Rossier* (16). This author found in mild attacks a slight increase in the minute volume, without changes in the respiratory rate; in moderately severe attacks, the minute volume increased from an average of 7.1 litres to an average of 10.5 litres, while the respiratory rate was increased from 16 to 21 litres. In very severe attacks, accompanied by an increased carbon dioxide tension, the average respiratory rate was 22, but the increase in minute volume was less pronounced, from an average of 6.5 litres to an average of 8.3 litres per minute.

Once the patient has entered the chronic asthmatic stage, besides the reversible functional changes, permanent anatomic lesions of lung emphysema occur: loss of elastic fibres and capillaries and tearing of alveolar septa.

The ventilatory changes in these patients are practically identical to those encountered during an acute attack: lowered maximum

breathing capacity and timed vital capacity, often a decreased vital capacity. These changes, which disappear completely in uncomplicated asthma, are permanently present in emphysema.

Administration of bronchodilating or antiasthmatic drugs can aid to some extent in the differentiation of anatomic and functional lesions. The ventilatory alterations hereby disappearing are without doubt due to functional bronchial obstruction; those which persist, however, cannot be ascribed with certitude to anatomic lesions as they may be attributed to other reasons such as resistance to the drug, retention of secretions etc. On the basis of respiratory tests alone, it is not always possible to confirm or exclude with certitude the presence of irreversible degenerative lesions in the lung tissues.

With regard to the other respiratory changes in relation to asthma, as well as the technique and the variations due to provoked asthma, the reader is referred to the chapter on "Provocation Tests" by H. Colldahl.

Complications

Complications frequently occur in asthma; they often induce irreversible changes and accelerate the evolution towards the chronic stage of the disease. In many cases the asthma itself may be well tolerated and allow the patient to lead an almost normal life, but the complications which may have resulted from it, handicap him more than the disease itself and can even lead to complete invalidism.

a. *Emphysema.*

Emphysema is so common in asthma of long duration that it could be considered as part of the condition, although it may be produced by other causes as well.

Acute emphysema, an over-expansion of the lungs, is present during every attack but retrogresses more or less rapidly when the attack subsides. Because of the bronchial obstruction and the resulting increase of the intra-alveolar pressure, the alveoli stretch.

When the asthma enters the chronic stage and the periods of freedom become fewer, the dilatation of the alveoli may become permanent, primarily due to the loss of elasticity of the tissues as a result of degeneration of the elastic fibers.

The main clinical symptom of an established emphysema is an aggravation of the dyspnea which tends to become more chronic and more extensively pronounced on exertion. On physical examination the chest becomes hyper-resonant by percussion, breath and heart sounds on auscultation are usually faint, and wheezing may or may not be heard. Cyanosis, caused by insufficient oxygenation of the arterial blood, may at times be noticed.

Characteristic findings are seen on fluoroscopic or x-ray examination: the lung fields appear more translucent than normally, the hilar shadows are increased as are the bronchial markings, the diaphragms are lowered and their mobility is greatly diminished. The heart is usually small and in a vertical position, the ribs appear horizontal and as a result the rib-interspaces are widened. The expansive movement of the thorax is limited. The alterations in pulmonary function tests have been mentioned above.

Great personal differences exist as to the development of emphysema. In some asthmatic patients, pronounced irreversible signs of emphysema occur within a short period of time, while in other cases of long duration, they may be surprisingly insignificant. The frequent occurrence of bronchial infections seems to be an important factor in accelerating the process of emphysema.

b. *Sinusitis and rhinopathy.*

In a large percentage of asthmatic cases, mild or gross pathologic changes are present in the nose and paranasal sinuses, although great discrepencies exist in literature as to their exact incidence. Differences in opinion exist also as to the relationship of the pathologic changes in nose and paranasal sinuses in regard to asthma as well as to the indications for radical treatment and the results of surgical intervention.

While some observers believe that in some cases surgery is indicated, the more conservative ones are of the opinion that the pathologic changes are only the result of the allergic process and cannot in any way be considered as an etiologic factor in the causation of asthma.

In the writer's opinion, nasal and sinus pathologic changes do not play a role in the etiology of asthma but are merely concomitant manifestations of the same condition in different parts of the respiratory tract and are often provoked by the same causative factors. Therefore, nasal and sinus operations should never be performed to cure the asthma but only when a definite indication exists, the management of the allergic problem being of primary importance.

It has been our experience as well as of most other observers that in cases of nasal or sinus allergy without asthma, surgical intervention in those organs tends to hasten the development of asthma and in cases where nasal polyps have been removed before the allergic condition is under control, a strong tendency for rapid recurrence prevails.

Each case presents its own individual problems to be considered; surgical operation in the nose and paranasal sinuses in allergic

patients should be performed only when a careful examination and follow-up studies have proven their absolute necessity and should remain as conservative as possible.

c. *Bronchitis and other bronchopulmonary infections.*

The role of bronchopulmonary infections is predominant in the evolution of asthma. Not only is the first attack frequently preceded by an infection of the upper or lower respiratory tract but subsequently they play an important role in eliciting and aggravating the asthmatic symptoms.

The question as to whether the microorganisms act as an antigen in inducing the attacks or whether the inflammation of the bronchial mucosa is merely a predisposing factor for an extrinsic allergic reaction to take place, has to be determined in each case separately on the basis of clinical and laboratory findings.

In the chronic stage of asthma the acute episodes of bronchitis are sometimes substituted by an almost continuously present latent infection of the bronchi, which may result in pronounced and irreversible damage to the bronchial walls. The mucosa becomes thickened and the ciliary function, which is of primordial necessity to remove the bronchial secretions, is progressively lost. The submucosal layers become enlarged and signs of peribronchial inflammation appear.

d. *Bronchiectasis.*

Bronchiectasis can occur in asthma, although it is difficult to determine whether or not it is a direct consequence of asthma or merely a concomitant disease. In regard to the incidence, reliable figures are not available and percentages advanced by different authors vary widely. The reason is that a definite diagnosis cannot be made by clinical means or an ordinary chest x-ray. A bronchoscopic examination and/or bronchography using iodized oil are necessary to provide convincing evidence.

Bronchiectasis should be suspected whenever the patient expectorates a considerable amount of mucopurulent sputum in the morning. Areas of dullness and moist rales may be found on clinical examination. The chest x-ray usually shows a shadow in the mediastino-diaphragmatic area, but only the bronchography can evidence the cylindric or saccular dilated bronchial tubes. The former type seems to be far more common in asthmatics than the latter.

In the past years more emphasis has been put on the role of allergy in the etiology of bronchiectasis. This opinion is based on (1) the

frequency with which other allergic manifestations such as rhinitis, sinusitis, asthma, urticaria, eczema etc. are found in these patients; (2) the frequent finding of a high percentage of eosinophils in the sputum or bronchoscopic aspiration products; (3) the results obtained through allergic management.

Although medical treatment does not aid to a great extent when advanced changes have occurred, it has been proven that in many cases the changes are not necessarily irreversible. Results may be obtained through allergic treatment, elimination of foci of infection, antibiotics or bronchoscopic aspiration as indicated.

c. *Rupture of the pleura or lung tissue.*

Spontaneous pneumothorax: Rupture of the pleura, resulting in spontaneous pneumothorax, is sometimes encountered in the course of asthma; it is almost always due to a rupture of a superficial emphysematous bleb. It may occur during an asthmatic paroxysm, a severe coughing spell, a strenous exercise or even when the patient is in an asymptomatic period and at rest.

The symptoms, which depend to a great extent on the speed with which the air enters the pleural cavity, are sometimes mild, consisting in a dry cough and a sensation of heaviness in the chest. In more severe cases, a sudden pronounced difficulty in breathing is experienced by the patient, accompanied by a sharp pain in the affected thorax side and referred to the shoulder, arm, or even to the abdomen. Cyanosis and fever may complete the clinical picture; occasionally signs of shock and circulatory collapse may appear.

Absence of breath sounds and hyper-resonance by percussion are the predominant clinical signs. The x-ray, showing the air in the intrapleural spaces and the displacement of the heart and mediastinum to the unaffected side, confirms the diagnosis.

Generally no special treatment is required outside purely symptomatic measures as indicated, the air being allowed to be absorbed spontaneously under radiological control. Its withdrawal is only indicated when the air is under tension and pressure symptoms occur.

Since the tendency for bleb formation remains, even after the lung has re-expanded, recurrences are frequent. In this case a special treatment with the aim of provoking a pleural symphysis may be considered.

Interstitial, mediastinal and subcutaneous emphysema: In case of multiple ruptures of alveoli, as a result of overinflation and overexpansion, especially of the marginal ones whose bases rest against the blood vessels, the air may escape along their sheaths, giving rise to pulmonic interstitial emphysema. From there the escaped air may

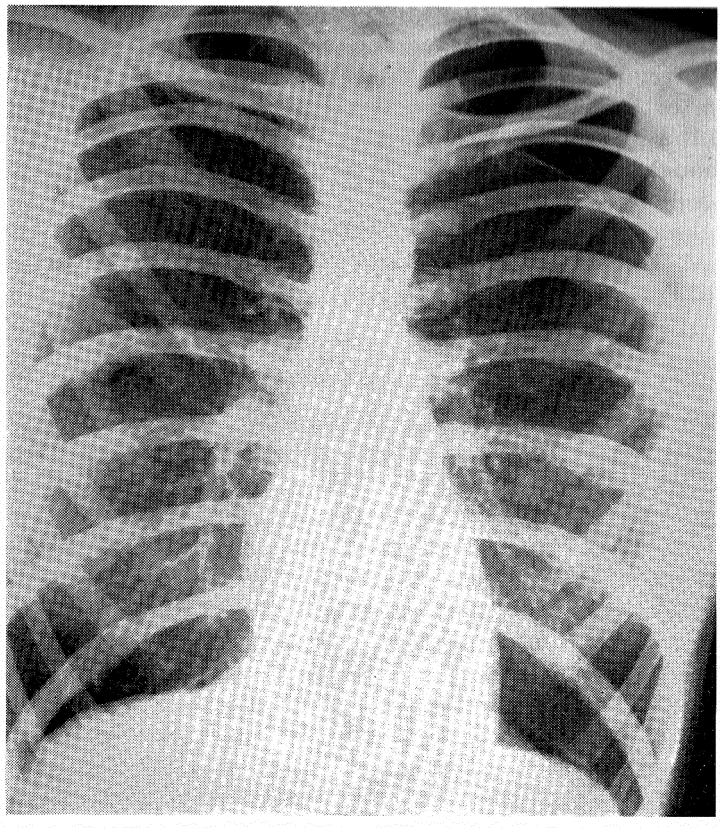


Fig. 5.
Bilateral spontaneous pneumothorax.

find its way to the mediastinum causing mediastinal emphysema and may even extend to the neck, face, thorax or upper extremities, producing a subcutaneous emphysema. It may also go downward along the aorta and esophagus into the retroperitoneal space or may rupture into the pleura or peritoneum causing a spontaneous pneumothorax or pneumoperitoneum.

The symptoms associated with interstitial, mediastinal or subcutaneous emphysema depend on the rapidity of its development, the degree of interference caused in the circulation by air compression of blood vessels and heart and in respiratory function by inhibition of the respiratory movements.

Sudden severe mediastinal emphysema is associated with dyspnea, cyanosis, a fall in blood pressure and an intense retrosternal pain, extending to the neck or shoulders, which may resemble coronary

thrombosis, pericarditis or pulmonary infarction. The percussion note in the affected area is hyper-resonant and the cardiac dullness is obliterated. A peculiar crackling sound synchronous with the heart-beats may be heard in the precordial area.

In subcutaneous emphysema a characteristic crepitation is felt on digital pressure over the swollen areas.

The presence of aberrant air in the mediastinum can readily be detected by x-ray examination.

Although usually a dramatic condition, most patients recover. Bed-rest, prophylactic antibiotics, sedatives, oxygen and supportive measures are indicated according to the circumstances. Letting the air escape from the mediastinum by introducing a needle in the supra-sternal notch, or from the subcutaneous tissues by multiple incisions in the skin, should be done when the mediastinal emphysema increases and the tension has to be relieved.

f. *Atelectasis.*

Obstruction of small or medium sized bronchi by mucus plugs, is a not infrequent complication, especially in children with severe asthma. A complete obstruction, in which a stop valve mechanism prevents the in- and outflow of air, is followed by atelectasis of the affected segment, as the air trapped in the alveoli is quickly absorbed by the capillaries. Small areas of atelectasis usually do not give rise to any symptoms and generally the condition is readily relieved by coughing up the plug. In case a larger bronchus is involved, a more extensive atelectasis of the lobular or even lobar type is produced, inducing a sudden cough, wheezing, and dyspnea; the sputum, mucoid in the beginning, later becomes purulent and is often bloody; hemoptysis is occasionally an early event.

The x-ray reveals the atelectatic dense zone, which may assume variable locations and shapes; the high negativity of the intrapleural pressure draws the heart and mediastinum towards the affected side and the diaphragm is in an elevated position.

Prolonged bronchial obstruction is followed sooner or later by infection, giving rise to fibrosis, retraction and bronchiectasis.

Massive collapse of the lung, caused by obstruction of a main bronchus, is a very rare occurrence in asthma.

g. *Other complications.*

The employment of the accessory muscles of respiration as well as fatigue of the diaphragm in severe attacks of long duration, sometimes cause a sensation of soreness in the lower thorax and upper

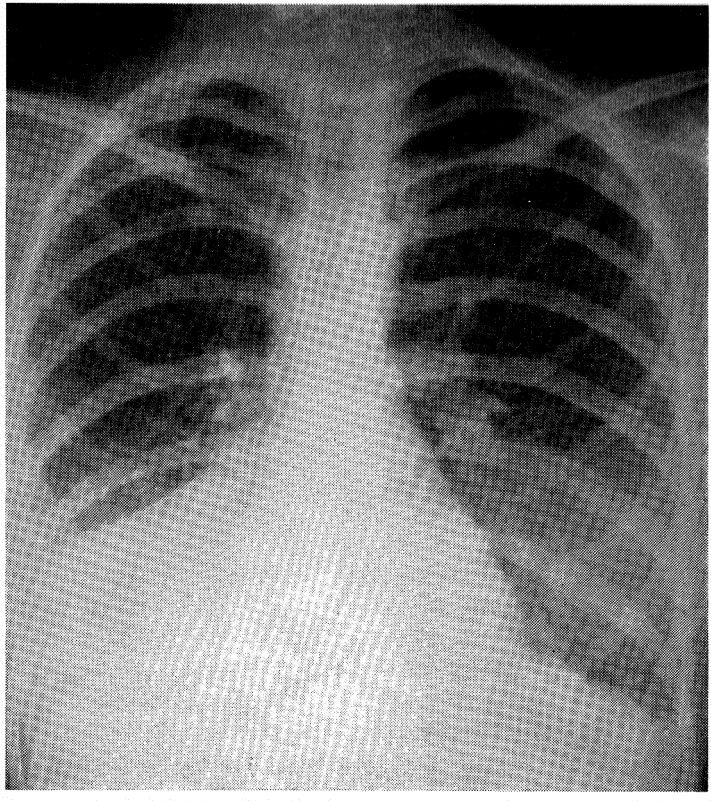
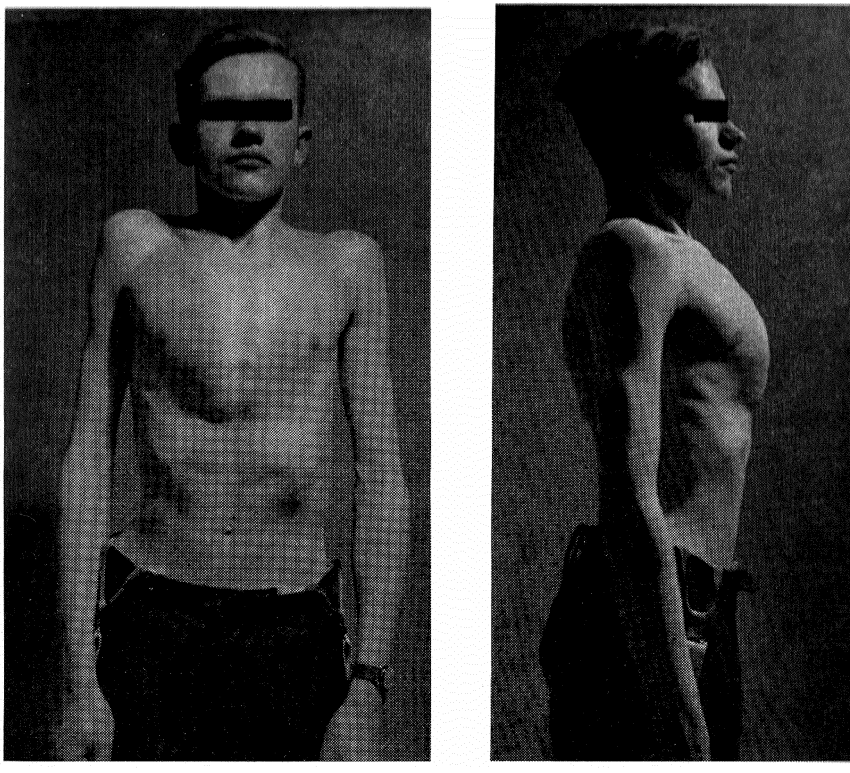


Fig. 6.
Atelectasis of the right lower lobe in an asthmatic girl of 14, caused by a mucus plug.

abdomen, aggravating still further the respiratory difficulty. Likewise, those patients particularly in whom long barking coughing spells are a predominant feature, complain of pain in the region of dorsal and neck muscles. Rare cases in which violent paroxysms of cough were the cause of rib fracture, have been reported in the literature (7).

In severe cases of asthma in childhood the abnormal muscle pull on the growing thorax may, after a variable length of time, result in a more or less pronounced thorax deformity. This is characterized most frequently by an increase in the antero-posterior diameter of the thorax with prominence of the sternum and especially of the xiphoid process, a flattening of the lower ribs and kyphosis; this is called a pigeon breast.

Loeffler's disease, periarteritis nodosa, allergic angiitis, tropical



Figs. 7 a and b.
Pronounced thorax deformity in a boy of 16 suffering from bronchial asthma since the age of 2.

cosinophilia are sometimes encountered in the course of asthma. As these conditions are described extensively in the chapter on "Collagen and Vascular Diseases" by C. Jiménez Díaz, they will only be mentioned here.

Of course any non-allergic condition, e.g. pulmonary tuberculosis, carcinoma, diabetes etc., can coexist with asthma.

The influence asthma bears on the general state of health is obvious in many an asthmatic patient, especially in the growing child. The often interrupted night rest, the inadequate nourishment during the asthmatic seizures, especially when they are of such a frequency that insufficient time is allowed for recuperation, handicap their normal development.

The mental disturbances which result from, accompany, and influence the course of the disease, are described in detail in the chapter on this subject by B. Stokvis.

The Heart of the Asthmatic

Asthma can exert an influence on the heart, the recognition of which can be of utmost importance, not only in the treatment, but also in the prognosis of an individual case.

Although this influence is mostly limited to a change in position as a result of acute or chronic emphysema, in a small percentage of cases hemodynamic changes occur in the pulmonary circulation which may result in permanent damage to the heart.

The description of the abnormalities found on cardiac examination can, for practical reasons, be divided into those encountered between and during attacks.

I. *Cardiac Examination Between Attacks.*

Examination of the heart during this period provides more accurate information as to the presence of permanent alterations in the cardiac function as a result of asthma as well as for the exclusion of other cardiopathies.

Not only is the auscultation of the heart easier in the absence of wheezing but the acute emphysema during an attack may also provoke changes in the position of the heart, producing electrocardiographic variations somewhat similar to those caused by hypertension in the pulmonary artery and right ventricular hypertrophy.

If no other cardiac illness is present, experience has shown that in most asthmatic patients the heart remains undamaged even after a long duration of the disease.

The radiologic and electrocardiographic signs encountered during this period are primarily provoked by changes in position of the heart due to the existence of chronic emphysema and in a minority of cases to hypertension in the pulmonary artery and hypertrophy of the right ventricle, occasionally resulting in right heart failure.

a. *Signs produced by chronic emphysema.*

Radiologic signs: As long as the emphysema is not in a pronounced stage, the appearance of the heart on x-ray does not differ much from what is normally encountered. In more pronounced emphysema, however, a characteristic picture of the heart can be described. It is narrow and in vertical position, creating the impression of being elongated and of hanging down from the great vessels with a flattened angle. The aortic knob usually does not reach much farther than the shadow of the vertebrae and in oblique view the aorta is located close to the spine. The middle convex curve of the left border, formed by the trunk of the pulmonary artery, protrudes. The ventri-

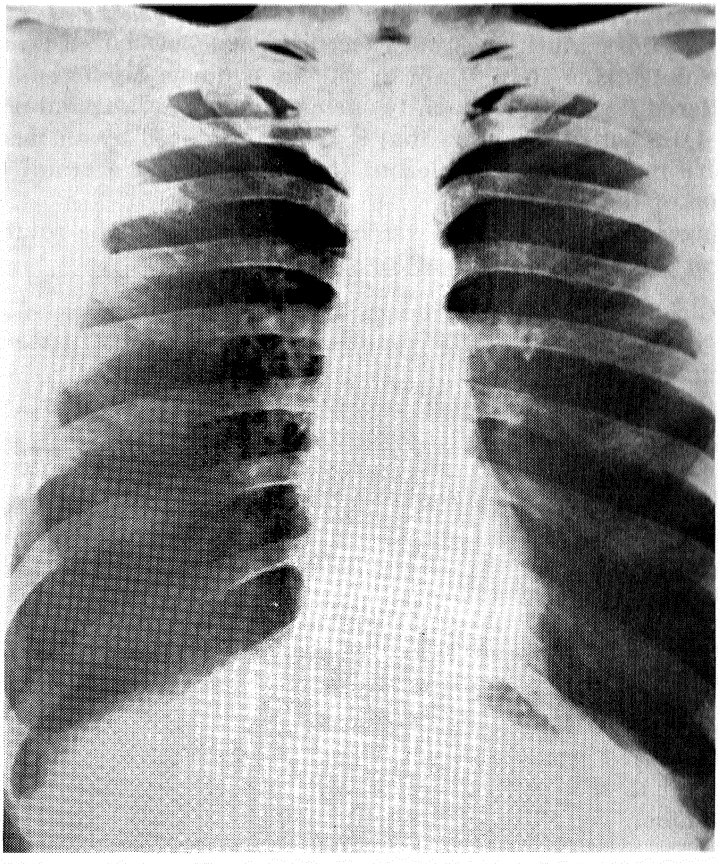


Fig. 8.
Pronounced emphysema.
Both lungs are hyperilluminated, the heart is small and in a vertical position.

cular shadows appear small and the apex low. The hilar shadows, formed by the right and left main branches of the pulmonary artery, are increased and the markings of their branches can be followed for some distance into the lung fields.

The influence of the respiratory movements on the position of the heart and hilar shadows is seen to be diminished on fluoroscopic examination.

Electrocardiographic signs: Chronic emphysema can produce alterations in the electrocardiogram, resulting primarily from changes in the position of the heart, and which are somewhat similar to those produced by right ventricular hypertrophy.

The asthmatic P wave: P is peaked, its two branches forming a sharp edge. Its width does not exceed normal limits, and its amplitude is not higher than 2 mm in D_2 and 1 mm in D_3. The fact that this altered P wave is frequently encountered alone, without changes in the QRS complex, shows that it is not produced by an increased pressure in the right auricle but that it is merely a result of the rotation of the heart.

Changes in QRS complex which may derive from the rotation of the heart around its different axes:

a. Clockwise rotation around its antero-posterior axis; consequently the axis of the QRS complex deviates to the right, never exceeding, however, $+90°$.

b. Clockwise rotation around its long axis producing an S_1Q_3 pattern; precordial leads through V_5 or V_6 may face the right epicordial surface. A deep S may be found over the entire precordium: rS patterns in the right and rS and RS patterns in the left precordial leads.

c. Backward rotation of the apex around the transverse axis producing an S pattern in $D_{1, 2, 3}$.

Infrequently, in extreme rotations, the following patterns may be encountered:

Downward T wave in $D_{2, 3}$ or in D_3 alone.
Downward T wave in $V_{1, 2, 3}$.
S larger than R in V_5 or S more than twice the height of R in V_6.
Incomplete right bundle branch block.

It cannot be said however that a complete parallelism exists between the electrocardiographic axis deviations and the anatomic position of the heart, as determined by fluoroscopic and x-ray examination.

b. *Signs produced by hypertension in the pulmonary artery and right ventricular hypertrophy.*

In the chronic stage of asthma, particularly when chronic or frequent recurring acute infections of the bronchi complicate the disease, permanent changes may occur in the cardiac and pulmonary circulation.

The narrowing of the arterioles produced by marked emphysema causes an increased resistance in the pulmonary blood flow and hypertension in the pulmonary artery. The right ventricle adapts itself to this increased pressure and hypertrophies. This is called chronic cor pulmonale.

Radiologic findings: The most evident change in the radiologic picture of the heart in this stage is the enlargement of the right ventricle; the anterior oblique position is the most suitable in revealing the forward bulging of the right ventricle.

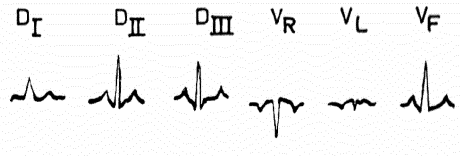


Fig. 9.
P pulmonale.

Electrocardiographic signs: P Pulmonale: the P wave is peaked, unnotched, not enlarged but taller than normal. This alteration of the P wave results from hypertension, hypertrophy and enlargement of the right auricle.

The changes in the QRS complex are similar to those described in emphysema although some criteria can be of significance in the differentiation of these two conditions:

a. A right axis deviation of the QRS complex of more than 110° can be considered as pathognomonic for cor pulmonale.

b. A left axis deviation of the T wave—a downward T wave in D_2 and D_3 or in D_3 alone—is typical for a right ventricular hypertrophy when the distension of the thorax is not pronounced, when it is accompanied by P pulmonale, or if it persists when the clinical symptoms of emphysema tend to diminish.

c. *Right heart failure.*

Although generally the heart muscle can maintain a satisfactory circulation even in severe cases of asthma of long duration, in some patients, usually on the occasion of a severe attack, a status asthmaticus or an acute bronchitis, the hypertrophied right heart muscle becomes unable to compensate for the increased tension in the pulmonary circulation and right heart failure occurs.

The first clinical sign usually is a tenderness or a sharp pain felt in the right hypochodrium even before the liver is enlarged. The dyspnea becomes more pronounced especially on exertion, excitement, or in recumbent position. Cyanosis is more marked particularly at the lips, ears, and extremities.

The pulse rate is rapid and generally regular, the arterial blood pressure is usually decreased while the venous pressure is abnormally high. The neck veins are engorged, the liver is increased in size,

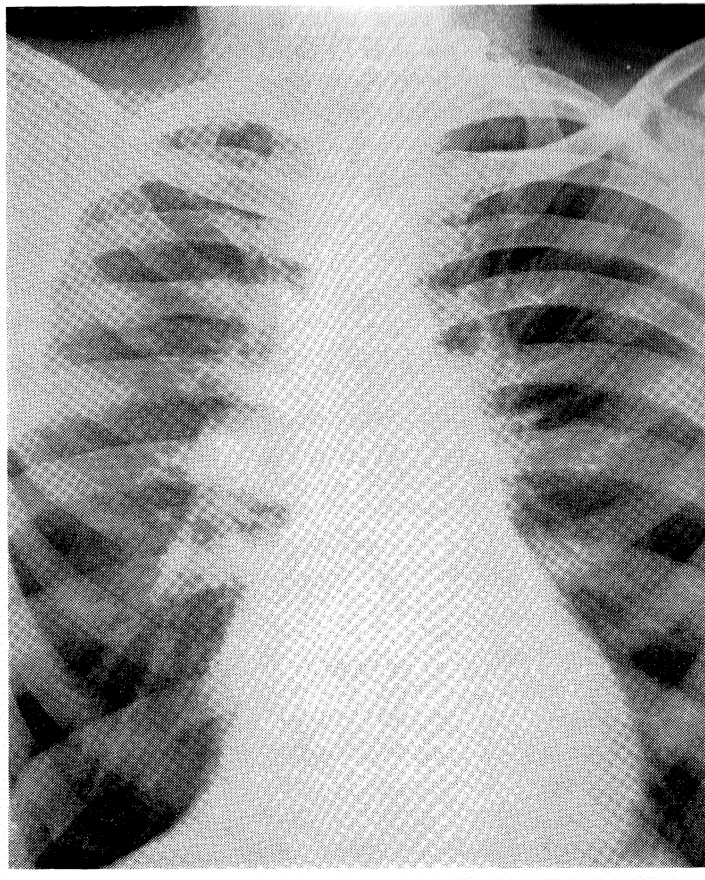


Fig. 10.
Roentgenogram of an asthmatic patient aged 52 with emphysema and right heart failure.

reaching at times the level of the umbilicus; edema of the lower extremities and in severe cases ascites are found. The apex of the heart is displaced to the left, and on auscultation sometimes a gallop rhythm or a systolic murmur can be heard in the region of the xiphoid process. Oliguria is always present and the urine examination frequently reveals the presence of albumen.

Radiologic signs: The silhouette of the heart is enlarged in toto and acquires a triangular shape. On the anterior oblique view the abnormal enlargement of the pulmonary artery and of the right ventricle can best be evidenced. The lung fields appear clear and contrast with the marked hilar shadows.

Electrocardiographic signs: 1. Signs of right auricular strain: the P wave is tall and peaked in $D_{2,3}$ and VF, and biphasic (+ -) but not enlarged in the precordial leads.

2. Signs of right ventricular strain: Deviation of the QRS axis to the right, while the axis of the T waves deviates to the left. The R/S ratio in the right precordial leads is larger than 1, or an rS pattern is present in the precordial leads from V_1 through V_6.

Characteristic findings in right heart failure due to asthma are:

a. A pronounced right axis deviation of the QRS complex, from 115° to 170°.

b. A pronounced left axis deviation of the T waves, from -40° to -70°.

c. The presence of simultaneous signs of right auricular and ventricular strain.

d. The frequent occurrence of an incomplete right bundle branch block.

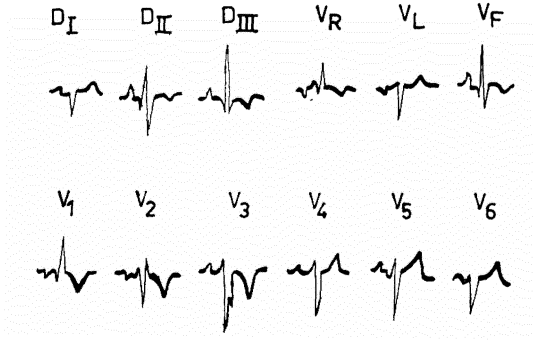


Fig. 11.
E.K.G. in chronic right heart failure.

II. *Examination of the Heart During the Attack.*

The pressure of the alveoli, overly inflated with air and distended, on the thin peripheral branches of the pulmonary artery, causes an increased tension in the pulmonary circulation. The obstruction on the other side of the smaller bronchi and bronchioli causes a state of hypoxia and decreased oxygen saturation of the arterial blood. This produces a reflex constriction of the arterioles of the pulmonary circulation and increases the tension still further.

As a result of the acute emphysema the position of the heart undergoes changes in its position. The heart becomes vertical; as the diminished area of functioning lung tissue causes compensatory hyperventilation, the diaphragm descends, pulling the heart in a vertical position. During this movement the heart rotates around

its long axis, the right heart takes an anterior position and the left ventricle a more posterior one. Moreover, the heart turns around its transverse axis, the apex rotating backwards.

Radiologic signs: The radiologic appearance of the heart is the same as in chronic emphysema, although the changes in position are frequently more pronounced. In very severe dyspnea the elongation of the heart can be so pronounced that it looks like a rod, possessing almost the same diameter over its entire length. The engorgement of the blood vessels produces dark hilar shadows which are in contrast with the clear lung fields.

Electrocardiographic signs: The electrocardiographic alterations during an acute attack proceed from the rotation of the heart around its different axes. As a result a complete normal heart may show gross variations on an electrocardiogram taken during an attack. The alterations which may be encountered are the same as those described under emphysema.

Unless permanent lesions are present, the hypertension in the pulmonary artery and the radiologic and electrocardiographic alterations return to normal as soon as the attack subsides.

Status asthmaticus.

The radiologic and electrocardiographic variations provoked by an acute attack are also encountered in status asthmaticus but generally in a more pronounced form.

The intra-alveolar pressure may reach such levels that in spite of the distension of the thorax, the intra-thoracal pressure may rise above the tension in the right ventricle inducing peripheral venous congestion.

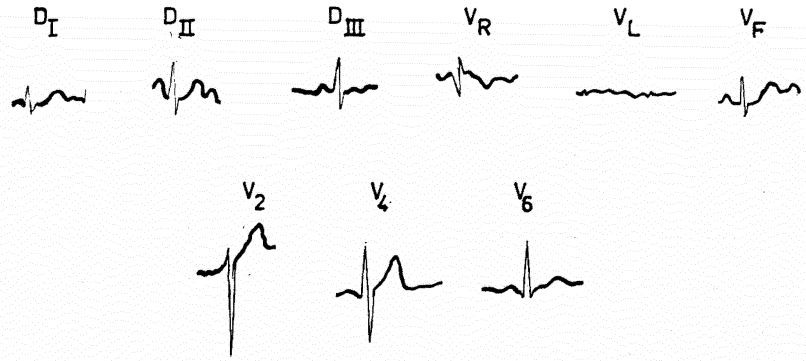


Fig. 12.
E.K.G. in status asthmaticus.

In rare instances the sudden massive obstruction of the pulmonary circulation may be sufficient to cause a dilatation of the right ventricle such as encountered in extensive pulmonary embolism, giving rise to a condition called acute cor pulmonale. If this situation persists for some time the complete picture of right heart failure may ensue.

Differential Diagnosis

Although in the majority of cases the diagnosis of asthma can easily be made on the basis of the history and the current methods of investigation, some patients present themselves with complaints of dyspnea and wheezing, whose symptoms are caused by another underlying disease.

As, in our opinion, the term asthma should be employed only when referring to the illness which has been defined in the beginning of this chapter, all organic or other diseases which may at times cause dyspnea or wheezing should be considered in the differential diagnosis and not, as is seen at times, in the classification of asthma.

Conditions which may present a differential diagnostic problem are mainly those where the bronchial obstruction is caused by tumors, foreign bodies, or compression; dyspnea of cardiac origin and some pulmonary diseases may also have to be considered in the differential diagnosis.

a. *Bronchial obstruction caused by organic diseases, compression, or foreign bodies.*

Symptomatology produced by obstructive causes other than asthma, located within or outside the respiratory tract, may be somewhat similar to the asthmatic symptoms. These include benign and malignant bronchial and lung tumors, foreign bodies, tracheobronchial stenosis, diphtheric or pseudocroup, compression of a bronchus or the trachea by a retropharyngeal abscess, aortic aneurysm, enlarged hilar or mediastinal lymph nodes, a substernal goiter, an enlarged thymus etc.

In case the obstruction is localized either in the laryngo-pharynx, the larynx, or upper part of the trachea, an indrawing of the suprasternal notch and supraclavicular spaces is often obvious during inspiration which is generally not present when the obstruction is located lower; wheezing in those cases is generally absent.

In infants a constant wheezing, not relieved by bronchodilating drugs, may sometimes be produced by an enlarged thymus or enlarged tracheo-bronchial lymph nodes of tuberculous or other infectious origin.

Bronchiogenic carcinomas or benign bronchial tumors such as adenomas, fibromas, chondromas, myomas, or neurogenic tumors, may produce dyspnea and wheezing, mostly unilateral. When the complaints start at an older age, or when the physical chest findings are unilateral, the possibility of a bronchial neoplasm should always be kept in mind.

In these various conditions the chest x-rays, eventually after introduction of lipiodol in the bronchi, as well as the laryngo- or bronchoscopic examination, eventually with removal of a biopsy specimen for histologic study, examination of the sputum for malignant cells etc., generally will reveal the true nature of the disease.

b. *Dyspnea of cardiac origin.*

Hemodynamic circulatory changes act on the respiration, just as respiratory changes affect circulation. Heart and lungs indeed are anatomically and physiologically related, their function consisting in the circulation and oxidation of the blood. Consequently the symptoms arising both from pulmonary and cardiac insufficiency, essentially expressed in anoxia, although resulting in both conditions from a different underlying physiological process, may resemble each other so closely, that it is often difficult to differentiate the one from the other. This becomes even more difficult when both conditions coexist as is the case in chronic asthma, with degenerative lesions of the lung tissues, in which the condition becomes complicated by a chronic cor pulmonale. It may be almost impossible in those cases to state to what extent the signs and symptoms are due to pulmonary or to cardiac insufficiency, which is nevertheless of great importance in order to provide these patients with adequate treatment.

Laboratory tests which may be of aid in the differentiation of these two conditions are the measurement of the venous pressure, which is elevated in cardiac insufficiency, and the circulation time, arm-to-tongue or arm-to-lung time, which is prolonged in this latter condition. Pulmonary function studies and electrocardiographic examination may also be helpful.

In more advanced cases the appearance of peripheral edema, an enlarged tender liver, ascites and engorgement of the great veins, dilatation of the pulmonary artery and right ventricle on the x-ray, are clear indications of cardiac failure.

Acute failure of the left ventricle, occurring mostly at night in recumbency, may give rise to a symptom complex resembling an acute asthmatic attack, and which is caused by the sudden pulmonary vascular engorgement. Their differentiation is, however, of ut-

most importance and the failure to do so may be fatal to the patient.

The history of the onset of symptoms at an older age, the presence on physical examination of abundant moist râles at both lung bases, the character of the wheezing which is more coarse and usually lacks the sibilant high pitch feature, the finding of a markedly enlarged heart and eventually of other cardiovascular diseases, especially those involving the left ventricle (hypertensive and coronary heart diseases, aortic regurgitation etc.), the prolonged circulation time, the elevated venous pressure, and the alterations in the electrocardiographic pattern are the basic points in the differential diagnosis. The x-ray of the thorax is also helpful in determining the cardiac enlargement and gives useful information concerning the congestion of the lungs (accentuation of the hilar shadows and adjacent lung markings, in extreme cases even pulmonary edema).

Likewise the initial manifestations of chronic left ventricular failure, under the effect of strains of various kinds (hypertension, valvular defects etc.) refer generally to the lungs. The predominant symptom caused by a failing left ventricle is dyspnea, caused primarily by congestion of the pulmonary circulation. This shortness of breath is produced at the beginning by only moderate exertion, but with increasing failure it comes on slight effort and finally even when the patient is completely at rest. It is more pronounced in recumbent position as the engorgement of the pulmonary circulation then increases.

c. *Other bronchopulmonary diseases.*

Bronchopulmonary diseases which at times may produce symptoms simulating asthma include pneumoconiosis, pneumonitis, infectious bronchitis, emphysema, the hyperventilation syndrome, tuberculous tracheobronchitis etc. Here also the x-ray, the bronchoscopy and the sputum examination will enable the diagnosis to be established.

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SPECIFIC TREATMENT OF BRONCHIAL ASTHMA

By

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When the allergologic diagnostic methods have revealed one or several allergens to be the cause of the patient's condition, there are two possibilities of specific anti-allergic treatment: *the elimination treatment*, which endeavors to keep the patient away from the allergen, and *the specific hyposensitization*, which attempts to gradually reduce his hypersensitiveness. Under practical conditions the treatment is not always an either-or; the two methods of treatment may often successfully supplement one another.

ELIMINATION TREATMENT

In dealing with this form of treatment it has not been possible to consider solely the elimination treatment of *bronchial asthma.* The allergic disorders are so closely related that it has been occasionally necessary to include other allergic manifestations as well. Generally speaking, however, the writer has attempted to confine himself to the elimination treatment of bronchial asthma.

Animals, animal hair, feathers.—Every cause of the disease should be removed when at all possible. When the diagnostic tests have shown, for instance, that the patient's asthma may be due to the family dog or cat, the doctor should use all of his authority to have the animal removed. True, a favourable result cannot always be expected immediately, as animal hair will remain in the furniture, carpets and other household belongings long after the domestic animal has been removed, but elimination is decidedly the most rational form of treatment. If the cause of the patient's asthma is found to be such a domestic animal, it is henceforth advisable to administer a series of hyposensitizing injections, at the same time as the animal is removed. In addition the patient should be asked to arrange for repeated "spring-cleaning" in his home, so that most of the animal hair may be eliminated.

Furthermore, it should be impressed upon the patient that *the*

elimination must be consistent. It is, for instance, of no advantage to a patient allergic to feathers to use a terylene quilt if he continues to employ a down pillow, or if his wife sleeps beside him using a feather quilt or pillow. All feathers and down should be removed from the bedroom and, if possible, from the other bedrooms as well. What has been stated above in the case of animal hair applies in the same manner to feather allergy, a good result cannot be expected the first night.

Attention should moreover be drawn to the fact that the absence of feathers in the bedroom is insufficient if the patient retains his lovebirds or canaries. Those who have never possessed cage birds do not realize how much the air may be contaminated by feather particles even by keeping a few birds.

It should also be remembered to warn feather allergic patients against the use of down-powder-puffs. One of the writer's patients with feather allergy had carried through a strict featherless regimen and had been hyposensitized with feather extracts—all in vain—until one day in the consulting room she powdered her face with a powder-puff of swansdown. As soon as it was removed, her symptoms were entirely relieved.

On the whole it must be said that to be able to carry through a strict elimination, the doctor must have a thorough knowledge as to the presence of the possible allergens in the patient's surroundings and clothes, and must make himself thoroughly acquainted with his habits, hobbies and interests.

Clothes.—Although allergy to wool and cotton-wool is not infrequent, clothes made of these materials do not necessarily give rise to allergic symptoms. The reason for this presumably is that in manufacturing, the materials undergo such thorough cleaning, bleaching, and dyeing processes that the active allergen is destroyed. The patients often relate that they do not feel any discomfort when wearing woolen or cotton-wool underwear, although knitting with woolen or cotton yarn produces asthma. It is, however, appropriate to advise wool allergic patients to avoid all fluffy woolen clothes, such as certain scarves and jumpers.

Similar considerations apply, though to a less degree, to furs; a Persian lamb coat, for instance, can almost always be tolerated, even though the patient is allergic to wool, whereas those allergic to cats cannot tolerate fur coats of wild cat, ocelot or leopard.

Silk allergy is rare in the northern countries but undoubtedly plays a greater role in the South. Orlons and perlons must be used as substitutes. The so called "buckram stiffening" composed of horsehair and used in men's tailored clothes may produce symptoms in patients allergic to horsehair.

Cosmetics. Respiratory allergy due to cosmetics was previously more frequent than at present, as orris root is now eliminated from most cosmetic products. It may be pointed out, however, that in spite of all medical warnings, orris root is still being used. In the summer of 1956 the writer visited one of the large French perfume and powder factories and to his amazement found that orris root was used as the basic substance in a great proportion of the products of the factory. Fortunately, superior qualities of powder, made without orris root, are available, but it should be realized that powder in which it still constitutes the basic ingredient continues to be sold.

Grease paint contained, at least previously, lycopodium, and, as early as 1935, cases of lycopodium allergy were described in actors by Salén (38). Pharmaceutical chemists, too, may be exposed to sensitization to this product, which is used as an excipient for pills.

Lipstick allergy has been described several times, among others by Pirilä (35). The writer himself has seen a case of chronic oedema of the lips resulting from the use of lipstick and another case of oedema of the eyebrows and forehead caused by an eyebrow pencil. These were cases of contact allergy to the dye in the sticks. On the whole, cosmetics produce contact allergy (resulting in dermatitis) more frequently than respiratory allergy.

Furniture.—Furniture covers, especially those containing horsehair as a reinforcing material, will, upon becoming worn, fill the air in the rooms with particles of horsehair. The doctor therefore should not accept the patient's assertion that he has never had any contact with horses, and that for this reason the diagnosis of horsehair allergy cannot be correct, as it may develop in patients who have never seen a horse. Horsehair is also still being used frequently in mattress stuffing, and an old mattress containing it is repeatedly the cause of the patient's nocturnal attacks of asthma. Cowhair may be found in the homes as well. It was previously used in the manufacture of felt, and old, dusty felt may henceforth give rise to cowhair allergy in a patient who similarly has never come into contact with this animal.

Upholstery is another cause of allergic symptoms. Various species of African grasses and palm leaves are used in upholstery and may produce allergic symptoms in upholsterers. This is possibly a pollen allergy, as microscopical examination may reveal the presence of pollen on the grass and palm leaves.

Indoor plants.—The eczema-producing antigen in Primula obconica is well known, but there are also other plants which contain substances with antigenic properties, e.g., rose geranium. It is doubtful, however, whether these plants produce asthma, although all

grasses and flowers may, of course, give rise to pollen asthma when kept in rooms.

Foodstuffs.—There is little doubt that food allergy plays a greater part in allergic disorders than hitherto supposed. The more one studies this problem, the more one becomes convinced of its importance. The reason why food allergy has been relatively neglected by most workers (except by certain authors like Coca (7), Rinkel (36), and Rowe (37)) is presumably that this concept has indeed been known but considered rather exceptional, occurring mostly in the form of an allergy to shellfish and fish or to cow's milk in infants and being of no appreciable importance in general allergologic treatment. This opinion is undoubtedly wrong. In regard to the recognition of the importance of food allergy, we are today at the same stage as we were 25 years ago concerning the significance of the inhalants in asthma. The relatively exceptional cases of asthma attributed to cat or dog hair sensitivity etc., were recognized, but the innumerable cases due to allergy to house dust, moulds and feathers, things to which the patients are exposed in daily life and which generally cannot be avoided were unknown.

The evolution of food allergy will undoubtedly follow the same lines in the near future. It is *not* the occasionally consumed foods which should be investigated primarily, but those composing the daily nourishment: cereals, rye and wheat, milk, egg, meat, fruit, vegetables, and potatoes. Allergy to these aliments is without doubt much more common than previously supposed.

The diagnosis is not as difficult as may be believed. Contrary to many other authors, I must emphasize that the methods of cutaneous diagnosis are not quite as worthless as has been alleged by some; moreover, when the patient has become symptom-free after an elimination diet, it is not difficult to verify the diagnosis by means of provocation tests.

Of great importance in the treatment of food allergy is the composition of the elimination diet. If a patient is allergic to eggs, it would be short-sighted to allow a full diet minus eggs, for he would then, with a clear conscience, eat foods containing eggs, for instance thick soups and cakes. Furthermore, he *may* present allergic reactions to foodstuffs other than eggs, namely various foods for which he has *not* been examined, since the examination is necessarily limited. *The diet should therefore consist only of the foods to which the patient has shown a negative skin reaction and those which he states have previously agreed with him.* This diet should be strictly observed for at least one month before conclusions may be drawn as to its effect. Thereafter a more varied diet may gradually be composed.

It may seem exaggerated to require that the diet be adhered to for a month; in most clinics the period is confined to 5–10 days, after which additional foods are allowed. It must be admitted that a clinical result is often evidenced within a few days, but cases have also been observed where the improvement did not occur until several weeks had passed. In one of our cases the urticarial eruptions continued to appear one month after exposure to the allergen. Finally, in serum sickness, where the influence of the allergen can readily be determined as to its length of time, eruptions have been seen up to 30 days after its administration.

It is inconceivable that the allergen should remain in the intestinal tract for 30 days, and hardly probable that the foodstuff remains in the organism in a decomposed or converted state for such a long period of time; henceforth, it is more probable that a reaction mechanism is involved which, once started, may react also to unspecific stimuli.

A fact, mentioned amongst others by Feinberg (15), is often observed: during certain periods, for instance the hay fever season, patients with hay fever may present symptoms of food allergy, though they do not have these symptoms during the rest of the year. This means that these patients have a latent food allergy which becomes manifest at certain periods. In such cases the patients should, of course, adhere to the diet only "during the season" or "in the period".

Recurrent food allergy.—Similarly, patients are encountered who do not tolerate certain kinds of food during some periods of their lives, whereas it agrees with them at other times. Bruun & Dragsted (5) reported a patient who had attacks of Quincke's oedema after eating eggs from 1932–34, 1941–42, and again from 1949–50, whereas she could eat them without developing troublesome symptoms during the intervening years.

Drug allergy.—Many severe, sometimes fatal, cases of asthma have been caused by allergy to acetylsalicylic acid, and it is needless to say that patients allergic to salicyl preparations should avoid these; the same applies, of course, to other drugs, for instance, barbiturates, iodine, bromine, and codeine. Generally it is not difficult to ascertain allergy to acetylsalicylic acid preparations, but it may be difficult to decide whether a patient is allergic, e.g., to iodine or bromine, when function tests with these substances are to be made (bronchography, bromsulphalein test). As the cutaneous tests with iodine and bromine are of no value, the precaution should be taken to administer a trial dose one or two days before the examination. When iodine allergy is suspected, 0.5 g. of potassium iodide may be administered up to three times in 24 hours; in the

absence of signs of urticaria, oedema or asthma, the bronchography may be performed the next day, but adrenaline should always be at hand. Similarly, one-tenth of the dose of bromsulphalein to be used for the test may be injected 24 hours prior to the actual examination; if this small dose produces no allergic symptoms, the test may be performed.

Penicillin and streptomycin allergy also require watchfulness. In dealing with drug allergy it may be mentioned that cow's milk may contain penicillin, so that a patient sensitive to it may develop symptoms after drinking milk, though he is not allergic to milk. The minimal amounts of penicillin added to the poliomyelitis vaccine may also give rise to allergic symptoms (Lorenzen (29)).

House dust, moulds.—The inhalation allergens which are constantly present in the air are difficult to eliminate. In many countries, house dust is the most frequent cause of asthma. The concept of house dust in itself is difficult to define as an allergologic entity, and in quite a number of cases it has been possible to demonstrate certain elements in the house dust, for instance, animal hair or moulds, to be the cause of the allergy. These are not actually cases of house dust allergy. It is, however, a well-known fact that ordinarily this is not the case, so that house dust itself must be considered as the cause of the allergy—and it is undoubtedly a specific factor.

In cases of house dust allergy a thorough cleaning of the house should be carried through. Dust traps, such as door curtains and old worn carpets and rugs should be discarded. The wall paper should be removed, and the walls painted with oil or plastic paint. Old furniture which the patient is reluctant to part with may be impregnated against dust with various agents, for instance the American preparation, "Dust Seal". With regard to mould allergy in patients living in damp houses, however, these measures are not always helpful and even a thorough insulation of the house may be insufficient. The patient should then be advised to move to another house, possibly to another part of the country. A stay in a mountainous region with a dry and stable climate has generally a beneficial effect on asthmatics, and if it is possible for a patient to establish himself permanently in such regions, he should be urged to do so. If this cannot be done, intermittent stays at suitable health resorts may also be advantageous.

In Denmark we have at our disposal three homes for asthmatic children, two in our own country and a third in the Norwegian mountains. Although a number of these children have a recurrence of their disease upon returning to their usual surroundings, an analysis has shown that 55 per cent of the Danish asthmatic children sent to the health resort in Norway presented an improvement

lasting at least one year. The duration of the stay is of essential importance; in the analysis referred to above the patients had remained in Norway for 4 months.

In connection with the description of the elimination treatment it may be mentioned what might be termed "the reverse of elimination", namely, chronic exposure of a sufficient degree, which apparently exerts a beneficial effect. By way of example, hay fever is less common in the rural than in the urban population, and bee-keepers seldomly become allergic to bee-stings. The constant exposure probably acts as a hyposensitization. If, on the other hand, the exposure becomes too massive, the organism may react allergically, as is relatively often the case in bakers who develop flour asthma.

Specific Hyposensitization

Hypodermic Hyposensitization.

Technique.—When the diagnosis has been established and the allergen provoking the attacks has been found on the basis of the past history, cutaneous reactions and exposure and provocation tests, an allergometrical titration in the skin is made in order to determine the initial dose for hyposensitization. Intradermal tests are performed with a series of dilutions of the allergen, for example, 1:10,000,000 – 1:1,000,000 – 1:100,000 – 1:10,000 – 1:1,000. The hyposensitization is generally commenced with the lowest concentration producing a positive reaction, as a rule, 1:1,000,000 or 1:100,000. A hypodermic injection of 0.1 ml. of this dilution is given, and injections are then administered about every other day, 0.2 – 0.4 – 0.7 ml. being injected in sequence, followed by 0.1 – 0.2 – 0.4 – 0.7 ml. of the next concentration, and so on.

This progressive dosage requires, however, that any possible local reaction at the site of the injection should be closely observed. The patient is therefore requested to inspect the site of injection from half an hour to one hour and again 12 hours after the injection. Before the next one is administered, the patient should *always* be asked whether he has had any appreciable local or focal reaction after his previous injection. If so, the dosage must not be increased, and an injection of the same strength as the last one should be given; sometimes the same dose has to be injected three or four times before it can be increased. With the concentrations 1:1,000 and 1:100 it is advisable to be even more cautious, and, perhaps, to increase the dose only by 0.1 ml. each time.

It has often been surprisingly observed that a change from one concentration to the next—e.g. 1:1,000 0.1 ml after 1:10,000 0.7 ml.—may cause a vigorous local reaction to 1:1,000 0.1 ml., though the preceding injection did not produce any. The explanation seems to be that the antigen adheres to the glass wall of the vial in quantities which cannot be given in per cent; apparently a constant dilution of the extract takes place in regard to its antigen content. This means that the lesser the amount of extract in the vial, the greater proportionately is the amount of antigen that adheres to the glass wall (N. Hjorth (27)). As the hyposensitization treatment will generally be continued from a half empty or almost empty vial to a full one, the allergen dosage is consequently not increased quantitatively as desired, but by more than intended. Investigations on these phenomena are in progress and have not as yet been concluded; it may, however, be pointed out that caution should be taken when treatment is continued with another concentration of the allergen.

The entire treatment requires tolerance on behalf of the patient as well as the doctor, but when the above mentioned precautions are observed, it should be possible to eliminate severe systemic reactions, provided, of course, that intravenous injection is avoided. In Denmark the general practitioners largely perform the hyposensitizing injections according to the directions given by the allergologist and based on the methods mentioned above. The cooperation between specialists and general practitioners is excellent.

The hyposensitizing injections are given *hypodermically* on the dorsal side of the forearm. Though it must otherwise be considered a technical error, there are two reasons why the forearm has been chosen as the site of injection: first a possible local reaction can more easily be read in the tenser tissue of the forearm than on the thigh, secondly,—and this was decisive as to the choice of the site of injection—a possible constitutional reaction can more effectively be treated as the forearm can readily be isolated from the rest of the organism by means of a rubber-tube tourniquet (see Risks p. 287).

When the highest dose which the patient can tolerate has been reached—generally 1:100 0.4 – 0.5 – 0.6 or 0.7 ml.—treatment is continued with this strength as a maintenance dose once every second, third or fourth week, perhaps for years.

For many years Hansel has advocated the so-called "small dosage therapy"; a treatment consisting of repeated injections of small quantities of antigen, always of the same dosage. The theoretical foundation of this theory is that the immunological reactions of the organism apparently adapts to small as well as to large quantities of the antigen and results in the same clinical response (21 a). The

advantage of this method of treatment is that it excludes almost entirely the risk of systemic reactions.

However, it has been shown by Frankland (18) that a high dosage of pollen extract gave significantly better results in the treatment of both hay fever and hay asthma than a low dosage scheme, and the same applies to the treatment of other types of asthma (Bruun).

When the highest dose of the allergen has been reached and it has been explained to the patient that he has to continue the injections at intervals of 2, 3 or 4 weeks, the question arises: "How long must one continue in this manner?" Until present no definite rules have been established; on the basis of many years of experience we endeavor in Copenhagen to carry through the hyposensitization until the patient has been free of symptoms for at least one year, whilst at the same time a definite decrease of the cutaneous allergy is ascertained (see also the section on clinical results).

Rush-Hyposensitization.

Specific hyposensitization has the drawback that a long period of time is generally required before a clinical result is obtained. If the injections are given at 2 or 3 days interval, it takes from 2 to 3 months before the maximal dosage is reached. In 1930 Freeman (19) introduced the so-called rush-hyposensitization, whereby 4 to 6 injections are administered daily. In this way the maximal dose can be reached in less than a week, and the clinical results are claimed to be as good as with the ordinary form of treatment. However, the risk of troublesome local and systemic reactions in the course of treatment is highly increased, and the method should, therefore, only be used if the patient is hospitalized.

In several cases the principle of the rush-method can successfully be combined with the usual form of treatment, so that injections are given 2 to 3 times daily at the beginning of the hyposensitization when the risk of systemic reactions is lowest, and the intervals between injections are later extended to several days when local reactions begin to appear.

Mode of Action of Specific Hyposensitization.

In an animal which has survived an anaphylactic shock a reduction in the amount of anaphylactic antibodies can be ascertained immediately after the shock, in many cases they cannot be evidenced any more at all. The animal has thus become anti-anaphylactic or desensitized. Such a complete desensitization cannot be seen in the allergic patient; generally no reduction in the amount of circulating

antibodies can be demonstrated after an allergic shock, and in some cases the Prausnitz-Küstner reaction is even more pronounced after a successful hyposensitization than it was before. The content of circulating reagins in the blood thus cannot provide information about the mode of action of specific hyposensitization. Another factor which possibly might afford information is the content of reagins in the tissues, especially the skin, before and after specific hyposensitization. Most authors agree that the cutaneous reactivity is generally lowered after successful hyposensitization, although it must be admitted that in very rare cases it is increased. A few authors mention that the cutaneous reactions are not impaired by hyposensitization, and Markow & Spain (33) maintained that the skin should be considered the constant factor and the antigen extract the variable one. They are of the opinion that the less pronounced cutaneous reactions after hyposensitization are due, not to a lowered content of reagins in the skin, but to the fact that in the course of time the strength of the allergen extract has been attenuated. In contrast however with this view, mention may be made of Colme's (8) investigations as early as 1932 in hay fever patients, where he had secured the stability of the extract and where a definite reduction of the cutaneous allergy could be demonstrated in 91 per cent of the patients after specific hyposensitization. Harley (22) (1937) and Bruun & Lous (6) (1946) have made similar observations. Harley even considers that the content of reagins in the skin may disappear entirely after intensive treatment.

Generally speaking, it may be said that a lowered cutaneous reactivity is seen after specific hyposensitization, and that there is, as a rule, parallelism between a good clinical result and a lowered cutaneous sensitivity. However, already in 1933 Colmes & Rackemann (9) proposed the idea that the clinical effect of hyposensitization and the lowered cutaneous allergy following hyposensitization might depend on two different factors, independent of each other. This view is strongly supported by the discovery a few years later by Cooke and co-workers (11) of the so-called blocking antibody. They showed that blood transfusions from hyposensitized hay fever patients might improve hay fever in non-hyposensitized patients. In 16 out of 20 patients of the latter category a good clinical result was obtained with transfusion. The content of reagins in the blood of the recipients showed no or very slight changes, and thus the clinical result could not be attributed to a lowered amount of circulating antibodies. Cooke and co-workers therefore thought that a special antibody was formed in the course of specific hyposensitization—"a peculiar blocking or inhibiting type of immune antibody that prevented the action of the allergen on the sensitizing antibody"—

and, when transferred to non-hyposensitized hay fever patients, this blocking antibody exerted the clinical effect.

In subsequent studies Cooke and co-workers (11) showed that the blocking antibodies may develop in non-allergic persons without the simultaneous formation of skin-sensitizing antibodies. However, to obtain the formation of blocking antibodies in normal individuals, a more intensive treatment is required than in allergic patients. Loveless (30, 31) demonstrated that the blocking antibody is thermostable, whereas the skin-sensitizing reagin is thermolabile.

The discovery of the thermostable, blocking antibody, which hypothetically inhibits the fixation between the antigen and the natural thermolabile antibody, was soon confirmed by other investigators, although its clinical importance readily became the subject of discussion. In 1941 Scully & Rackemann (42) demonstrated that there was no correlation between the amount of demonstrable blocking antibodies and the clinical result of specific hyposensitization, and in a case of clinically successful hyposensitization (dust allergy) van Dishoeck & Klein (14) (1943) could not evidence the formation of blocking antibodies.

Another fact seems difficult to interpret: if the favourable effect of specific hyposensitization is due to the formation of blocking antibodies, how then can these antibodies reduce the susceptibility of the mucous membranes of the eyes and respiratory tract without simultaneously producing a similar decrease in the sensitivity of the skin?

This is a crucial point, and the question arises whether the specific hyposensitization does not activate several, mutually independent factors, the lowered cutaneous allergy representing one factor, the formation of blocking antibodies being caused by another. Probably, several other factors which are still unknown are involved as well. Cooke (10) wrote (1947) about the blocking antibody: "Possibly it is a factor in clinical immunity, but in view of what has been said I do not think there is yet sufficient proof that it is the most important factor ... Evidence has been submitted to show that there is some other unknown mechanism of immunity which operates in the complete absence of demonstrable blocking antibody".

In this connection, mention may be made of Wiener's and Heidelberger's investigations on antibody formation. Heidelberger (23, 24) worked with protein antigens in horses, and Wiener (47) demonstrated that rhesus-negative individuals who were sensitized with the rhesus factor form two types of antibodies: (1) a divalent type which possesses points of resemblance to agglutinins; the skin-sensitizing reagins in allergic individuals belong to this group, (2) a monovalent type, termed glutinin; to this group belong the block-

ing antibodies. These two types of antibodies can be separated by simple methods, for example, dialysis (Witebsky et al. (48)).

It has often been assumed that the allergic reaction should depend on a lack of circulating antibodies, whose amount is insufficient to "neutralize" the invading antigen, and that the principle of hyposensitization treatment is to increase the amount of circulating antibodies. Although this theory has now been abandoned by most workers, it still emerges, and was mentioned as late as 1956 by Herxheimer (26); it may therefore be briefly referred to here. It must be pointed out that it is not the amount of circulating natural antibodies which is increased by hyposensitization, but that blocking antibodies are formed; nor can it be the amount of circulating natural antibodies which is too small in the allergic state; it seems to be the amount of sessile, tissue-fixing antibodies which is too large.

It might, of course, be tempting to assume that if large amounts of circulating antibodies had been available for "neutralization", no allergic reaction would appear. This theory cannot be correct, considering, for instance, that in latent allergic individuals skin antibodies but no circulating antibodies can be demonstrated, hence it will be understood that the manifest allergic condition cannot be due to the lack of circulating antibodies. The latent allergic persons simply lack circulating antibodies, and they have no clinical symptoms of allergy.

Moreover, J. Blamoutier (1) has demonstrated that venoesections in patients with hay fever, performed immediately before or during the season, have a good, though transient, effect on hay fever. This contradicts the point of view that the allergic condition is due to a too small amount of circulating antibodies (as the venoesections must reduce it further). On the other hand, some of the clinical effect of venoesection may possibly be interpreted as a result of an increased secretion of ACTH.

Summarizing, it may be said that in specific hyposensitization both blocking antibodies and bodies exerting an effect on the skin-sensitizing reagins are formed. In all probability other factors are included in the mechanism as well.

Clinical Results.

It is hardly likely that other forms of treatment exist whose effectiveness has been more disputed than that of specific hyposensitization. This is not surprising when one considers how capricious a disease asthma is and bears in mind that it is only since the last 10 to 20 years that the importance of a number of the common aller-

gens of everyday life, such as house dust, moulds, feathers, etc. has been realized.

We are now aware of the fact that a positive skin reaction alone is not a sufficient indication for hyposensitization. First of all it is necessary that the positive skin reactions be corroborated by the patient's history and preferably be confirmed by a positive provocation test. The whole concept of latent allergy passed unnoticed until it was described in 1935 by Salén & Juhlin-Dannfelt (40), and therefore, in the nineteen-twenties and well into the thirties, many disappointments were experienced in the treatment. In a number of cases, hyposensitization was commenced on a false assumption, a more or less haphazard positive cutaneous reaction, and poor results were henceforth obtained.

It should moreover be realized that in asthma specific hyposensitization is only effective in *bronchial* asthma, that it is, of course, ineffective in cardiac asthma and, similarly, that it can bear no effect in emphysema. A patient who suffers *only* from dyspnea on exertion cannot improve through hyposensitization. It is also obvious that hyposensitization cannot influence purulent sinusitis, purulent bronchitis and bronchiectasis. It is, however, still necessary to draw attention to these facts as long as the allergologists are reproached with poor results in the complications of asthma.

After we have obtained better criteria for the indications of specific hyposensitization, the results improve correspondingly. It must be constantly pointed out that all other forms of therapy, including ACTH and steroids, are *symptomatic* treatments, whereas the elimination treatment and specific hyposensitization are the only methods of causal therapy.

It has moreover been realized that if the patient remains in the surroundings containing the provoking allergen, it is not sufficient to carry through a hyposensitization up to the so-called maximal dose, and then to conclude the treatment. Even though the patient has thus improved considerably, and is possibly free of symptoms, the hyposensitization should be continued for a long period, probably for years. A distinction should be made here between two principles of treatment: (1) if the patient presents an allergic reaction to a factor which is removed from his surroundings, e.g. a cat, short-term hyposensitization, lasting a few months after the cat has been removed and until the patient is free of symptoms, will generally suffice; (2) if, on the other hand, the patient's disease is caused by an allergen which cannot be removed from his surroundings, such as house dust, the hyposensitization must be continued for years. True, in these cases a good effect is generally seen after some months, but experience has shown that a considerable number of

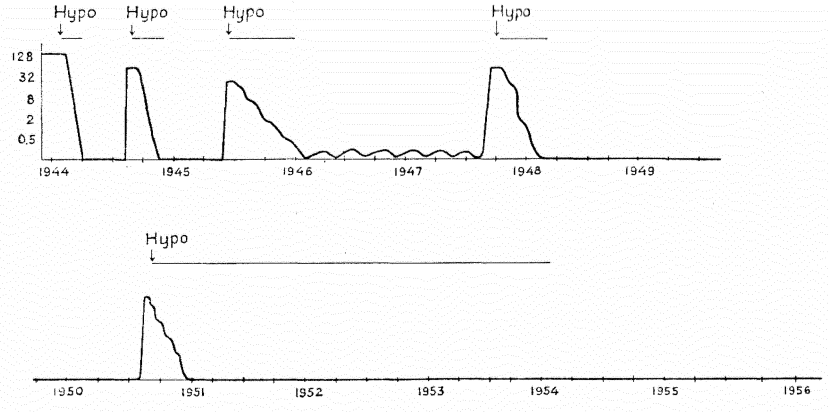

Diagram I.
Rec. No. 662/44. ♀ *1890. Asthma since 1933. Allergic to house dust.
Ordinate: Average duration of asthma attacks (hours per month).
Hypo = Specific Hyposensitization. See text page 284.

patients have a recurrence after a certain period of time. It seems, however, that repeated hyposensitization treatments increase the percentage of good results and it is likely moreover that prolonged hyposensitization, lasting for years, can keep the patients symptom free or greatly improved for a number of years after the treatment has been concluded (Bruun (3, 4)).

This may be illustrated by an example (Diagram 1). A woman, aged 54, consulted in 1944 the Clinic for Allergic Diseases, Copenhagen, for bronchial asthma. Her complaints began in 1933, thus lasting 11 years. She presented a pronounced allergic reaction to house dust. During recent years she had been greatly affected by her disease; she stated that during these years she had severe attacks of asthma on the average of more than 5 days every month. From February to April, 1944, she was hyposensitized with house dust, and became free of symptoms during the period of April to September, 1944, when she had a recurrence. Another hyposensitization from September to December, 1944, resulted in a relief of the symptoms from November, 1944, until June, 1945. Once again severe attacks recurred and she was therefore hyposensitized for another, somewhat longer period, from June to December, 1945. She was then almost symptom free from January, 1946, to August, 1947, when she had a recurrence again. Renewed hyposensitization from September, 1947, to February, 1948, resulted in freedom of symptoms from February, 1948, to September, 1950. At the time it was realized that the symptom-free intervals became longer after each treatment. In September, 1950, she had another recurrence, and it was then de-

cided to carry through a long-term hyposensitization. She was treated for over 3 years (from September, 1950, to January, 1954), and not only was she free of symptoms during the treatment, but also during the ensuing period of observation lasting now over 4 years.

It appears from this observation that the clinical result improves with regard to the duration of the symptom-free periods after each hyposensitization; moreover a specific hyposensitization may give results of long duration after discontinuance of the treatment, exceeding one's expectations. Apparently a sufficiently prolonged and intensive treatment may take the patient over the asthmatic condition even though she remains in her usual environment.

It may be noted that the example given above was not purposely selected; it represents the first of a great number of asthmatics who have received maintenance treatment over a duration of years. It may also be mentioned that the patient referred to above received no other treatment during the period from 1944 to 1957 than the specific hyposensitization, except symptomatic treatment with the hecto-spray she was using when the specific hyposensitization was started.

The diagram shows how difficult it may be to estimate the effect of specific hyposensitization. The doctor, or the hospital department, who see the patients only during their bad periods, may be inclined to deny that hyposensitization has any effect. If, on the other hand, the patient is followed for years, and a diagram is made showing the relation of the patient's condition to specific treatment, the effectiveness of hyposensitization is convincing.

Furthermore, when the fate of patients who have been subjected to specific treatment is examined in regard to death rates caused by asthma and the granting of disablement pensions as a consequence of the disease, it appears that these patients manage better than the controls (Malmros & Rydberg (32), Henriksen (25)), i.e. asthmatics who have received symptomatic treatment only.

It is obvious that both patient and doctor are interested in the question of the duration of the specific hyposensitization as a long-term treatment in order to obtain the optimal result. The natural question proposed to the doctor is, "How long am I going to have injections?" And even more often, "How long will the effect last?"

The answer to the first question undoubtly is that the treatment will probably have to be carried on for years, and that there are great individual differences. On the other hand, the patient may be reassured when he is told that, after the first three months or so, the treatment will be very easy and convenient to follow, as it shall be necessary to return to his doctor to receive his maintenance dose only once or twice a month and to come for control to the aller-

gologist once or twice a year. When it is further explained that his condition is not attributed to an infection which can soon be cured with an antibiotic, or is not to be compared to a fracture, the healing of which can be predicted fairly precisely as to its length of time, but that asthma is a *constitutional anomaly,* requiring prolonged treatment and control, it is seldom difficult to secure the understanding and ready cooperation of the patient.

As already mentioned, no definite general outlines have been established as to the duration of hyposensitization. On a purely empirical basis we require at the Clinic for Allergic Diseases in Copenhagen that two criteria be fulfilled before the treatment is discontinued: the patient must be free of asthma for at least a year, and the cutaneous reactions to the provoking allergens must be distinctly reduced. Even though opinions differ as to the behaviour of the cutaneous reactions during and immediately after specific hyposensitization, as mentioned above, there is no doubt that they are practically always reduced in the course of treatment, and Markow & Spain's interpretation of the content of reagins in the skin being the constant, and the antigen extract the variable factor, must be wrong. If the patients are tested at intervals of 6 months during a period of treatment lasting for years, and on each occasion with fresh, biologically standardized extracts, a gradual decrease in the cutaneous allergy will be observed in the long run.

The second question, how long will the effect last, must be answered rather vaguely. The doctor may, with a clear conscience, recommend specific hyposensitization to the patients as the only existing form of causal therapy and, referring to what was said above concerning asthma as a constitutional anomaly, may say that there is a fair chance of freedom of symptoms, but should not promise recovery.

A third question, which is almost always asked by the parents of asthmatic children, is "Will the child "outgrow" his asthma?" It is true that a certain percentage of asthmatic children are apparently spontaneously freed from the disease at the time of puberty; however, a sober analysis shows that this applies at most to about 20 per cent of the cases. In contrast with this it may be stated that the corresponding percentage of improvement in asthmatic children subjected to specific hyposensitization is about 85 per cent. In children, too, specific treatment should generally, therefore, be recommended.

On the specificity of the specific hyposensiization.

Is hyposensitization accurately termed a specific treatment? It has been said that it might be a purely psychic treatment, or that

the effect is due to unspecific protein therapy, as the antigen extracts always contain small amounts of protein.

In 1935 Hurst was unable to demonstrate any difference between the effect of hyposensitization with that of injections of an isotonic saline solution; this, of course, might suggest that any possible effect of hyposensitization is of a purely psychic nature.

However, in 1947–48 a well controlled placebo experiment was performed in Copenhagen in 189 asthmatics, 100 receiving specific treatment, and 89 being treated with placebo. It appeared that 34 per cent of the placebo patients stated that they felt a distinct improvement during the treatment, but in the group subjected to specific treatment, under exactly the same conditions and with the same criteria, an improvement of 78 per cent was ascertained. It then appeared in a duplicate experiment that the patients who did not improve under placebo treatment could improve in 75 per cent of the cases in the course of a subsequent specific hyposensitization.

Consequently, there can be no doubt that specific hyposensitization affords decidedly more than a purely psychic treatment, but the experiment denotes interesting information about the importance of psychic factors in the treatment of asthma. When the patients believe they are treated with skill by a specialist—and presumably by any doctor in whom they have confidence—about one-third will improve, no matter what kind of treatment they are given. An essential part of the improvement among this third will, however, be due to the spontaneous fluctuations in the disease. This fact must be considered in every form of treatment of asthma, and a preparation which can show only an approximate 35 per cent improvement, probably does not possess any pharmacological effect on asthma.

Can the result of specific hyposensitization be due to unspecific protein effect? In reply to this question it may be answered that the protein content in the allergen extracts is so small that, for this reason alone, the possibility that it might exert an appreciable effect as a method of unspecific treatment, can be excluded. Furthermore, it has never been possible to ascertain any accordance between the protein content of an extract and its antigenic properties, nor is there apparently any correlation between the protein content of the extracts and the results obtained by hyposensitization.

Risks.

Hyposensitization has often been referred to as a risky form of treatment, and it is true that deaths have occurred owing to the injection of antigens. In some cases, death was due to the fact that the injection had been given intravenously instead of hypodermic-

ally, in which case death may follow very rapidly; however, a single case has also been described (Salén & Björnstjerna (39)) where the injection was given *secundum artem* and death occurred several hours later.

It must, however, be stressed that fatal accidents are so relatively few in comparison with the large number of patients treated, that they cannot contravene this form of treatment (for the frequency of allergic systemic reactions, see p. 291). But the treatment does call for caution and attention. Except for Salén & Björnstjerna's case, all the severe complications have occurred within a few minutes after the injection of the antigen. The patient should therefore always remain under the doctor's control for 20 minutes after the injection. In addition, the patient ought to be told that if symptoms of a systemic reaction develop, he should inform the doctor immediately.

Symptomatology.

The general reactions which may occur in connection with the allergologic diagnostic methods and anti-allergic treatment are generally divided into two groups: systemic and constitutional reactions. An allergic systemic reaction may develop into a constitutional reaction, but generally subsides under proper treatment. In a third group may be mentioned the abdominal reaction, which in its pure form, is an extremely rare occurrence.

The allergic systemic reaction appears within the first 10 minutes after the injection of the antigen; its first symptom is an intense local reaction at the site of injection with streaky lymphangitis extending up the arm (it is taken for granted that diagnostic and therapeutic antigen injections are always given into the forearm, see later paragraphs). The patient then complains of itching of the eyes; the conjunctivae become injected, face congested, and gradually a generalized redness and urticaria develop. The pulse is now hard and the blood pressure normal. If adequate treatment is then given immediately, the reaction will soon subside. If the symptoms are neglected, the patient will develop an oedema of the face and fauces, accompanied by a dry cough caused by oedema of the mucous membrane of the respiratory tract, and gradually a typical attack of asthma occurs. Thus far the condition can generally be effectively controlled, and the patient sometimes improves spontaneously; nevertheless this is a possibility one should never consider. The patient is now in danger of passing into the state of shock: his skin, congested until now, turns greyish pale, or greyish cyanotic; the pulse becomes low and feeble, possibly unperceptible; the blood

pressure falls; involuntary evacuation of excreta occurs; and death may now ensue owing to circulatory collapse with cerebral anoxia.

This form of shock, occurring after an allergic systemic reaction, can usually be avoided. As already mentioned, the symptoms appear in the course of the first 10 to 15 minutes after the injection, and develop comparatively slow during the next 10 to 20 minutes. They are preceded by such characteristic prodromal signs that any alert physician has the opportunity of interfering in time.

The allergic constitutional reaction, which starts with symptoms of shock, including a rapid fall in blood pressure, develops so acutely that it is not always possible to commence treatment before the injury is irreparable. It takes place with extreme suddenness, and death may occur within a few minutes.

If the cause of the shock is an intravenous injection of antigen, the symptoms may appear within ½ to 1 minute, although generally, as in the systemic reaction, they do not occur until approximately 10 minutes after the injection has been given. There are few or no prodromal symptoms; the patient suddenly turns greyish pale, the pulse is barely perceptible, breathing becomes shallow. The patient falls into unconsciousness and may develop clonic convulsions; in many cases there is involuntary evacuation of excreta. Death may occur within a few minutes.

It may seem astonishing that the disaster can happen so rapidly in an otherwise healthy patient. In all probability the explanation must be that a more or less complete paralysis of the musculature of the capillaries occurs. These have a surface area of about 6300 square metres, which is about 3000 times the body surface; and it has been calculated that, if there were no antagonistic forces in the capillaries, the total volume of plasma would be able to pass into the tissues in the course of 10 seconds (Vaughan & Black (45 a)).

The abdominal type. In Quincke's oedema, gastro-intestinal forms of allergy may sometimes be seen which may be difficult to diagnose, and have induced surgeons to perform laparotomy in several cases. The allergic systemic reaction may also, though seldom, appear in the form of an acute abdomen, where the shocked patient complains of violent abdominal pain, constant or occurring in attacks, and where the abdomen is hard and tense. Sooner or later, generalized urticaria or oedema of the face appears, but, in the purely abdominal phase the diagnosis may be difficult to establish if the possibility of abdominal symptoms as part of an allergic systemic reaction is not realized.

Treatment.

The allergic systemic reaction.—As soon as the symptoms begin to appear a rubber-tube tourniquet is applied proximal to the site of injection. As previously mentioned, the diagnostic and hyposensitizing injections should always be given in the forearm, so that the tourniquet may be applied to the upper arm, thus producing an effective arrest of the circulation from the rest of the body. When the tourniquet has been applied, 0.5 ml. of a 1–1000 adrenalin solution is administered at the site of injection of the antigen, and a similar dose is injected into one of the lower extremities. If the reaction is not extremely violent, this dose of adrenalin will suffice, and the troublesome side-effects of adrenalin administered in higher dosage are avoided.

Within a few minutes the patient will state that he feels better; the tourniquet is then replaced by a blood pressure cuff, and the tension is kept between systolic and diastolic pressure. If the patient continues to feel all right, the cuff is deflated, but should be left on the arm to be rapidly inflated again in case of recurrence of symptoms.

When the patient feels free of symptoms, he should be urged to remain in the consultation room for another hour. If he is still feeling well, he should be given an antihistaminic tablet and enjoined, when discharged, to remain quiet the rest of the day.

The allergic constitutional reaction is treated on the same principle as the systemic reaction without shock: application of a tourniquet above the site of injection, and adrenalin injection(s). In such cases, however, a higher dose of adrenalin should be given at once into the lower extremity, for instance, 1 ml. As soon as this has been done, a needle is inserted into a vein and a syringe containing a 1–1000 solution of adrenalin is connected to it. An assistant or a nurse holds the syringe. It is important that the needle should be introduced into a vein before the veins collapse. At the slightest sign of unconsciousness or collapse, adrenalin should be injected intravenously, slowly or more rapidly according to the patient's condition.

Adrenalin should be given intravenously when the life of the patient is in danger, but should not be administered in this manner unless it is absolutely necessary, as it is one of the most unpleasant forms of treatment to which the patient can be exposed. After an intravenous administration of adrenalin, the patient feels as though he was going to explode. He is distressed, saying that he would rather die, and that his head feels as if it was being blown up; his mind may actually become confused and he could become quite

unmanageable. Nevertheless the physician should not hesitate to use this form of treatment when considered necessary. On two occasions the writer has seen that it saved the patient's life, and he would consider it his duty to use it again in similar situations.

If it is not possible to introduce the needle into a vein or if the patient is unconscious, adrenalin should be given into the heart. Some workers prefer to give aminophylline or theophylline intravenously instead of adrenalin, and in most cases of allergic reaction this form of therapy is sufficient. In critical situations, however, the small quantity of adrenalin is easier to handle than the rather big quantity (10–20 ml.) of aminophylline. Besides, adrenalin seems to be quicker acting.

It may be mentioned that other forms of therapy, especially the intravenous injection of calcium, have proved rather ineffective in the case of constitutional reactions. In Copenhagen, we have administered up to 30 ml. of a 10 per cent calcium solution intravenously without effect. The action of the antihistaminic preparations and of ephedrine is too slow to be of any use in the case of acute shock, nor can ACTH and cortisone exert their effect during the short decisive period of time. In case of pharyngeal oedema, spraying with a 10 per cent solution of adrenalin has proven helpful.

Incidence.

With regard to the incidence of *the allergic systemic reaction*, Schwartz (41) stated in 1943 that he had found from 1 to 10 per cent of systemic reactions in testing and treatment with inhalants. Flensborg (17) (1950) found 26 per cent of systemic reactions in treatment with bacterial antigens.

There are several reasons why such a wide margin, varying from 1 to 10 per cent, are given by Schwartz. The technique of testing and treatment plays a great part. If tests are performed uncritically with potent extracts, there will be a relatively high incidence of systemic reactions. With scratch tests the systemic reactions are less frequent than with intradermal tests. If hyposensitization is performed according to a fixed schedule reaching high concentrations of the antigen, a greater number of systemic reactions will appear than in the case of individualized treatment. If a vigorous local reaction following the last injection is neglected, there is a risk of a systemic reaction which otherwise might have been avoided. The nature of the allergy also plays a part; patients allergic to pollens rather often develop systemic reactions, because they generally have a very pronounced sensitivity to pollen, or possibly because pollen is an especially pure antigen. This is illustrated by Fursten-

berg & Gay's publication (20) in which they mention that they have seen 75 cases of severe shock in 29,547 pollen injections, but only 2 cases following 7,744 injections of other antigens.

In the Allergy Clinic in Copenhagen it is estimated that from 10 to 20 systemic reactions occur in 100,000 to 150,000 injections per year.

With regard to the incidence of *the constitutional reactions*, i.e. the truly dangerous cases, there are exactly the same possibilities as in the case of the systemic reactions. In 1927 Vander Veer & Spain (44) observed 96 constitutional reactions in 14,280 pollen injections; Waldbott & Ascher (46) had 141 cases in 51,036 pollen injections. In Copenhagen, Schwartz found 5 cases of constitutional reactions in the treatment of 183 allergic patients, about half of them being asthmatics. In Henriksen's series from the same Clinic, however, there was only one case of constitutional reaction in the testing and treatment of 538 patients, all asthmatics. With the technique that has now been developed at the Allergy Clinic there are but few constitutional reactions, hardly more than 1 or 2 per year, and chiefly occurring in patients allergic to pollen and animal hair.

The *abdominal type* is very rare; the writer considers that he has observed only two cases of this kind.

With regard to the incidence of *fatal constitutional reactions*, reference may be made to surveys by Henriksen (25), Midttun (34), Salén & Björnstjerna (39), and Vaughan & Black (45 b). In all, the literature hardly contains more than 75 cases of fatal constitutional reactions; this figure includes 28 patients who died after injections of serum and antitoxin, several cases of death following bee-stings, administration of aspirin and quinine, injections of novocaine etc. The number of published fatal constitutional reactions following allergic diagnosis and anti-allergic treatment scarcely exceeds 20. During the last few years a rather shocking figure of deaths due to penicillin allergy has been reported, but these cases have not occurred during allergic diagnosis and anti-allergic treatment. Twenty cases is, of course, a great number, but it should be regarded, taking into consideration the enormous number of antigen injections given each year all over the world. Assuming that there are 5 million patients with hay fever in the U.S.A. (Feinberg (16) states from 5 to 7 million), and supposing that only 1 per cent of these are hyposensitized, each patient receiving 40 injections, 2 million injections per year are given in the U.S.A. to patients with hay fever only. Furthermore, an estimate should be made of the number of hyposensitizing injections to other patients in the U.S.A. as well as those administered in the rest of the world. The 20 fatal cases date back to 1911 when hyposensitization was introduced. It is true that hardly all fatal cases have been published, but the 20 deaths, or

more, should be considered in relation to at least a hundred million injections. In the Allergy Clinic in Copenhagen, where, broadly speaking, from 2 to 2½ million antigen injections have been given since 1941, there have been no fatal reactions.

What can be done to avoid allergic systemic reactions?

1) A number of obvious measures which are nevertheless most frequently overlooked may first be mentioned:
   a) The antigen vials should not be confused; the physician should take great care that he is using the proper extract each time in the right dilution.
   b) The dose of antigen should be exactly as prescribed. It must be urgently advised not to "take a short cut" by increasing the dose too rapidly.
   c) If a preceding injection has produced a local reaction of long duration, the dose must not be increased, but the same dosage as the previous one should be given.
   d) Care should always be taken not to give the injection intravenously.
   e) The patient should be under observation for at least 20 minutes after receiving the injection.
   f) In titration of positive reacting allergens, tests with more than two allergens should not be made on the same day.
2) The patients should be advised to avoid exposure to heat and exertion, for instance steam baths and tennis games, immediately after the antigen injection.
3) Some patients are more liable to develop systemic reactions, the so-called "habitual shock patients". They should be given an antihistaminic tablet 30 minutes before each injection of antigen, and 0.2 ml. of adrenalin (1:1000) should be added to each injection.
4) Certain allergens are inclined to produce systemic reactions; this applies, e.g. to pollen. Therefore, if pollen allergy is suspected, tests should not be made with concentrated pollen extracts, but with concentrations not exceeding 1:1000. If egg allergy is suspected, still greater caution is called for.

Another risk consists in *treatment with mixed extracts,* in which the separate allergen component constitutes only a fraction. This form of risk will not involve such direct serious consequences as the systemic reactions, but it may compromise the specific hyposensitization treatment. Many physicians—even allergologists—prefer to compose the therapeutical extract with due regard to all the

patient's positive cutaneous reactions. We may, for instance, be consulted by patients who have been treated with extracts composed of 3/10 of house dust, 1/10 of feathers, 2/10 of cat's hair, 1/10 of aspergillus, 1/10 of shellfish, and 2/10 of grass pollen. This represents the whole range of positive cutaneous reactions in the patient, but it is evident that no attempt has been made to evaluate the significance of the cutaneous reactions, and that an exact allergic diagnosis has not been made. When such a patient is more thoroughly examined, it will usually be possible to demonstrate that he is manifestly allergic, for instance, only to cat's hair, and that the other reactions have been indicative of latent allergy. The patient can, however, justly maintain that he *has* previously been hyposensitized with cat's hair (cfr the extract mentioned above) without any appreciable effect. It must then be explained to him that the extract with which he has been treated has been too weak in regard to cat's hair, and that he has now to be treated with an extract made exclusively of this antigen.

Even though the patient might be manifestly allergic to several allergens, the best procedure is to use only pure, unmixed extracts. The patient may be treated with two extracts at the same time, for instance, house dust and feathers, the former being injected into the right arm, the latter into the left. If the patient should be manifestly allergic to more than two allergens, treatment with the other allergens must wait until he has reached the maintenance dose of the first two. When these are given once every three weeks, treatment with another possible allergen may be commenced.

This, of course, may become somewhat troublesome, but provides in turn a much better result. It must actually be considered a technical error to treat with so diluted extracts that the clinical result is exposed to risk, and the treatment compromised.

One exception, is however, treatment with extracts of mixed grass pollen. This preparation is composed of different species of grass pollen, and the majority of patients with grass hay fever react to the species of grass of common occurrence. For several years, however, such hay fever patients have been treated in Sweden with an extract consisting exclusively of timothy pollen, and the results obtained have been just as good as those with composite extracts elsewhere.

Grass pollens are thus so closely related that a mixed preparation of grass pollens is just as effective as one consisting exclusively of the pollens to which the patient responds most vigorously. But a patient with tree hay fever, or one with ragweed hay fever, cannot be treated with grass pollen extract. Of the three types of hay fever (trees, grasses, compositae) each requires its individual treatment.

Oral Hyposensitization

Oral hyposensitization with allergens in the form of tablets or drops has often been attempted, and theoretically hyposensitization in this way should be a usable method. Dencker & Schwartz (13) have shown that such a complex allergen as soya-bean meal can pass the mucous membrane of the intestines in an allergenic active state.

Oral hyposensitization was introduced as early as 1921 by Pasteur Vallery-Radot & co-workers (43) in a case of vasomotor rhinitis allergic to foods, and it is especially in food allergy that this form of treatment has been applied. Children with allergy to cow's milk may be successfully hyposensitized by giving them one drop of cow's milk diluted e.g. in 15 g. of water, the next day 2 drops and then consecutively 4, 8, 16, 32 drops etc. In the case of any recrudescence of the allergic symptoms the treatment must be discontinued for some time; it is then resumed with an appreciably lower dose than that last administered, and the dose is then more cautiously increased; instead of passing from 32 to 64 drops, it is increased, for instance, only by 8, possibly even fewer, drops at a time.

Similarly, a patient with allergy to shrimps may be hyposensitized by eating 1 shrimp the first day, the next one 2, then 4 and so on. Patients with wheat allergy may start by eating 1 g. of white bread, the next day 2 g. and so on. Disappointments and recrudescence can be expected, but in many cases patients with food allergy can be helped towards a tolerable existence in this way.

With inhalants, on the other hand, oral hyposensitization has not been as successful. Experiments have been made with pollen, dust, animal hair and other inhalants in the form of tablets but, generally, the results have not been very satisfactory, possibly because these allergens are influenced by the digestive secretions. Hansel (21 b) has introduced the *sublingual* application of the allergen tablets, and states that results can be obtained with this method which "has been comparable to those obtained by injection".

Inhalation Hyposensitization

In 1951 Herxheimer (26) introduced a method of hyposensitization by inhalation. The antigen is inhaled by the patient through an aerosol apparatus, and a possible asthmatic reaction during treatment can be graphically recorded by a spirometer. If the spirometer registers a lowered respiratory volume and a decreased vital capacity, the treatment can be interrupted at once, and an aerosol containing aleudrine or some other anti-asthmatic drug can be connected with the system.

According to Herxheimer, the advantages of the inhalation method are as follows: the antigen acts directly on the shock organ, the bronchi, and its action can be read graphically at once, so that the dose of the antigen which the patient can tolerate can be determined with a fair degree of certainty. The method is of considerable scientific interest, especially in allergological diagnosis, but as a method of treatment it is time-consuming and hardly superior to the injection method.

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NON-SPECIFIC AND SYMPTOMATIC TREATMENT OF BRONCHIAL ASTHMA

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An adequate treatment of bronchial asthma requires precise information concerning the etiologic factors, which can be acquired by the means ordinarily used in the diagnosis of allergic diseases. In cases where the allergens responsible for the clinical manifestations have been determined, the prophylactic and therapeutic measures known under the term "specific therapy" (described in Chapt. XI) should be employed. If, on the contrary, the etiology has not been established, one generally has recourse to a complex of therapeutic measures, which, not being specific, are covered by the general expression "non-specific therapy". Furthermore, it must be emphasized that this treatment is often used in addition to specific therapy.

It is impossible to enumerate here the various therapeutic procedures used in non-specific therapy of bronchial asthma; we shall, therefore, confine ourselves to the most interesting, both from a theoretical and from a practical standpoint.

In view of the particular importance presented by the asthmatic attack, the symptomatic means used in this clinical manifestations shall be considered first.

Among these, the *sympathomimetic* drugs remain, even today, most useful and are generally employed in the treatment of this condition. It is well known that *epinephrine (adrenalin)* produces a beneficial effect administered subcutaneously (in aqueous solutions or with substances delaying its absorption), by aerosol or intravenously.

With regard to epinephrine, it may be useful to recall that in status asthmaticus one frequently encounters a state of non-reactivity to this drug, called the epinephrine-refractory state. As a result of investigations carried out by Staub, Farrerons-Co, Yonkman and Mohr, the possibility has been advanced that epinephrine, administered in large doses to patients suffering from asthma, pro-

duces a liberation of histamine and contributes in this way to the persistance of the bronchiolar obstruction. According to recent investigations by Blumenthal and collaborators, this condition depends on a state of general or local acidosis.

In these cases one resorts to other drugs, for instance antihistamines (Segal 1948), ACTH and adrenocorticosteroids, as well as theophylline, which usually produces a beneficial effect.

As far as the administration of epinephrine in aerosol form is concerned - in continuous nebulizations or by means of a spray we may point out that it can be effective even in patients in whom it has not proved useful when administered subcutaneously.

It should be borne in mind that epinephrine, administered by aerosol, in addition to its local effect, has a general action, due to the fact that it is easily absorbed through the lungs (Serafini and collaborators). Furthermore, one should not forget that repeated administrations of epinephrine by this means can result in significant changes in the bronchial mucosa.

Another drug frequently employed, orally or by aerosol, is *isopropyl-adrenalin,* which possesses a considerable bronchodilating but no vasoconstrive effect. Consequently, it does not change the values of the arterial pressure.

Ephedrine, which has the same pharmacologic action as epinephine, is given orally (alone or together with other substances, as for instance theophylline-ethylene-diamine, barbiturates etc.) and has proved particularly useful in slight attacks.

Among the *parasympatholytic* substances, *atropine* should be kept in mind. It has been used in large doses (up to 8 or 10 mgm. in 24 hours) with beneficial results (Melli). Its application, however, is limited, primarily because of its side-effects, among which the diminution of the bronchial secretion constitutes an unfavourable factor during the attack.

Among the medicaments of this group, *stramonium,* used in powder form or in cigarettes, exerts a beneficial effect in slight attacks by means of a mechanism dilating the bronchi.

Within the group of *xanthine-derivatives* theophylline-ethylene-diamine is the drug used most frequently. As a rule it is efficacious in the asthmatic attack, not only because it produces a bronchospasmolytic action, but also because it raises the efficiency of the pulmonary circulation.

It is administered intravenously (slow injection or infusion), intramuscularly, orally (also in keratinized capsules), and rectally. It will be noted that the effect of theophylline-ethylene-diamine is evident also in patients in whom epinephrine does not seem beneficial. A phenomenon we had the occasion to observe is that in asth-

matic patients treated with ACTH, the intravenous administration of theophylline-ethylene-diamine brings about a more marked increase (31.7 %) in the vital capacity than in the same patients before this treatment (4.6 %) (Piersanti).

Side-effects produced by xanthine-derivatives are few and consist particularly in gastralgia, nausea, and sometimes vomiting. Recently, we have been informed of pronounced side-effects occurring in children (Nolke).

Progress in the xanthine-derivatives was made with the introduction of theophylline salts, especially choline theophyllinate, which, compared to theophylline-ethylene-diamine, is more soluble, more stable and less irritating to the mucous membrane of the stomach.

In the opinion of some authors (Franceschini and Mafei etc.) the use of khellin (2-methyl-5.8 dimethoxyfuranochromone), the most active principle of Amni Visnaga (orally, intramuscularly, rectally), which has an antispasmodic effect on the smooth musculature, has proved to be of some utility in the treatment of the asthmatic attack and status asthmaticus.

Among the symptomatic remedies, the *synthetic antihistamines* are generally of no particular value in the asthmatic attack (Frugoni and Serafini, etc.), even if they prove efficacious in other allergic syndromes (urticaria, rhinitis, etc.). A certain beneficial effect may, however, be observed on the central nervous system, particularly in children (Rose).

This absence of therapeutic effect during the asthmatic attack is due to the liberation of "intrinsic histamine" (Dale) the effect of which is only inhibited with difficulty by the antihistamines. In this connection it should be remembered that during the allergic and anaphylactic reactions other substances than histamine are liberated as well, for instance the so-called "slow reacting substance", recently discovered by Brocklehurst in the isolated human bronchi, and serotonin, which is liberated from mast cells by the action of different agents, in the same manner as histamine (Weisner). These substances are only partially affected by the action of the antihistamines.

Recently, the therapy of bronchial asthma has been enriched with efficacious and reliable drugs namely *ACTH* and the *corticosteroids* which have strongly suspensive, although temporary effect on the asthmatic symptomatology. This form of treatment is dealt with in detail in a special chapter. Corticotropin, administered intramuscularly as well as by slow drip-infusion, constitutes today one of the most important life-saving procedures. The same can be said of the corticosteroids (prednisone and prednisolone) which were administered only orally at the beginning, but may now be given paren-

terally (intramuscularly and intravenously) and which bring about immediate therapeutic effects.

During the asthmatic attack one has often recourse to *sedatives*, among which the derivatives of barbituric acid have proved useful. It should be borne in mind that the majority of authors agree that the use of morphine and its derivatives should definitely be forbidden in status asthmaticus, as shall be discussed later.

After having briefly outlined the most important drugs with symptomatic action, we would like to draw attention to the complex of therapeutic measures which are not specific or symptomatic, and to which one can resort to when it is impossible to make use of a specific therapy, or when it is preferable not to use this therapy as the sole form of treatment.

For a long time non-specific therapeutic measures have been recommended, which, being based on empirical practice or on often doubtful physiopathologic opinions, have only yielded results of slight importance. The consequence was that among the numerous non-specific therapies which have been proposed, only very few have reached beyond the experimental stage and painstaking clinical investigations.

In this field, the complex of therapeutic remedies which is intended to reduce in a non-specific way the reactivity of the tissues against stimulants of varying nature (including the antigen-antibody reaction) is of particular importance. According to certain authors, the introduction into the organism of different substances, such as heterologous proteins (milk, lactalbumin, casein, non-specific sera, peptone, the patient's own blood or serum, tuberculin, vaccines, colloidal metals, etc.) would result in a non-specific hyposensitization, because these substances, owing to the formation of intermediary split products, would stimulate the organism, particularly the reticulo-endothelial system, in such a way that its immunologic activity is increased. On the basis of this hypothesis this kind of therapy has been called "stimulating therapy". At present, some authors (Schwartz 1950, etc.) interpret the effects as being secondary to stimulation of the hypophysis-adrenocortical axis.

The *heterologous proteins* most commonly used have been milk and its constituents (lactalbumin, casein, etc.). This therapy is seldom used nowadays, because of the serious reactions it may entail in patients allergic to milk.

Peptone has been used by some authors (Pasteur Vallery-Radot), particularly in intradermal injections in increasing doses, sometimes with beneficial results. At present time, this and similar therapies (autohemotherapy, tuberculin, urinary proteose, etc.) are on the point of becoming obsolete because of some contraindications deter-

mined by the presence of latent sources of infection, and owing to their sometimes serious side-effects. Moreover, the therapeutic results are very inconstant.

Among this group, *induced fever* (hyperpyrexia) deserves to be mentioned, as it may often reveal itself beneficial even in cases where other means of therapy have failed. It is based on some well-known experiments namely that an induced febrile condition (pyrexia) has been proved capable of protecting rabbits and guinea pigs against anaphylactic shock (Gernez and Eloire 1937, etc.), of preventing the Sanarelli-Shwartzmann phenomenon, the histopathologic picture of allergic phlogosis (Luccherini and collaborators 1946, etc.), the experimental sensitization of the skin (Grifoni 1953, etc.) and of rendering the tuberculin skin reaction negative (Gernez 1935).

In humans, fever therapy leads to some hemochemical alterations (Serafini and collaborators 1946, etc.) which manifest themselves by a diminution of the alkaline reserve, a fall in circulating eosinophils and neutrophils, lymphocytopenia, decrease in serum potassium and an inconstant rise in serum calcium. During induced fever, an increase in activity of the adrenal cortex has recently been demonstrated (Rose 1955).

Among the numerous agents used to produce hyperpyrexia it may be worth mentioning vaccines (administered intravenously), colloidal sulphur preparations and diathermy (Feinberg and collaborators).

In this connection special mention may be made of *histamine therapy,* which consists in an administration of small doses of histamine by different approaches: subcutaneously, intradermally, ionization, aerosols, etc., in order to obtain a decrease of the sensitivity of the patient to histamine, liberated in the shock tissues by the antigen-antibody reaction and other stimulants. Histamine therapy has been used in different allergic conditions, but seldom in asthma, since it very often produces an exacerbation of symptoms. Walker, however, has recently obtained beneficial results in 55 percent of asthmatic patients without emphysema and in 45 percent of those with emphysema.

The observations made by Greppi, Sicuterni and Monfardini deserve special mention. These authors have introduced a new method of administration called "protected histamine therapy". The method consists in a daily administration (by aerosol, intramuscularly or intravenously) of large and increasing doses of histamine, whose toxic effects are prevented by intravenous administration of an antihistamine. In an endeavour to explain the mechanism by means of which the favourable effect is produced, the writers advance the

hypothesis that histamine, given in large doses, may be able to produce a phenomenon of acquired tolerance, although its effects are neutralized by simultaneous administration of an antihistamine.

Bacterial vaccines. The bacterial vaccines (stock or autovaccines) are often used (subcutaneously or intracutaneously) in the therapy of bronchial asthma of infectious origin or complicated by infectious processes. Although most authors believe that their effect is due to a non-specific mechanism, similar to that of protein therapy, others admit that vaccines, especially if they consist of staphylococci, may display a specific activity (Bergquist).

The clinical results obtained by this treatment generally appear beneficial, (according to Shinefield, better results are observed with autovaccines than with polyvalent vaccines) especially if the therapy is undertaken during symptom-free intervals. It should further, however, be pointed out that it is very difficult to produce positive proof of the beneficial effects obtained by this therapy, and that some recent observations did not show a positive therapeutic effect (Frankland and collaborators).

Collateral effects of different nature may supervene during vaccine treatment: general manifestations (fever) or local (edema, erythema, pain at the site of injection); in addition, aggravation of the asthmatic symptomatology, at times persisting indefinitely, may occur.

Hormone therapy. Hormone therapy is principally undertaken on the basis of the well-known relationship existing between endocrine glands and bronchial asthma. On the one hand there is the often observed connection between exacerbations or onset of asthma with the different phases in menstrual cycle, and on the other hand the different clinical conditions where normalization of an endocrine deficiency or overproduction is followed by a temporary improvement of asthmatic symptoms. Various hormones can exert a beneficial effect, either by correcting a state of deficient glandular function possibly associated with the asthmatic syndrome (for instance in hyperthyroidism and hypergenitalism etc.), by a specific pharmacological action (e.g. the antireactive action of ACTH and corticosteroids or the effect of adrenalin on bronchospasm).

Regarding female hormone therapy, it should be pointed out that in addition to their indication in cases of hormonal disturbances, they may be administered in small increasing doses (specific hyposensitization) in the particular clinical conditions where it is possible to demonstrate a specific sensitivity to the hormones (Zondek and Bromberg, Biozzi, Serafini, Malizia, etc.).

Different hormones have been used, sometimes with good results, in the treatment of bronchial asthma, but their mode of action has

not been very easy to understand (gonadotropic hormones, Condorelli; sex hormones, Introzzi and Larizza). At present, the therapeutic effect of centropnein (Santenoise and collaborators), a supposed pancreatic hormone, offers no definite proof. Finally, treatment with insulin shock holds a special position. This form of treatment was introduced by Wegierko (1935) in the treatment of bronchial asthma, and is still used by some physicians with satisfactory results. Its mechanism of action is supposed to be analogous to that of other shock treatments. Hormone therapy with ACTH and corticosteroids at present yields the most constant and certain results.

Different therapeutic procedures. Iodine is often used, administered by mouth or parenterally (intramuscularly and intravenously), both on account of its vasodilatory and hypersecretory action and because of its probable stimulating and resolving effect in chronic bronchitis.

Gold salts (administered perorally or parenterally) are still employed by some with satisfactory results, however, pronounced collateral phenomena are not uncommon.

Chloramine-T or *azoiprit* were first introduced in therapy as cytostatic or anticancerogenic substances, but have proved to be of beneficial effect in bronchial asthma. (Jiménez Díaz and coll., Corelli and Marinosci; Malaguzzi Valeri and Di Raimando, etc.).

Some authors maintain the utility of trivalent *arsenic* in the form of arsenobenzol which is supposed to have an aspecific antireactive action. However, secondary effects are rather frequent and may assume a violent character.

Numerous *vitamins* have also been used because it has been supposed that a vitamin deficiency could be present in asthmatics (possibly due to dietary restrictions instituted for therapeutic purposes and to the contributory chronic infectious processes). Results obtained by different authors with various vitamins, are, however, contradictory and generally not convincing. Recently, good results have been obtained with cyanocobalamine, especially in children (Crocket).

Calcium salts, owing to their anti-edematous and antiphlogistic properties, as well as *sodium* and *magnesium hyposulfites* for activating cholinesterases, have been used formerly and are still employed with some beneficial results.

Antibiotics are used when an infectious process complicates the clinical picture or in asthma of infectious origin. The choice of the antibiotic in an individual case should preferably be made according to a preliminary examination of the bacteria in the sputum.

Asthmatic patients are frequently dehydrated on account of a reduction in fluid intake and by sweating. In such cases administra-

tion of a 5 percent *glucose* solution by intravenous drip will relieve the dehydration and contribute to reduce the sticky and adherent nature of the bronchial secretion.

In this connection it is necessary to bear in mind the significance of variations in electrolyte balance, particularly with regard to Na and K (Wittich), whereupon several therapeutic treatments have been developed, such as reduction of Na in the diet and administration of K.

During asthmatic attacks, recourse is frequently made to the use of *oxygen* (pure or mixed with other gases, such as helium), whereby a certain benefit is oftentimes obtained. It is of some interest to note that patients who have become resistant to adrenalin frequently improve following a prolonged oxygen-helium therapy.

With regard to oxygen therapy it must be remembered that in patients with chronic anoxia, due to variations in gaseous exchange, shock and coma may develop, in some cases with fatal outcome (Barach, Comroe and collaborators, Mithoefer). The reason for such accidents is that the respiratory centre in these patients has become less sensitive to CO_2, and respiration takes place in particular through stimulation of the chemoreceptive centres by the low oxygen tension. When oxygen is given, the stimulus to the chemoreceptors is lost, and the minute respiratory volume decreases. Under these circumstances a rise in CO_2 tension and a decrease in pH develop; shock and coma are in fact due to the uncompensated acidosis.

In some cases, recourse has been made to *venesection* and, less frequently, to *narcosis* and general *anesthesia* in its various forms: ether, cyclopropane, chloroform by inhalation, etc.

Physical therapy. Roentgen therapy was introduced in the treatment of asthma by Schilling (1909), on the basis of the observation that an asthmatic patient was seen to improve following repeated and prolonged X-ray screening. The favourable therapeutic effect in a certain number of cases (Pasteur Vallery-Radot, Blamoutier) have been attributed to an antiphlogistic, antiseptic action on the bronchi, in addition to a general non-specific effect.

Ultraviolet rays and *short-wave therapy* have been rarely employed.

Climatic treatment and hydrotherapy. Climatic therapy can exert a favourable effect in a specific manner (elimination or reduction of antigens) and by a non-specific action due to the physical characteristics of the climate (temperature, humidity, barometric pressure, ionization of the air, variations of atmosphere, etc.) and changes in milieu (the favourable effects on the patient's psyche of a stay in a peaceful and beautiful spot is well-known).

When choosing a climate one should give preference to an average

altitude with a stable barometric pressure, a not too high temperature, and dry pure air.

Hydrotherapy may be advised at the same time. It also owes its effect to a non-specific action as that of protein therapy (Messini) and to a pharmacological effect, by improving the condition of the bronchial mucous membranes (reduction of secretion, etc.).

These mineral waters usually contain salts of bromine, sulphur and iodine, and are used for bathing, inhalation and drinking.

Surgical therapy. Surgical intervention is advised only in exceptional cases resistant to all other forms of treatment (sympathectomy of the stellate ganglion, right-sided vagotomy).

In some cases of status asthmaticus in which a major bronchial obstruction is involved, bronchial aspiration may be carried out to advantage. The mechanical removal of mucus has proved to be a life-saving procedure in many patients.

Intervention in the nasal cavity may be carried out, not with the intention of influencing the asthmatic symptomatology, but with "the aim of re-establishing the function and eliminating the infection, basing the indications on the symptoms and on the pathological lesions, as if the asthmatic condition did not exist". (Hansel).

General management. In the treatment of asthma, even of more importance than the specific, symptomatic and non-specific means, are the hygienic measures as indicated in each individual case. These consist in eliminating or improving possible associated pathological conditions, reducing factors which favour or lead to attacks, and ameliorating the patient's general health.

With this aim in view, and as has been previously mentioned, the physician should attempt to relieve any possible primary disease of the respiratory tract. Furthermore, special treatment should be directed against concomitant bronchial infections, disturbances in metabolism (e.g. obesity), cardiovascular complications, liver insufficiency, endocrine disturbances. etc.

An evaluation of the psychic factors also deserves special attention. After gaining the confidence of the patient, the physician should carry out a suitable psychotherapy, eliminating these conditions (fear, emotional or sexual disturbances, etc.), which contribute to produce and maintain the asthmatic symptoms.

We may finally point out that Rackemann has directed attention to the so-called "depletion" in bronchial asthma. Many asthmatics are in a weakened state because of loss of weight and vigour, both prior to the development of asthma and as a result of the disease. This author has stressed that in such cases a general treatment, even without anti-allergic drugs (rest, fresh air, physical exercise, satisfactory nutrition, vitamins, tonics) leads to an appreciable increase

in body weight, improvement in the general condition and disappearance of symptoms. The reason for this phenomenon is not clear, but it may presumably involve recovery of the "resistance factor", which is not easy to define, together with renewal of the adrenocortical activity.

Asthmatic patients should live in a quiet, peaceful surrounding, avoid emotions and overwork. Furthermore, as far as possible one should attempt to remove from the milieu, such factors as humidity, dust, smoke, gases, etc., which contribute to maintain or aggravate the asthmatic condition.

Breathing exercises have been shown particularly effective in certain cases (Quarles van Ufford, etc.). Their aim is mainly to raise the vital capacity of the patient, to improve his type of breathing, to prevent or eventually improve a faulty carriage and thorax deformities, and to exert a relaxing action on the breathing muscles as well as on the entire organism. Further, a varied and nourishing diet is to be recommended, eliminating the items which have been shown to be responsible for the allergic phenomena.

With respect to the use of specific and symptomatic therapy, we believe, lastly, that we must stress the important fact that in asthmatic patients reactions to drugs occur more frequently and often assume a serious character.

It may be recalled, that during recent years the medical literature has not uncommonly recorded fatal accidents following the use of morphine and similar preparations. Consequently the use of this alkaloid in bronchial asthma is absolutely contraindicated, particularly in the chronic untractable cases. One of the authors (Serafini) has been able to observe three cases of bronchial asthma with fatal outcome, where there was no doubt as to the relation between cause and effect with morphine injections. A knowledge of the various pharmacological effects of morphine (reduction of activity of the respiratory centres, inhibition of cough reflex, bronchospastic effect) stresses the danger of such injections in patients who, instead, require maximum strength in their respiratory organs and must avoid accumulation of bronchial secretions.

Among the drugs which can produce allergic types of reaction in asthmatics, at times with fatal outcome, we may mention: aspirin, sulphonamides, arsenic, iodine (used in bronchography), penicillin, streptomycin, etc.

With regard to ACTH, the possibility should be kept in mind that a sensitivity to this hormone may develop and that a subsequent injection may result in an anaphylactic shock.

It should also be recalled that treatment with synthetic corticosteroids, particularly if continued for a long period of time, not only

exposes the patient to the complications associated with adrenocortical hyperfunction, but also to effects determined by the therapy: in the first place a functional inhibition of the adrenal cortex with its most striking consequences, and the possibility of producing changes in the patient's "reactivity type" shown by the occurrence of "mesenchymal reactions" with the clinical characteristics of systemic lupus erythematosus or periarteritis nodosa, analogous to what has been observed by Slocumb in rheumatoid arthritis.

These various phenomena emphasize the necessity of treating the asthmatic patient with the greatest care, carrying out a thorough clinical examination in order to evidence even the slightest sign of abnormal reaction to the drugs which are to be administered.

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STATUS ASTHMATICUS

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When an asthmatic attack fails to respond to the usual remedies in normal dosage, status asthmaticus is said to be present. This condition may continue for a period varying from a few hours to a week or more. The patient is anxious, dyspnoeic and cyanosed; he sits leaning forward with his chest held in the inspiratory position, using the accessory muscles of respiration in an attempt to inspire a still greater volume of air. Expiration is severely obstructed and during this phase wheezing is often audible from the end of the bed. If relief is not achieved the patient becomes increasingly distressed, his eyes are sunken and his tongue dry; sweat often covers his features. As his exhaustion increases the expiratory effort diminishes, so that the characteristic expiratory wheeze may not even be audible with a stethoscope. At this stage the patient is breathing shallowly and rapidly near the limits of inspiratory effort. Loss of consciousness due to anoxaemia may take place. Although recovery is the rule, death sometimes occurs, either gradually with increasing evidence of anoxia or suddenly and often unexpectedly, perhaps when the patient has already shown some evidence of improvement.

In analyzing 650 cases of asthma attending as out-patients, 100 (15.4 %) gave a history of one or more attacks of status; in 76 of these, attacks had taken place on more than one occasion, and of these 16 eventually died in status. Three more patients in the series died in their first attack of status. The mortality for the entire series from all cases connected directly with their asthmatic condition was 4 % over the period of observation. Repeated status asthmaticus therefore materially worsens the prognosis of asthma. It seldom causes death before the age of 20.

Further analysis of these 100 cases shows that allergic factors were at some time present in 56 patients (pollen sensitive 29), infection in 83 and emotional disturbances in 40. Eleven had nasal polyps. It is significant that infection appeared to play a major part and

was usually present at the time of admission in status. Table 1 shows further details:

TABLE 1

Age and Sex Distribution of 100 cases with Status Asthmaticus.

	Age groups in Decades	Age at first Attendance	Age of Onset	Age at Death
No. of Cases:	0– 9	4	31	0
100	10–19	13	13	0
Male: 41	20–29	16	19	3
Female: 59	30–39	18	11	0
Died:	40–49	25	14	8
Male: 9	50–59	18	10	3
Female: 7	60+	6	2	2

Although status is commonest between 20 and 50 years of age, approximately one third first developed asthma before the age of 10 years including four of those who died. Some of these had only mild attacks for years until a sudden deterioration took place, often following infection of the respiratory tract, or an emotional disturbance. Other cases, particularly those whose asthma began in middle life, died in the second or third attack of status within a year or so of onset.

Treatment.

Although bronchodilator drugs, corticotrophin and corticosteroids or their derivatives are of predominant importance in the treatment of this condition, an attempt should always be made to determine the factors which are responsible for precipitating the attack since failure to appreciate these may have serious consequences in treatment.

The importance of allergic factors should be considered first since these are perhaps the easiest to deal with. For example it is clearly important in pollen-sensitive cases that contact with grass pollen should be reduced to a minimum by closing windows, removing the patient to a hospital in a suitable environment, or nursing him in an allergen-free chamber. Similar steps may be taken when atmospheric moulds are suspected to be the precipitating agents. Materials in the house such as feathers from bedding or cage birds, animal dander, or freshly applied paint are sometimes important and in such cases the irritant or allergenic materials must be removed or the patient taken to hospital. Dust from industry may also precipitate attacks: Ordman refers to epidemic status caused by castor bean dust polluting the atmosphere. Infection is very frequently present during attacks of status and this applies not only to cases of so-called infec-

tive asthma or of asthma secondary to bronchitis, but even to those with an allergic basis: thus if the sputum of pollen sensitive patients admitted to hospital during the pollen season is examined, pus and pathogenic organisms will commonly be discovered. Examination of the sputum is therefore an essential part of the investigation of every case of status. If microscopy shows that eosinophils are present exclusively or in high proportion, an allergic basis is almost certain, whereas the presence of pus cells and pathogens will indicate that respiratory tract infection is either the primary cause or has become superimposed on a respiratory allergy of extrinsic origin. Sinus infection must also be excluded. All infected cases should be treated with suitable antibiotics in addition to non-specific measures.

Emotional factors may also play a prominent part in precipitating status. This should be recognized although it is seldom either practicable or wise to investigate this aspect of the case during the acute attack. One patient had repeated attacks of status during the time she was going through divorce proceedings, on one occasion becoming unconscious for several hours. Following termination of the legal proceedings and the readjustment of her life, the attacks ceased and she remained in good health for a number of years. In cases where an emotional factor is thought to be present, psychological investigation after recovery is justifiable; care must be taken however not to probe too deeply if the patient shows resistance, especially when feelings of guilt are aroused, since the unwise disclosure of distressing subconscious conflicts may well cause deterioration in the patient's condition. The author has personal knowledge of at least one case of death in status which took place within a few hours of the recollection during psychotherapy of behaviour associated with severe feelings of guilt (Leigh).

Secondary anxiety is invariably present during status and this is greatly mitigated by a confident and considerate attitude on the part of the medical attendant.

General Measures.

Admission to hospital is advisable in all cases of status, not only because the patient may in this way be removed from contact with allergens to which he is sensitive, and sometimes from an unfavourable emotional atmosphere at home, but also because continuous medical and nursing care is necessary for satisfactory treatment. The patient's recognition of the fact that he will be given appropriate remedies at any hour of the day or night in itself possesses therapeutic value.

The patient should be nursed sitting up, with a bed table upon which he can lean in front of him. The bed should have a firm mattress and a foot rest should be inserted to prevent him from sliding down into a horizontal position.

Oxygen delivered by a loosely fitting plastic mask, or less satisfactorily by nasal tube, may give some relief: the flow rate should be maintained at 4–6 litres per minute, an additional reason for preferring the use of a mask, since oxygen delivered at this rate by nasal tube will both cool and dry the nasal mucous membrane, thus causing considerable discomfort. A mixture of oxygen and helium is sometimes employed because of the low density of the latter. The patient should be watched carefully during oxygen therapy, particularly if it is suspected that recurrent attacks of bronchitis with accompanying destructive emphysema have been superimposed on the asthmatic condition. In these patients the accumulation of carbon dioxide in the blood over a period of time may have caused the respiratory centre to become insensitive to it. The anoxic stimulus to nerve endings in the aorta and carotid body thus becomes the only effective one and in such cases the patient may be seen to lapse into coma with shallow inadequate respiratory movements as the administration of oxygen relieves the cyanosis (Beale, Schiller, Halperin and Franklin and Lowell). In this event the oxygen should be stopped, but after resumption of normal respiratory effort it may be given for short periods, say ten minutes in each quarter of an hour: alternatively the rate of delivery may be considerably reduced, for example to 2–3 litres per minute. Analeptic drugs such as nikethamide may temporarily increase the sensitivity of the respiratory centre, and are of great value if consciousness is lost in the manner described.

Dehydration indicated by inelastic skin, dry mouth and sunken eyes, may be encountered in the patient who has already been in status for several days. In these cases moderate re-hydration with a normal saline drip, given intravenously, alternating with 4% glucose in fifth-normal saline should be instituted, if the patient is too dyspnoeic to take an adequate amount of fluid by mouth. This may help to liquefy the viscid and tenacious sputum and assist expectoration. A drip is also useful for the administration of bronchodilator agents such as aminophylline or of corticotrophin. During treatment careful watch should be kept on the neck veins to ensure that there is no rise of venous pressure during inspiration, due to the onset of right-sided heart failure. If asthma has been complicated by repeated attacks of bronchitis with resulting emphysema, the intra-cranial pressure may be raised as the result of long-standing hypoxia with increased permeability of the smaller cerebral

vessels. This condition may be recognized by the presence of papilloedema and should be taken as a contra-indication to the giving of intravenous fluids which may cause a further rise in pressure, with the possibility of cerebellar coning and fatal pressure on the medullary centres.

Bronchodilator Drugs.

Theophylline, preferably given intravenously as aminophylline (Theophylline with ethylene diamine) 0.24–0.48 grammes, may be life saving. It is not only an effective bronchodilator but a cardiac stimulant and for this reason should be injected very slowly: too rapid administration may cause transient increase in spasm and has been known to precipitate ventricular fibrillation. It can be given intramuscularly but this method is painful and less effective. Injections may safely be repeated after two to four hours, but the total dose for an adult should not exceed 3 grammes in twenty-four hours. In those patients receiving fluid by saline drip aminophylline may be given, 0.5–1.0 grammes per litre of saline run in at approximately 45 drops per minute.

Adrenaline will usually have been given, perhaps by the patient himself, in the early stages of the illness. The majority of patients with status asthmaticus are 'fast' to adrenaline, but in those cases who have not already received an adequate dose, 0.5–1 ml of a 1: 1000 solution of adrenaline hydrochloride given subcutaneously may be followed by 0.05 ml each minute until relief is obtained or a total of 3–4 ml is reached, or the appearance of extreme pallor, distressing palpitations and tremor make it unwise to continue. The prior administration of aminophylline may increase the effect of adrenaline. Although asthmatics are usually very tolerant to adrenaline injections, its unintelligent use in excessive dosage may cause loss of consciousness or adrenaline shock, a condition associated with low blood pressure due to interference with the transmission of the tonic sympathetic impulses through the synapses at the ganglia. (Bülbring & Burn). It must also be remembered that accidental injection of adrenaline 1: 1000 intravenously has given rise to hemiplegia, cardiac arrhythmias and loss of consciousness. Accidental overdosage may be counteracted by giving Imidazoline (5–10 mgm) or Benzodioxane (10–20 mgm) intravenously (Freedman).

Isoprenaline delivered as an aerosol spray for periods of ten to thirty minutes every 2–3 hours is valuable in less severe cases. This is best given by passing oxygen under pressure through an aerosol pump, and delivering by means of a plastic face mask.

It must be remembered that in the early stages of status improve-

ment is often very temporary and treatment may need to be repeated several times in twenty-four hours, particularly at night. Nevertheless the majority of patients will show a definite response within this time.

Corticotrophin and Corticosteroid Drugs.

If the patient is judged to be critically ill or if bronchodilator drugs together with general measures have failed to bring about appreciable improvement within 24 hours, the use of corticotrophin or corticosteroid preparations should be considered. There is often a lag of from 12 hours to four days before these substances exert their effect, so that their use is never an excuse for inadequate general and symptomatic treatment.

Many reports of the value of these drugs in status asthmaticus have now been published (Lockel et al., Baldwin et al., Ball, Pearson) and statistical evidence is available in the report of the Medical Research Council of Great Britain of a double blind controlled trial with Cortisone. Cases were treated in ten hospitals and only those who had failed to respond to adrenaline and aminophylline during the first twenty-four hours after admission were included. Since most cases did respond to these measures only 32 were available for the trial, and these alternate cases were treated with placebo tablets or cortisone, in addition to bronchodilators as required. Analysis of the results showed a distinct advantage to the cortisone treated group, who were more rapidly relieved and returned to a normal condition sooner than those treated with placebo.

In prescribing treatment it is of great importance to give an adequate initial dose and to reduce this gradually over the period of treatment required: too small a dose at the beginning of treatment may fail to cause improvement while sudden termination of treatment after several days may be followed by a severe relapse. Careful watch must be kept on the patient so that unfavourable side effects can be detected early; these are discussed more fully later. Contraindications to this form of treatment in such a serious emergency are few, but discretion should be exercised in known cases of gastric or duodenal ulcer because of the risk of perforation or haemorrhage; alkali by mouth should be given to such patients. The presence of valvular heart disease or hypertension also presents a special risk particularly if cortisone, hydrocortisone or corticotrophin are used, since the retention of salt will in these cases lead to increase in venous pressure and may precipitate heart failure. These drugs should also be cautiously employed if there is any evidence of right heart strain due to the presence of emphysema. In diabetes the insulin requirements will need adjustment.

TABLE 2

Scheme of Dosage for Various Preparations of Corticotrophin, Corticosteroids and their Derivatives.

Type of Drug.	Preparation	Method of administration	Dose for first 24 hours	Maintenance dose for 24 hours	Comments
Corticotrophin	Corticotrophin powder. 25 unit doses.	Intramuscular injection in solution	200 units	100 units	Injections 4–8 hourly.
	Corticotrophin powder. 25 unit doses.	Intravenous drip	40–80 units	10–20 units	Continuous drip; unsuitable for more than a few days.
	Corticotrophin gel. 40 units per ml.	Intramuscular injection	40–80 units	20–40 units	Injections divided at first. then once daily.
	Cortocotrophin aqueous suspension 40 units per ml.	Intramuscular injection	40–80 units	20–40 units	
Cortisone	Cortisone acetate tablets. 25 mgm.	Oral	200–400 mgm	50–100 mgm	3 hourly at first. 2–4 times daily after control achieved.
	Cortisone acetate suspension. 25 mgm per ml.	Intramuscular injection	200–300 mgm	100 mgm	Divided doses 4 hourly prescribed only until oral preparation can be taken.
Hydrocortisone	Hydrocortisone acetate tablets 20 mgm.	Oral	160–300 mgm	40–80 mgm	3 hourly at first. 2–4 times daily after control is achieved.
	Hydrocortisone free alcohol solution 100 mgm in 20 ml of 50 % alcohol	Intravenous injection in 500 ml saline	100–200 mgm	–	For emergency only: given as drip 100 mgm per litre of saline.
	Hydrocortisone sodium hemisuccinate solution 100 mgm in 2 ml.	Intravenous injection	100–200 mgm	–	2 ml (100 mgm) given in emergency: oral preparations subsequently.
Prednisone	Prednisone tablets 5 mgm.	Oral	40–60 mgm	15–25 mgm	3 hourly at first. 2–4 times daily after control achieved.
Prednisolone	Prednisolone acetate tablets 5 mgm.	Oral	40–60 mgm	15–25 mgm	3 hourly at first. 2–4 times daily after control is achieved.

Treatment will seldom be required for more than 2– 3 weeks.

Table 2 suggests the initial dose and the maintenance dose for each of the preparations now available. The maintenance dose should be reached within 3–4 days and continued for 7–10 days, after which gradual reduction can usually be made so that the entire course of treatment lasts for two or three weeks. Intravenous corticotrophin given continuously, preferably through a fine catheter, is probably the most effective method, but the tendency to cause local venous thrombosis renders it unsuitable for prolonged use. Prednisone and Prednisolone have the advantage that they retain salt less than naturally occuring preparations, and for this reason are less likely to cause oedema or to precipitate heart failure. When the patient is too distressed to swallow, or if vomiting makes retention by mouth uncertain, corticotrophin, hydrocortisone or cortisone by the intramuscular or intravenous route should be used. Except in these special circumstances there is little to choose between the various preparations. During treatment daily blood pressure recordings should be made and the urine should be tested for albumin and sugar.

Failures or poor results are recorded in most series and in the author's experience such failures can usually be attributed to one of the following reasons:

1) Inadequate dosage or the use of inactive material.
2) Uncontrolled infection of respiratory tract or paranasal sinuses.
3) Organic lung damage such as pulmonary fibrosis, structual emphysema or bronchiectasis.
4) Harmful side effects.

Under the last heading are included persistent tachycardia, severe hypertension and venous engorgement with right sided heart failure. These events are probably associated with the salt retaining qualities of these drugs and the use of Prednisone and Prednisolone should reduce their incidence. Silent pneumonia without rise of pulse or temperature was recorded in one case, another died suddenly within a few minutes of the administration of intravenous corticotrophin by drip: this patient had been successfully treated in this way on several previous occasions and anaphylactic death was diagnosed. Other cases of death attributed to corticotrophin or cortisone have been recorded. (Hill & Swinburn, Bloom, Wolff, Burrage & Irwin, Quarles van Ufford). Repeated courses of intravenous corticotrophin are probably particularly likely to lead to anaphylactic reactions.

In concluding this section it is therefore important to recognize that these endocrine preparations are not given without risk, are

not necessarily effective in every case, and do not provide a substitute for the use of bronchodilator drugs; moreover antibiotics must be given at the same time if infection is present. With these qualifications it may be said that they often reduce the period of disability and discomfort materially, and that they may be life-saving.

Antibiotic Treatment.

Because of the frequency with which infection is encountered as either a main precipitating cause or as a complication in status asthmaticus, antibiotics play an important part in treatment. It is particularly important to deal with infection when corticosteroids are employed. Although ideally one would like to know the nature of the organism responsible and its sensitivity to the range of antibiotic drugs, this is seldom practicable initially. The severity of the patient's illness necessitates early treatment if pus (degenerated polymorphs) is present in the sputum or if there is other evidence of infection of the respiratory tract or sinuses. H. Influenzae and S. Pneumoniae are recognized to be the commonest infecting agents in bronchitis (Mulder, Helm et al.) and in our experience are also commonly cultured from asthmatic sputum. Staph. aureus (coagulase positive) is not uncommon, particularly when the antra are acting as foci of sepsis. Strept. viridans is found more commonly in asthmatic than normal sputum (Bergquist) but it is still doubtful whether it is to be regarded as a pathogen or not. It is therefore reasonable to start treatment with a combination of penicillin in doses of 1–2 million units daily together with streptomycin gm 1–2. These should be given in divided doses. In children and elderly patients oral phenoxymethyl penicillin may be given with sulphonamides in a dosage suitable to their age. In each case a specimen of sputum or laryngeal swab should be taken before treatment is begun. In the early stages little sputum may be produced because of bronchospasm so that it may not be easy to obtain a specimen. As the spasm is overcome a considerable quantity of infected sputum is often brought up. Tests should be repeated from time to time until recovery occurs. If evidence of infection persists a change to the tetracycline group of antibiotics or to erythromycin should be made, unless culture has shown an organism that is more sensitive to some other preparations. Chloramphenicol although often effective should be used only if other antibiotics are unsuitable because of the risk of agranulocytosis when repeated courses are necessary.

Although the use of antibiotics alone may be followed by dramatic improvement as the sputum is freed from pus and pathogens

disappear, eosinophil polymorphs sometimes appear in large numbers (Helm & Livingstone), and in these patients severe asthma may persist until corticosteroids are used. In some cases the original organisms are replaced by others insensitive to the antibiotic employed, B. Coli and St. pyogenes being not uncommon secondary invaders. The points which should be borne in mind in the antibiotic treatment of status asthmaticus are therefore:

1) That a preparation which is suitable for the predominent organism should be employed in adequate dosage.
2) That treatment should be continued for a sufficient period of time to overcome the infection, i.e., a minimum of from 5 7 days and often for 2–3 weeks.
3) That repeated examination of the sputum should be made, and treatment altered as indicated by the findings.

Sedatives.

The problem of getting sleep is a constant source of anxiety in these cases. The discomfort associated with respiratory distress keeps the patient awake and those sedatives which depress the respiratory centre must be avoided. Morphine is particularly dangerous, lulling the patient into a sleep from which he may never recover owing to the consequent reduction of respiratory effort. It may be said that sound sleep cannot be expected while status asthmaticus continues, and that repeated small doses of sedatives are preferable to larger doses given with a view of producing complete sedation.

Paraldehyde is the drug of choice and may be given orally (8–14 ml) or intramuscularly (5–10 ml) in divided doses over 4–8 hours. In the severe case of asthma this will induce a drowsy condition which will persist for a few hours, when it may need repeating. Rectal administration is sometimes preferable. Ether, which also has little effect upon the respiratory centre, may also be given rectally: an infusion of 60–80 ml of ether in 160 ml of olive oil is well absorbed. Ether is also soluble in saline up to about 3 per cent and may be given intravenously in this way, the rate of the drip being regulated so that the correct amount of sedation is obtained. The prescription of pethidine 50–100 mgm, because of its mild bronchodilator action and because its effect on the respiratory centre is less marked than that of morphine, is sometimes justifiable, but its bronchodilator effect is variable and its sedative action is only moderate. (Herschfus et al.). In some patients it causes a reduction of mucus secretion which may interfere with the expectoration of

sputum. The administration of Nalorphine or Levallorfan together with pethidine is reasonable and should prevent any depressing effect on the respiratory centre[1]. Barbiturates in safe doses are ineffective in severe status and are contra-indicated in larger doses because they too depress respiration. The best way to give sleep is by the adequate treatment of the status itself.

Miscellaneous Measures.

Bronchoscopy has been widely recommended by some workers (Waldbott). There is considerable technical difficulty in carrying this out unless the patient has lost consciousness, when it may be done without local or general anaesthesia. The object is to suck thick mucus from the obstructed airway. Though the main air passages may be cleared in this way, it is obvious that the smaller bronchi and bronchioles cannot be reached. Nevertheless it is regarded by some as a life-saving procedure and should be employed if circumstances demand.

Other forms of treatment, for example with nitrogen mustard or intravenous procaine, have been rendered unnecessary by the introduction of corticosteroid preparations and corticotrophin. Bronchodilators and expectorants not referred to in the text may be of value during the recovery phase: thus potassium iodide or caffeine iodide may help in the expectoration of mucus at this time. Long acting preparations of adrenaline in oil or as a mucate (0.5–1.0 ml) may also be useful.

The following principles should be remembered during treatment and after the acute attack has subsided.

1) Apprehension and anxiety are the natural accompaniments of a disorder threatening the act of respiration. This does not imply that the patient is neurotic, or that he will improve if ignored, nor does it render him immune from a fatal outcome.

2) Repeated symptomatic therapy is usually required during the first few days and constant supervision is necessary.

3) Treatment may require to be altered during the illness for many reasons, but ought not to be changed as long as improvement is taking place.

4) Status does not take place without a cause, and if this is not recognized at the time of the attack every effort should be made to determine the precipitating factor after recovery has taken place in order that treatment may be initiated to prevent further attacks.

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[1] A combination of pethidine and levallorfan is marketed under the trade name of Pethilorfan (Roche).

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THE CLINICAL USE OF CORTICOTROPIN AND ADRENOCORTICAL STEROIDS IN ALLERGIC DISEASES

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With the introduction of ACTH and Cortisone by Hench and Kendall (1) for the management of rheumatoid arthritis there began an enormous amount of clinical and experimental observations on these and related compounds. Nevertheless it had been recognized many years ago that the functions of the anterior pituitary and the adrenal cortex were related in some manner to mechanisms of hypersensitivity. For example, it had been noted that removal of the hypophysis or the adrenal gland in the experimental animal led to a decrease in resistance both to classical anaphylaxis and the effects of histamine. These observations were in part clarified by the finding that adrenalectomy in the rat was accompanied by an increase of the tissue and blood histamine as well as a decrease in the capacity of the tissues to inactivate or remove histamine. A decrease in the activity of the enzyme histaminase was shown to be responsible in part for these alterations (2). More recently, it has been found that if the tissues are first depleted of their histamine content by the action of histamine liberators, the administration of Cortisone will prevent the re-accumulation of histamine (3). In addition to these relationships, other tissues which in all probability are intimately concerned with the allergic state such as the lymphoid mass and the eosinophils depend in part on the activity of the adrenal cortex. Thus removal of the adrenal leads to marked increase of lymphoid tissue, whereas the administration of Cortisone or one of its derivatives results in a dissolution of lymphoid tissues and a depression of the circulating eosinophils.

In spite of a large amount of experimental data both in animals and man, the exact mechanism whereby the steroids of the adrenal cortex exert their beneficial effects in the allergic states is still not

clear. While in animals certain forms of antibody formation are suppressed by the administration of Cortisone, many others do not appear to be influenced and this is particularly true of those which have been studied in man. It seems clear that only actively induced antibody formation can be suppressed, for when antibody in the form of immune serum is transferred passively, Cortisone administration has no effect. It is furthermore of some considerable interest that adreno-cortical function appears to be normal in children with agammaglobulinemia since these children do not have the capacity to form antibody to the majority of known antigens (4). In a recent review, Germuth (5) comes to the conclusion that the beneficial effects of steroid therapy in allergic states must be due to the non-specific anti-inflammatory properties of these compounds rather than to any capacity to suppress antibody formation. Further clarification of this problem is obviously desirable.

Following the demonstration in man that the administration of Corticotropin (ACTH) led to a decrease in circulating eosinophils, studies of the effects of this hormone in patients with diseases of allergy, asthma in particular, were carried out and the first reports were published in 1949 and 1950 (6) (7). Since that time Corticotropin and the various steroids with gluco-corticoid activity have been used extensively as therapeutic agents for the management of every known form of allergy (8) (9) (10). It soon became apparent that not only did symptoms recur on cessation of therapy but that undesirable side-effects might appear. Further experience over the past eight years now allows a clearer definition of conditions and situations in which the use of these agents is indicated. It is now universally accepted that these compounds should not be used lightly or in place of the more accepted forms of therapy and never, with rare exceptions, until a thorough history, physical examination and a reasonable trial of the more conventional means of allergic management and treatment has been undertaken. Because of the possible dangers accompanying the use of these compounds, some knowledge of their properties and mode of action is desirable before attempting to use them.

Properties and Mode of Action.

Corticotropin or ACTH (Adrenocorticotrophic Hormone) exerts its action indirectly by stimulating the adrenal cortex. The final effect is due to the increased production of endogenous adrenal steroids, the most important of which quantitatively and qualitatively is Compound F (Hydrocortisone, Cortisol, Hydrocortone). Administered adrenal steroids exert their effects directly and con-

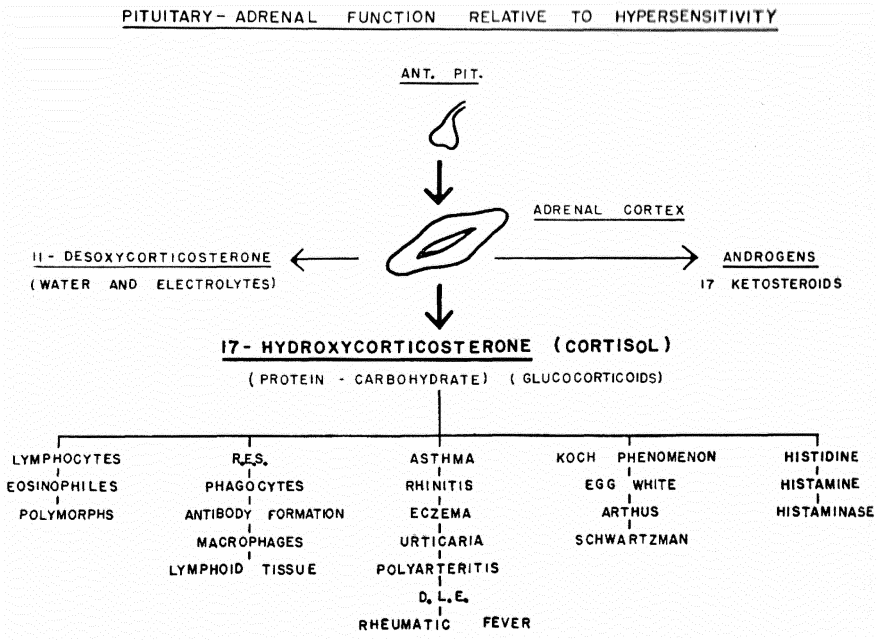

Fig. 1.

sequently it is necessary only to describe the properties of Cortisol. It should be noted that all of the newer derivatives of Cortisol have similar properties with certain modifications. Cortisol, a gluco-corticoid, is concerned primarily with carbohydrate and protein metabolism. At least two other groups of steroids are released by Corticotropin. These are the androgenic steroids of which Testosterone is an example, and the mineralocorticoids which regulate salt and water metabolism. Neither the mineralocorticoids nor the androgenic compounds exert any major known effect on immune mechanisms although they may play some role in the appearance of undesirable side-effects when ACTH is used for prolonged periods. The more recently described aldosterone, a salt and water hormone, also bears no known relationship to hypersensitivity and since aldosterone output is only partly influenced by ACTH it need not be discussed here.

Pituitary adrenal relationships are shown in Fig. 1, in which most of the known properties as they relate to mechanisms of hypersensitivity are listed. These include effects on the formed blood elements, the Arthus and other phenomena. The effect of administered ACTH and Cortisone on the function of the anterior pituitary and the adrenal cortex are outlined in Fig. 2. It will be clear that Cortisone and like compounds suppress both glands. ACTH, while stimulating

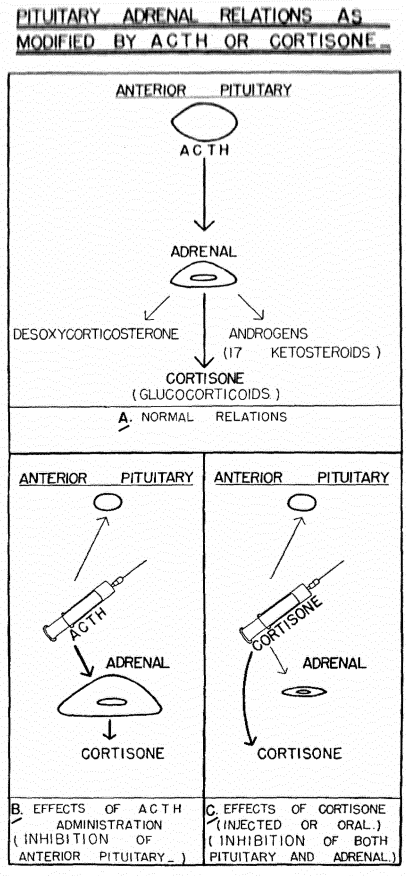

Fig. 2.

the adrenal cortex, also suppresses the anterior pituitary and as such is capable of leading to withdrawal symptoms when it is stopped.

In addition to the properties of Cortisol which relate to allergy and hypersensitivity, there are other important attributes which must be known and recognized. These are listed in Table I. It will be clear that these and other side-effects can be at best troublesome and some may, if not dealt with promptly and properly, lead to the death of the patient. Finally, it should be clearly understood that the average daily output of the anterior pituitary in terms of ACTH in man is 1 unit per 24 hours, and the normal output of the adrenal cortex in terms of Cortisol is approximately 20 mgm. per 24 hours. It will be obvious then that in most instances therapeutic dosage schedules are not examples of replacement therapy and the side-effects which

TABLE I

Some Properties of Adrenocortical Steroids.

Physiopathology	*Clinical Manifestation*
1. Impaired Carbohydrate tolerance.	Steroid Diabetes.
2. Depletion of body nitrogen.	Weakness, Osteoporosis.
3. Abnormalities of water and electrolytes.	Edema, Hypokalemia, Hypernatremia.
4. Calcium loss.	Osteoporosis, collapse of vertebrae.
5. Increased appetite[1].	Obesity.
6. Decreased resistance to infection.	Infection may have fulminating downhill course.
7. Depression of pituitary-adrenal activity.	Sudden withdrawal of treatment or failure to meet increased requirements may result in an iatrogenic Addisonian crisis.
8. Anti-inflammatory.	Masking of clinical signs and symptoms so that an acute episode such as perforation of an ulcer may be difficult to diagnose.
9. Unknown.	Hypertension.
10. Unknown.	Psychoses.
12. Unknown.	Impairment of growth in children.
13. Unknown.	Acute perforation of a viscus.

[1] These changes are less apt to occur with the newer compounds Prednisone, Prednisolone and Triamcinolone because of the relatively lower dose required and because of inherent changes in the properties.

appear are in consequence often signs and symptoms of hyperadrenalcorticism.

Rationale for the Use of Hormones.

There is no clear cut evidence that inadequate function of the anterior pituitary or the adrenal cortex play any etiologic role in the development of diseases of allergy. Rose, Fyles and Venning (11) found that in adults, urinary gluco-corticoid output was lower in asthmatics than in a group of normals of similar age, but this has been found to be true in other chronic diseases such as rheumatoid arthritis. It was also noted that there was no increase in glucocorticoid output under the stress of a severe exacerbation of asthma. On the other hand an elevation of the blood 17 hydroxycorticoids

TABLE II

Types of Corticotropin (ACTH) available for Use in Allergic States.

Type	*Duration of Action*	*Route of Administration*	*Dose*
ACTH (Lyophilized)	4–6 hours	Intramuscular	10–20 units q.6.h.
		Intravenous.	10–20 units in 500 cc glucose and water as a slow drip over 8–10 hours.
ACTH – Zinc (long-acting)	12–36 hours	Intramuscular Subcutaneous	10–40 units b.i.d. or q.d. or q.2.d.

was found in children with severe asthma as compared to normals (12).

Perhaps the major incentive to use steroids is simply that they work at least temporarily. While the exact mechanism is unknown, virtually every sign and symptom known to be characteristic of an allergic response including eczema, certain forms of angioedema and urticaria, rhinitis, bronchospasm, sputum production, eosinophilia, lymphocytosis and so on can be suppressed or reversed by these compounds. The one striking exception is the immediate reacting skin test, which is unaltered. Delayed skin tests of the tuberculin variety are however suppressed. In certain instances these drugs may be life-saving by virtue of this ability to suppress manifestations of a hypersensitivity reaction. However, their indiscriminate use may lead to disaster.

Available Preparations.

Preparations available are divisible into two groups. These are Corticotropin and the steroid compounds. The former are listed in Table II. As can be seen, Corticotropin requires parenteral routes of administration. It nevertheless is a useful preparation and is believed by some to be more rapidly effective when given intravenously than is intravenous Hydrocortisone or intravenous Prednisolone. Since Corticotropin exerts its effects by stimulating the adrenal cortex to liberate other steroids as well as Cortisol, certain precautioins are necessary. These are:

1) Restriction of Sodium intake to not more than 1 gm. per day.
2) A potassium supplement of 3–5 gm. of KCl per day.

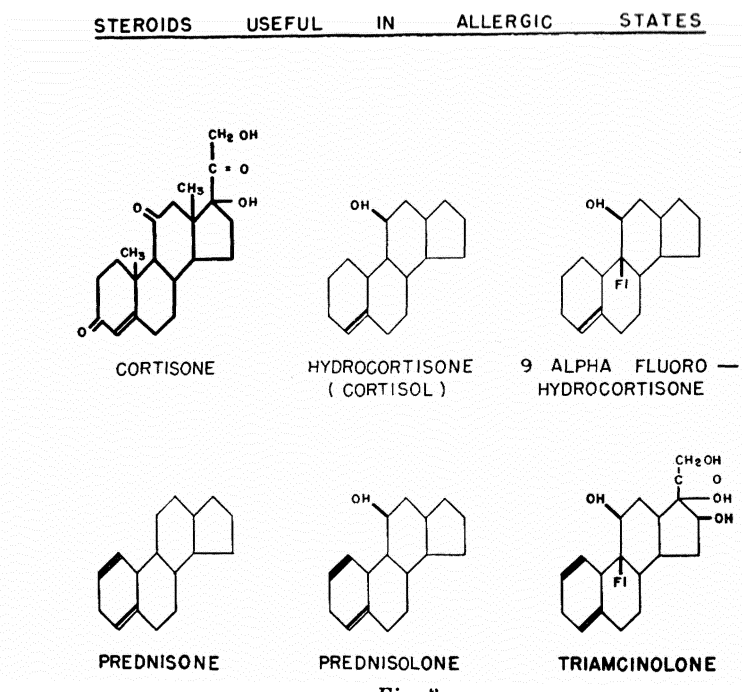

Fig. 3.

3) Fluid intake should not exceed 2–3 litres per 24 hours. This is of importance in intravenous therapy, as well as with injection therapy involving high dosage of Corticotropin.

In general the use of Corticotropin has decreased considerably in favour of the orally active steroids because of the convenience of the latter form of therapy. Also ACTH is a protein extracted from animal pituitaries (usually hog or beef) and may contain traces of foreign material to which a patient may be sensitive or develop allergy. Thus the preparation may in itself produce acute asthma, anaphylactic shock or angioedema. However, sensitivity reactions to ACTH have become much rarer with the newer more purified products.

The chemical structure of the adrenocortical steroid compounds are shown in Fig. 3. Cortisone is depicted in the upper left hand of the figure. Originally synthesized by Kendall, it was the first to receive clinical trials by Hench and Kendall in 1949. Subsequently, other steroids with Cortisone-like activity have become available. The original steroid nucleus of Cortisone is shown in heavy lines and alterations in chemical structure by which each compound differs from the preceeding one is shown in heavy print. Thus Cortisol

TABLE III

Comparative Dose Ranges of Steroids in Allergy.

Compound	Strength (MG)	Normal output	Dose Range	Maintenance
Cortisone[1]	25	15 30	300 50	25 75
Cortisol[1] ..... (Hydrocortisone)	20	12.5 20	240 40	20 60
Prednisone	5	1 5	60 10	5 15
Prednisolone	5	1–5	60 10	5 15
Triamcinolone ...	2	0.5–2	20 4	2 6

[1] = Salt restriction and potassium supplement required.

(Compound F) differs from Cortisone in having a Hydroxyl group at carbon atom II instead of a ketone. The 9 alpha-fluoro derivative of hydrocortisone is also shown although it is not used orally in the management of allergic states because of its marked capacity to retain salt and water and to excrete potassium. It is useful however, as an 0.1 % concentration applied locally to the skin in a suitable base. The more recent derivatives of Cortisone and Cortisol are shown at the lower left. These are Prednisone and Prednisolone both of which differ from the parent compound by desaturation of Ring A in the 1–2 or Δ position and are known as Delta Compounds. These newer steroids, Prednisone in particular, are being very widely used

TABLE IV

Steroid Preparations for Parenteral Use.

Compound	*Strength*	*Type*	*Use*
Cortisone Acetate	25 mg/cc	Suspension	Intramuscular administration
Hydrocortisone Acetate	25 mg/cc	Suspension	Intramuscular administration Intra-articular administration
„	1–2 %	„	Ophthalmic
„	1–2 %	Ointment	Local application to skin
Prednisolone Acetate	25 mg/cc	Suspension	Intramuscular administration
Hydrocortisone Hemisuccinate	100 mg	Powder	For intravenous administration soluble in 2 cc sterile water.
Prednisolone Succinate	50 mg	Powder	For intravenous administration soluble in 5 cc sterile water.

and have displaced Cortisone and Cortisol to a considerable extent since they have comparatively less effect on electrolyte and water metabolism and are more potent in equivalent dosage. Thus when the Delta Compounds are used in therapeutic doses there is usually no need to restrict Sodium or to give supplementary Potassium (13). All the other undesirable side-effects characteristic of steroid therapy occur with at least as great a frequency with Prednisone and Prednisolone as with Cortisone and Cortisol. Finally, in Fig. 3, there is shown one other more recent modification, Triamcinolone. While this compound shows great promise in initial surveys the side-effects are not yet known. Like Prednisone and Prednisolone, Triamcinolone is even more potent in equivalent dosage than its precursor.

The various types of steroid preparations useful for oral administration are listed along with their equivalent dosage in Table III. It is extremely important to emphasize that all these compounds are more rapidly effective when given by mouth than by the intramuscular route. The free steroids are insoluble and are usually prepared as the acetate salt which is inactive. Free steroid is rapidly released in the stomach but very slowly when injected into the tissues. It is also important to recognize that there are several types of preparation available for parenteral use. These are listed in Table IV. For example Hydrocortisone and Prednisolone are prepared as suspensions of the acetate salt for intramuscular or intra-articular injection. Similar preparations are available for use as drops in the eye. This suspension should not be used intravenously. For intravenous use only the hemisuccinate should be administered in a slow drip. It is strongly recommended therefore, that the label and the printed brochure accompanying each preparation be read carefully. In an acutely ill patient who cannot take the drug orally, it should be administered intravenously for a period of 36 hours after the first intramuscular injection or continued intravenously until the patient can take oral medication.

Indications.

The indications for steroid therapy may be conveniently classified into three groups, and are shown in Table V. In those of Group A, there is clearly no time to lose and one has no choice but to proceed with full-scale dosage. Undesirable side-effects or contraindications have to be dealt with and it is here that a knowledge of the potential dangers is essential. Because of the disastrous results which may ensue as a result of hormone therapy in some patients, an ever increasing tendency to withhold such treatment is occurring in the hope that the patient will still respond to the more conventional

TABLE V

Indications for the Use of Hormones.

A. *Life-saving Emergencies.*

1. Acute Status Asthmaticus.
2. Exfoliative Dermatitis.
3. Pituitary-Adrenal Suppression due to previous therapy.
4. Acute Drug Reactions.
5. Acute Serum Sickness.
6. Polyarteritis.

B. *Self-limited Conditions.*

1. Seasonal Rhinitis (severe).
2. Seasonal Asthma (severe).
3. Some forms of Acute Urticaria and Angioedema.
4. Spreading contact Dermatitis.
5. Loeffler's syndrome (Eosinophilic Pneumonia).

C. *Chronic Intractable States.*

1. Chronic Asthma with or without Bronchitis.
2. Chronic Serum Sickness.
3. Polyarteritis.
4. Certain forms of Atopic Dermatitis.

and less harmful forms of treatment. By far the most satisfactory group to treat are those listed in group B. Since these conditions are self-limiting, one can be assured generally that the need for hormones will likewise be limited. In group C, and not infrequently in group A, once steroids have been started one is committed to long term therapy and thus ultimately will have to deal with one or another of the many undesirable side-effects.

Contraindications.

Contraindications are listed in Table VI. It is of interest to note that the majority of these are relative and there is no hard and fast rule. Of particular importance here is a careful personal and family history combined with a thorough physical examination and such general tests as may seem indicated. For example hypertension is much more likely in the patient with a family history of the disease. Diabetes Mellitus has been somewhat exacerbated by the administration of the steroid hormones, or uncovered in the patient with a family history. It has not been produced however by these compounds. One of the most sobering aspects of long-term therapy is the rapidity with which certain infections may spread and become overwhelming before they are recognized. In general, adrenocortical steroid hormones should not be administered to patients with active

TABLE VI

Contraindications to Hormone Therapy.

Hypertension.
Recent Coronary Disease.
Diabetes Mellitus (severe).
Tuberculosis.
Infections for which there is no good chemotherapy.
Osteoporosis.
Ulcer.
Depression or Psychosis.
Negative history of Varicella.

tuberculosis or those with a history of this disease. It is true that phthysiologists use Cortisone and similar compounds in the treatment of certain forms of tuberculosis but this is a special instance in which both steroids and antituberculous therapy are required.

Other infections may be spread by the careless use of these hormones, but the following are more serious in that no specific antibiotic therapy is available. These include moniliasis, purulent meningitis, Friedlanders' pneumonia, blastomycosis, and malaria (14). Recently, it has been observed that chicken-pox (varicella) may become a fulminating and fatal disease in children receiving steroids, and some ten deaths have been reported. It is always well to enquire both in children or adults whether the patient has ever had varicella before administering hormones (15).

Finally, it should be noted that growth may be retarded in children by the administration of hormones. In this connection it has been recommended that interrupted courses of steroids are preferable since normal growth rates will resume once steroids have been withdrawn.

A good general principle to adopt is that if these contraindications can be controlled or prevented, then steroids may be administered. If an exacerbation of the complicating condition should occur it may be necessary to withdraw steroids, but here again caution may be necessary depending on the amount of time that they have been given.

Routes of Administration, Choice of Drug and Dosage.

None of the steroid hormones is a substitute for other forms of therapy. Thus in the acute allergic states such agents as adrenalin, bronchodilators, expectorants, antihistamines, aminophyllin, oxygen, antibiotics or sedatives should be used when necessary. These standard forms of therapy should also be used in conjunction with steroids when the latter are given on a long-term basis. The aim

should be in every case towards withdrawing hormones as soon as possible in order to avoid the hazards of continued administration.

Except in acute emergencies these drugs should be given by mouth. If the patient is unable to take oral medication or where a rapid effect is desired the intravenous route should be used. For acute status asthmaticus, either Corticotropin (lyophilized) or Hydrocortisone Hemisuccinate or Prednisone Succinate should be administered intravenously. In our experience, the first two preparations are more satisfactory. Corticotropin, 20 units given in a slow drip in 1,000 ml of glucose and water over 8–12 hours and repeated once or twice as needed is usually effective in 6–36 hours. Hydrocortisone Hemisuccinate may be used instead, the dose being 100 mg. in 500 ml. given by slow drip over an 8 hour period and repeated as necessary. The response is about the same as that for ACTH. If the patient is unable to take medication by mouth, intramuscular Corticotropin, Hydrocortisone Acetate or Prednisolone Acetate may be given at the same time as the intravenous administration is begun. Oral preparations should be started as soon as the patient can swallow. This general scheme holds for almost all acute conditions with the exception of acute adrenocortical insufficiency such as may be encountered in a patient who has been on previous hormone therapy. Here it is essential to use one of the steroid preparations such as Hydrocortisone Succinate intravenously. It should be mentioned in this connection, that vasomotor collapse associated with acute anaphylaxis or the type often encountered in adrenocortical collapse must also be treated in the initial stages with adrenalin or intravenous nor-adrenalin. Neither ACTH nor hydrocortisone given intravenously will restore the blood pressure or maintain it for the first hour or so as a general rule and therefore these other measures must be adopted.

In most other situations where hormone therapy is indicated the oral route is preferable. It is again pointed out however that there may be a considerable variation between the requirements of different patients. As a rule the dosage is somewhat lower in children both in terms of initial and maintenance schedules. Since most patients to whom hormone therapy is given have a severe degree of allergy, the initial dose should be in the neighbourhood of 240 mg. Hydrocortone for the first 24 hours followed by 40 mg. every 4–6 hours depending on the severity of symptoms until a satisfactory response is obtained. This high initial dose will in the majority of cases bring about a rapid regression of the symptoms after which the dose can then be tapered until the maintenance dose for that particular patient is determined. The maintenance dose should be the smallest dose on which the patient can get along using adjuvant therapy if necessary. In general Prednisone or Prednisolone have largely supplanted the

older compounds Cortisone and Cortisol for oral steroid therapy. There is no detectable difference clinically between Prednisone and Prednisolone, but both are much more potent than their precursors, and when administered in therapeutic doses they seldom give rise to weight gain or electrolyte and water changes.

When it is felt that therapy can or should be terminated, it is essential that the hormone be withdrawn quite slowly. If the patient is receiving 80 mg. per day of Hydrocortone or its equivalent, decrease by 20 mg. per day every 4 days until a level of 40 mg. per day is reached. Following this a decrease of 10 mg. every 4–5 days is made. Since these compounds when given orally have a period of activity of about eight hours, it is better to decrease each of the three or four doses than it is to omit a dose. When the dose has reached the equivalent of 20 mg. of Hydrocortone a day, this is no longer practical, and one must now also omit a dose. Maintenance therapy with Corticotropin or the orally active steroids is very variable, and depends on adjuvant therapy as well as the severity of the particular disease. In some, for example, as much as 40–80 mg. of Hydrocortone or 10–20 of Prednisolone or 20 units of ACTH may be required per day. On the other hand as little as 5 mg of Prednisone every other day or 20 units of ACTH every third day may suffice for others. The question of intermittent versus continuous therapy has never been clarified and is a matter of judgment on the part of the physician.

No patient should be given hormone therapy without a full explanation of the hazards involved. He should be told which compound he is receiving, the importance of reporting infection early and of the possibility of adrenocortical insufficiency following withdrawal of the compound. He should be instructed to inform any other physician to whom he may go or any hospital to which he is admitted that he is or has been on hormone therapy. It has been suggested that such patients be given an identification card similar to that given to diabetics to carry at all times. Thus in the event of an accident the hospital to which he is admitted may treat him accordingly and thus avoid the disaster from relative or absolute adrenal insufficiency and may be on the alert for hidden infection or other hazards associated with long-term therapy.

Clinical Effectiveness and Duration of Remission.

Generally speaking, when properly used, these compounds will suppress most allergic states within 6–24 hours. In some however it may take from three to six days, particularly if the initial dose is not high enough or if other coexisting disease is unrecognized. Some

conditions, chronic urticaria in particular, may fail to respond to hormone therapy. The reasons for this are not clear. In general, cases of physical allergy do not respond to steroids or Corticotropin, however in these instances antihistaminics may be effective.

Remission following withdrawal of treatment may last from 24 hours to 6 weeks, the average being two to three weeks following which there is an exacerbation of symptoms. It is therefore important to use adjuvant treatment both during the period of hormone therapy and even more important following its withdrawal in order that remission may be prolonged. The only instances in which exacerbation does not follow withdrawal of treatment is in the case of seasonal forms of allergy or reactions to drugs of an allergic nature.

Long-Term Therapy.

In general, many patients who, prior to the advent of the steroids, were chronic invalids incapable of supporting themselves or their families have become self-supporting and useful citizens. It is these who warrant long-term therapy, and who justify its use. However, in view of the statistics quoted by Kern (16) regarding the increasing and alarming deaths from asthma as recorded both in the U.S.A. and New Zealand, one wonders if these agents should be used at all. The unfortunate part is that one cannot tell whether this increased rate is in fact due to steroid therapy. At the Royal Victoria Hospital in Montreal, steroids were first used for asthma in 1949 and well over 500 cases have been treated here since that time. While we do not have accurate figures, the general average of asthmatic deaths is certainly no greater than prior to the advent of these hormones. However, it is quite conceivable that many patients having access to steroids have used this form of therapy indiscriminately, and may have fallen into difficulties by inadequate dosage leading either to acute status or intercurrent infection, with subsequent death from either the one or the other. It is therefore the duty of every physician who starts a patient on steroids, to warm him of the potential dangers, and to follow him carefully, in order to avoid such disasters. These hormones do not appear to alter the effect of injections of pollen or other extracts as well as bacterial vaccines. Consequently there is no contraindication to beginning vaccine therapy or hyposensitization while the patient is still receiving hormones.

With reference to atopic or contact dermatitis, whenever possible local therapy is preferable and the two most useful compounds are Hydrocortone in 1–2 % or 9 alpha-fluoro-hydrocortone in a 0.1 % strength. These may be combined with antibiotics such as Terra-

mycin, Neomycin or Vioform, or any of the coal tar derivatives in a suitable base.

Pregnancy.

Although the steroids administered to pregnant animals may induce congenital anomalies in the offspring, this is apparently not so in the case of humans. Both severe asthma and atopic dermatitis have been adequately controlled by steroids in many cases of pregnancy.

Causes of Failure.

It would appear that certain patients fail to respond to hormone therapy, for reasons not clear at this time. However, there are a number of causes which should be recognized, the most common of which are:

1) *Wrong diagnosis:* This occurs most frequently in differentiating asthma from emphysema. Most individuals with the latter disease respond poorly if at all to hormone therapy. Cardiac dyspnea is another example.

2) Failure to recognize the presence of *infection* with consequent deterioration as infection spreads.

3) *Inadequate dosage:* This has been discussed above.

Complications (Undesirable Effects).

These may be divided into those of minor consequence and those of major importance and have been discussed in part in previous sections. Some are not as common now with the newer compounds as they were with Cortisone, Cortisol and Corticotropin. In most instances, the incidence of side effects increases with prolongation of treatment and the more serious of these may be discussed in some detail.

1. *Pituitary Adrenocortical Suppression.*

While it has been stated that a dose of Cortisol equal to or greater than 12.5 mg. per day for a period of three months or longer, may suppress both the anterior pituitary and the adrenal cortex for periods up to six months or longer, in many instances suppression has occurred after shorter periods of therapy. Post mortem examinations of patients who had been on steroid therapy have shown morphologic signs of atrophy of both adrenals and pituitary (17).

In contrast to the relative forms of adrenal failure which may occur as a result of hormone therapy it has been shown that normal individuals subjected to stress such as a severe infection, perforation of an ulcer or fracture of a bone will respond with an increase in

output of 17-hydroxycorticoids. Since there is no absolute relationship between either the size of the dose or duration of treatment on the one hand and the presence or absence of suppression of the anterior pituitary or the adrenal cortex on the other, it is wise to assume that suppression has occurred in any patient who has received steroid treatment and to be prepared to treat adrenal insufficiency, either absolute or relative, such as may occur with infection or operative procedures. Some authors feel that the patients' adrenals should be "primed" with Corticotropin following steroid therapy in order to avert suppression of the adrenals. However, as can be seen from Fig. 2, the injection of Corticotropin in itself suppresses the anterior pituitary and there is no way at the present time of stimulating the pituitary to increase the production of endogenous ACTH. It has been found that priming with Corticotropin or alternating Corticotropin with adrenocortical steroid therapy is of no particular benefit in our experience.

The consequent emergencies which may arise are of several types. Perhaps the most frequent is the patient maintained on a small dose of hormone, who contracts an infection, which may soon become fulminating since his own defence mechanism is suppressed. If the dose should be high, it may go unrecognized owing to the anti-inflammatory properties of these hormones and their capacity to suppress fever and the E.S.R. In this case the dose of hormones should be maintained, and antibiotics as well as other suitable therapy administered promptly. The patient who is on a low maintenance dose of hormone, or who may have been weaned off therapy some weeks or months previously is in great danger if severe asthma ensues with superadded infection. It is these cases which may suddenly go into acute status, or acute vasomotor collapse in a shock-like state. They require prompt intravenous therapy or adequate oral dosage.

Similarly, elective or acute operative procedures require the administration of the equivalent of 200 mg. of Cortisol on the two days prior to, the day of, and the day after operation. Following this the dose may gradually be tapered to the original maintenance level.

2. *Osteoporosis and Spontaneous Fractures.*

Although the incidence of this condition is low, there are undoubtedly many unreported cases. Apparently the hormones are capable in certain selected cases of inducing a marked increase in the excretion of calcium. A number have been described by Irwin et al. (17) and we have observed 3 in a large series of cases. It is possible to help prevent the advance in osteoporosis in some measure by the administration of a high protein diet, testosterone and Vitamin D.

However, the best approach is to avoid it by withholding hormone therapy from those patients who are immobile or bedridden for long periods. As a general rule, if a patient is on an adequate dietary intake and is physically active, osteoporosis is not likely to occur. The authors have observed several patients, one of whom was over 50, who sustained fractures owing to a fall or other trauma while on steroids. Healing occurred within 6 weeks even though steroids were continued. However these patients were encouraged to be quite active physically.

3. *Acute Perforation of a Viscus.*

Irritation of the stomach and duodenum secondary to increased acid secretion due to hormone therapy is not uncommon. Indeed, some of the commercial steroid products are combined with a form of antacid to counteract the heartburn which may occur. The incidence of epigastric distress and occasional nausea is variable. Acute perforation of the stomach, duodenum or some other region of the gastrointestinal tract is low in incidence in the group of allergic diseases. Nevertheless, the condition must be recognized immediately and treated surgically. Under these circumstances, priming of the patient with adequate steroid therapy is necessary to prevent postoperative collapse as previously described. Wound healing generally speaking is not interfered with unless the patient has been poorly nourished.

4. *Severe Hypertension.*

In the uncomplicated case, this condition is not likely to arise. Moderate hypertension is usually present in acute asthma but it will disappear as the asthma subsides. But if essential hypertension, kidney disease such as nephritis, or the renal lesions of the various collagen diseases supervene, it will not only occur, but may be made worse by hormones. Under these circumstances Corticotropin, Cortisone and Cortisol should be avoided, and Prednisone or Prednisolone used in preference. This is obvious since salt and water retention do not occur as readily with the latter compounds. However, it is necessary to treat the hypertension under these circumstances by whatever measures are indicated according to the type. It is also advisable to withdraw hormone therapy if at all possible.

5. *Infection.*

Although this has been referred to previously it may be discussed again here. Many chronic low-grade infections will disappear when

hormones are given to allergic patients. The reasons for this are not clear unless it be that general resistance to certain infections is imparted by these compounds. However, the opposite may occur, and often accounts for the fact that the patient fails to respond to a previously effective dose. It is always necessary under such circumstances to identify the nature of the infection in order to be sure that it can be controlled by a suitable antibiotic. In this connection one of the more troublesome infections is that due to Staphlococcus Pyogenes of the skin.

Some ten deaths due to varicella have been reported in children receiving steroids. In each there was no previous history of the disease. Therefore, if a child or an adult for that matter has never had varicella, Corticotropin or the various adrenal steroids should not be administered. It would appear that under the influence of steroids the disease is altered from its benign course to a general fulminating infection involving almost all organs, and terminating in some cases in death. However we have recently observed a child, who had been on Prednisone and Triamcinolone for a period of over eighteen months and who developed varicella for the first time. This child fortunately ran a conventional course.

Some of the above mentioned complications may arise during the course of steroid therapy both in children and more particularly in the older age group. It is therefore essential, that regular examinations be made, and they should include blood pressure readings, urinalysis and in patients with a family history of diabetes, AC and PC blood sugars. In patients who develop complaints which could be attributed to osteoporosis, a skeletal survey by x-ray may be helpful. If there is any suggestion of the development of ulcer, a barium meal should be carried out and antacid as well as antispasmodic therapy be instituted. In the majority of cases complications such as have been described may be prevented by keeping the dose as low as possible by the use of the adjunct therapy, and with exception of a collapsed vertebra, all will disappear once the hormone is withdrawn. If discontinuation of steroid therapy is not immediately practical, then treatment of the complication should be started without delay.

In summary it may be said that these hormones do not cure anything and the risks of their use must be balanced against their possible benefits. They are not at any time a substitute for the classical and well established forms of therapy. The results of long-term steroid therapy in patients where the compounds have been used indiscriminately or where the patients have been badly managed and supervision has been poor, are devastating and there appears to be some evidence that increase in deaths from asthma may be attributable to their improper use. In some instances these compounds may

be lifesaving and in these circumstances their use is mandatory, but in any other situation their use is only justified after failure of more conservative forms of therapy and with full realization by both the doctor and patient of the limitations and the hazards involved.

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THE USE OF ANTIHISTAMINES IN ALLERGIC DISEASES

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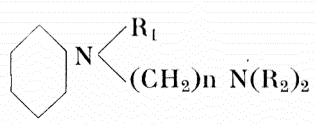
For some years a group of chemical substances has been known under the denomination of "synthetic antihistaminic substances" which protect against the pharmacological effects of histamine. The word synthetic is added in order to distinguish them from some organic derivatives with a more or less simple molecule which also possess an antihistaminic property such as certain amino acids: histidine, cystine and arginine as well as guanidine, spermine, cupleine, etc.

Although the main action of the synthetic antihistamines is an antagonistic one against histamine, they also possess an anticholinergic effect; some have a sympathicolytic, and the majority of them an effect on the capillary permeabilitiy. They are, nevertheless, called antihistamines when their effect against histamine is evident whether injected, inhaled, or tested on the intestinal strip of a guinea pig or some other biological preparation.

Attention to these substances was raised when *Bovet,* in the laboratory of Fourneau, investigated the antianaphylactic action of certain sympathicolytic substances. He first studied the action of compounds 883F and 933F as well as that of certain ethers of aminoalcohols and phenols, amongst them compounds 929F and 1571F. These, however, could not be used in medical practice as they produced toxic symptoms such as cyanosis, convulsions, etc. Injected in guinea pigs their antihistaminic properties were evident, permitting them to tolerate two to four lethal doses of histamine. They also neutralized the histaminic contraction of the intestinal strip of the guinea pig, but were unable to neutralize the hypotensive effect.

Real interest in the antihistamines started in 1942 when *Halpern* published the results of his studies on 24 organic substances synthesized by *Mosnier* and which constituted a series of derivatives of phenyl-polymethylenediamine whose general formula is as follows:

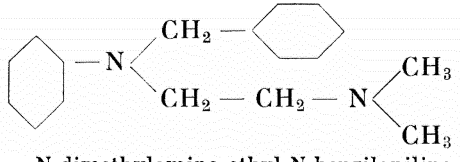


Among these 24, two compounds known as 2325 RP and 2339 RP, proved to be of special interest, the latter being the most active of this series.

Halpern in his work showed that these substances were capable of neutralizing the exciting effect of histamine on the smooth muscles of most organs, in particular those of the intestine and bronchi. After a preventive injection, guinea pigs were able to tolerate lethal doses of histamine to several powers of ten. The antagonistic effect of histaminic hypotension was also shown. Administered in larger amounts they prevented anaphylactic shock in the guinea pig as well as the symptomatology of the peptone shock in dogs.

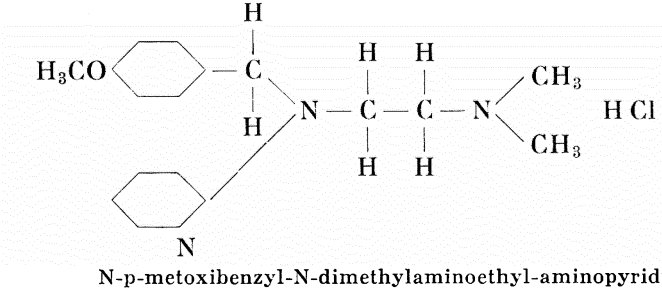
About the same time the first clinical results with compound 2339 RP, later receiving the trade name of Antergan, were published (Gate and his collaborators, Decourt, Aubertin, Sciclounoff and Junet, Serafini etc.).

Its chemical formula is as follows:



N-dimethylamino-ethyl-N-benzilaniline.

Bovet and his collaborators, in 1944, studied a new substance, 2786 RP or Neoantergan:



N-p-metoxibenzyl-N-dimethylaminoethyl-aminopyridine.

This compound, owing to its lower toxicity and greater clinical effect, is the one which has cleared the path for the therapeutic use of the antihistamines. The injection of one-tenth of a milligram per kilogram in a guinea pig protected it against ten lethal doses of histamine. Its effect on the capillary permeability was far more pronounced than that of any of these other substances.

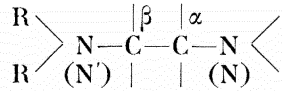
Since that time several commercial firms have been engaged in the study and the preparation of these drugs. In 1945 *Mayer* and his collaborators discovered Pyribenzamine, a derivative of pyridine. The same year *Loew* and his collaborators described Benadryl, an ether with a chemical structure somewhat similar to that of Antergan. Antistin, derived from imidazol, (*Meier* and *Bucher*, 1946), because of its low irritating effect, is of special use in external application such as in nose drops. *Halpern* and *Ducrot* in 1946 studied the antihistaminic effects of substances derived from phenotiazine.

Later, a true avalanche of preparations came on the market: Hetramine (*Feinstone, Williams* and *Rubin*, 1946), Neohetramine (*Reinhardt* and *Scudi*, 1947), Thenylene (*Wetson*, 1947), Histadyl (*Dimwiddie* and *Chen*, 1947), Tegathen (*Lichtfield, Adams, Goddard, Jagen* and *Alonso*, 1947), Chlorotene (ibid. 1947), Tephorin (*Lehman*, 1947), Antadril (*Cavallini*, 1947), Decapryn (*Brown* and *Werner*, 1948), Trimeton (*Le Belle* and *Tislow*, 1948), Chlortrimeton (*Le Belle* and *Tislow*, 1948), Diatrin (*Ercoli, Schachter, Hueper* and *Lewis*, 1948), Pyrrolazote (*van der Brook, Holgon, Richmond* and *Kulzenga*, 1948), Histaphène (*Pottier*, 1948), Synopen (*Stoll*, 1949), Perazil (*Juarro, Castillo* and *Beer*, 1949), Postafène and Longifène (*Grivski*, 1952) etc.

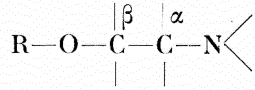
Classification.

The majority of them can be classified in the following manner:

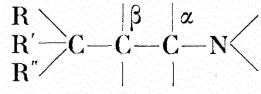
1. Derivatives of ethylenediamine:



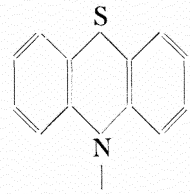
2. Derivatives of oxyethylenediamine:



3. Derivatives of aminopropane:



4. Derivatives of phenothiazine.



5. Diverse.

Main Pharmacological Effects of Antihistamines

Isolated heart.

The effect of antihistamines on the coronary flow has been studied in isolated cat and dog hearts. *Reuse* demonstrated that these drugs are capable of antagonizing the increase in coronary blood flow produced by histamine; this fact has largely been confirmed since. By means of cardiac recordings it has been shown that the increase in coronary circulation, provoked by an injection of histamine, is reduced to a great extent if an antihistamine has been administered previously.

Using the same method *Aparicio* found that they also antagonize an analogous effect produced by acetylcholine.

Blood pressure.

The hypotensive action of histamine has been known for a very long time. The neutralization of this effect by histamine-antagonists is most variable and depends first of all on the amount of histamine which has been injected. With large doses of histamine the neutralizing effect is hardly observed whereas with weaker ones, causing a moderate hypotension, this effect becomes very manifest and is almost proportionate to the injected dose of histamine. This neutralizing effect varies also according to the kind of antihistamine employed; Phenergan seems to exert the greatest effect, and in succession, Neoantergan, Benadryl, and Antistine.

Beside this neutralizing effect of histamine-induced hypotension, antihistamines also exert a marked vascular effect, depending too on the dosage. While very high doses will cause a marked hypotension with symptoms of circulatory collapse, weaker doses, within the therapeutic limits, will produce a temporary hypotension followed by a phase of hypertension of much longer duration. These vascular effects are influenced by the speed with which the drug is injected, and *Loew* (1947) has observed that the hypotension is almost suppressed when the injection is performed slowly.

Generally they possess a reinforcing effect on adrenergic hypertension, although some fail to do so.

Effects on respiration.

Not all compounds influence respiration; some produce an increase in the amplitude of the respiratory movements, which is, however, not observed when the injection is made slowly.

Effects on smooth muscles.

Antihistamines generally produce an inhibition of the tonus and motility of the smooth fibres. This effect was already confirmed in 1944–45 by *Velasquez* and his collaborators with derivatives of propanoldiamine on the isolated guinea pig intestine.

The tonic action of histamine on the smooth musculature of almost every organ in mammals has been known since the work of *Dale* and *Laidlaw* (1910–11). This fundamental property of histamine is neutralized to a great extent by the antihistamines. Generally the intensity of this action is measured by the concentration (or the inverse logarithm of the concentration) which will annul or reduce by one-half the effect of a standard dose of histamine (*Schild*).

Halpern and *Mauric* found that the antagonistic histamine-antihistaminic effect in the isolated intestine of a guinea pig follows a mathematical law which can be expressed by the following formula:

$$y = a\,x^2 + b$$

Employing the technique of *Bayo, Wildebrandt* and *Launer* (1948), the first named studied the effect of Benadryl. In very weak doses this substance bears no change on the intestinal tonus, but a dosage of 20 mg. per kilo administered intramuscularly will cause an increase in the frequency of the peristalsis by diminishing the length of the peristaltic waves.

Velasquez and collaborators, using the same technique, studied *in situ* the effect of Pyribenzamine and Novargene on the intestine of the guinea pig. They found that in the jejuno-ileum the tonus diminishes under their influence and that the peristaltic waves increase without loss in amplitude, while in the duodenum Novargene increases the frequency of the peristalsis as does Benadryl.

All these substances antagonize an experimentally induced intestinal spasm. Their effect on the smooth fibres of uterus and seminal vesicle, however, is variable as some will cause a contraction while others will bring about a relaxation.

Effect on the smooth musculature of the bronchi.

The effect of antihistamines on the bronchial spasm caused by histamine has been studied extensively. This influence can be verified either by registering the bronchial tonus (technique of *Kouwell* and *Roessler*, modified by *Halpern*) or by the histamine aerosol method. The latter consists in enclosing the guinea pig in a glass cage in which histamine is vaporized by aerosol. The time of appearance of the first convulsion, followed immediately by dyspnea, is noted (method suggested by *Kallós* and *Pagel*). With both methods it is possible to

evidence the protective effect of the antihistamines on the bronchial spasm and on the dyspnea produced by histamine aerosol.

The measurement of the resistance to bronchial spasm induced by inhalation of a histamine aerosol does not constitute, however, a specific criterion of the antihistaminic activity, as different substances considered as not being antihistaminic, such as adrenaline, nor-adrenaline, atropine, papaverine, theophyline-ethylene-diamine, dolantine, etc. possess a similar effect.

Many other pharmacological properities also have been studied such as the effect on gastric, salivary, lacrymal and pancreatic secretion produced by histamine. Their action on striated muscles and on the central nervous system, whether of a sedative, analgetic, or local anesthetic nature (*Halpern*, 1942), excel all others as to their effect on the capillary permeability, which has proved to be one of the most demonstrative. This is supported by the theory of *Halpern* that these drugs act through modifications produced in the capillary permeability. This author is of the opinion that antihistamines act on the capillary permeability only when it has been modified by the action of histamine or by other toxic factors such as the peptone shock, an injection of ovalbumen in rats, the action of war gases on the lungs of rabbits (chloropicrine or phosgene), an infectious experimental edema or an edema in rabbits caused by injection of paraphenylenediamine.

The effect on the capillary permeability can also be verified by a technique whereby dyes are injected into the anterior chamber of the eye or in the peritoneal cavity of rabbits. In all of these cases *Halpern* has been able to demonstrate the blocking action on the capillary permeability which had been increased through the above mentioned methods.

In regard to the experiments concerning the anaphylactic shock, reference is made to Chapter I. Considering the great variability of this phenomenon, not only as far as its intensity in the same animal species is concerned, but also taking into account the difficulty of producing the anaphylactic shock in one hundred per cent of cases, it follows that the conclusions drawn from the protective action of the antihistaminic drugs are, in all instances, very inconstant and deceiving.

Only with the guinea pig, the animal which can most easily be put into anaphylactic shock, can one draw some conclusions as to the quality of a particular antihistaminic substance. Dogs also lend themselves well to these types of experiments, but the results are less constant and therefore it is impossible to judge the efficiency of a particular antihistamine.

The lethal dose of histamine for the guinea pig, when injected in

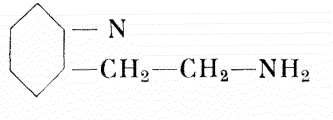
the jugular vein, varies between 0.4 mg. and 0.8 mg. per kilo. When an antihistamine has previously been injected, the animal will endure several such lethal doses, and it has thus been verified that a guinea pig will tolerate as much as 300 lethal doses after an injection of 20 mg/kg. of Neoantergan (*Bovet* and *Staub*), or even 1,500 to 1,600 lethal doses after a previous injection of 20 mg/kg. of Phenergan (*Halpern*). This method proves to be of great value in demonstrating the antitoxic activity of the various antihistamines which bears no relation however to their antianaphylactic, and still less to their antiallergic activity.

The Mechanism of Action

The theory according to which antihistamines exert their action through the intermediary of histaminase or cholinesterase, as maintained by *Meier* has now been discarded as well as the theory that the antihistamines act through hyaluronidase, the depolymerization ferment of hyaluronic acid (*Duesberg,* 1952). This theory originated from the observations of *Mayer* and *Kull* and from those of *Glick* and *Kauffmann,* that hyaluronidase favoured the diffusion of histamine, increasing its area of action, and that this effect of hyaluronidase is impeded by the antihistamines.

Staub, who found a foundation in the interaction and regulation of histamine and adrenaline, suggested the possibility that the antihistamines act against this balance and thus inhibit the liberation of histamine caused by adrenalin.

The most popular theory and the one which applies, for instance, to Neoantergan, Pyribenzamine, Hetramine and others having the radical:



is that they compete with histamine on the cellular receptors and block its action on the cell.

This point of view was corroborated by *Rocha e Silva* who demonstrated that by blocking the amine function in the lateral chain with aminoacids, introducing the group COOH as in histidine, the resultant elements will change into weak inhibitors of histamine.

There are however others, for instance Tephorine, Trimeton, Benadryl, etc. in which it is difficult to admit a true relationship with histamine such as has been proposed by Gaddum in the sense of a protective competition. For this reason it has been suggested that

there is another type of competition acting through continuous fixation or antagonism through destructive competition as shown by *Rocha e Silva.*

According to *Halpern,* however, their property of decreasing the capillary permeability, which all antihistamines possess to a more or less extent, is most important in explaining their mechanism of action.

Haley and *Harris* are of the same opinion, i.e. that the antihistamines act on the precapillary sphincters which they constrict after they have been relaxed by histamine.

Many other theories have been suggested, but we believe that in the foregoing analysis may be found the key of the mechanism of action of these drugs.

Therapeutic Use

Although cortiosteroids have displaced the therapeutic use of the antihistamines to a great extent, they still retain some precise indications.

They are today often associated with various pharmaceutical compounds, either as its main constituent, as an adjuvant to other pharmaceutical products or with the aim of preventing a possible noxious reaction of a drug (calcium, penicilline, syrups with ephedrine or expectorants, phenacetine and other analgetics).

It would be impossible to enumerate here the exhaustive literature dealing with the clinical use of antihistamines, the more or less efficiency of a particular brand, the comparative studies of their therapeutic effects etc. Among them we may mention the works of *Feinberg, Malkiel* and *Feinberg, Bassas Grau, Frugoni* and *Serafini, Kallós, Bain, Donald* and others.

Hayfever and allergic rhinitis. Approximately 70 per cent favourable results are reported in this condition (*Bickel, Loveless* and *Dworin*), while French authors report a higher percentage with Phenergan (*Pasteur Vallery-Radot, Blamoutier* and *Halpern*).

In perennial vasomotor rhinitis their effectiveness is much lower; according to our own experience, they are only of little use in this condition.

Bronchial asthma. The clinical evaluation of antihistamines in bronchial asthma calls for certain preliminary remarks. The term "asthma" includes also asthmatic manifestations which are not of an allergic nature as for instance infectious asthma in which the role of histamine in the bronchospasm has not been demonstrated. In addition psychogenic factors as well as hemodynamic alterations in pulmonary circulation constitute part of the asthmatic picture.

From this the following scheme can be made:

These various factors do not exclude one another but are in the majority of cases superimposed; the vectorial sum of them causing the asthmatic response.

Beside the fact that only one-fourth of these factors are affected by antihistamines, other agents than histamine play a role in the causation of bronchial spasm and edema which are not neutralized by the antihistamines.

For these various reasons, and as experience has confirmed, antihistamines are only of little value in the treatment of bronchial asthma.

Urticaria. Urticaria is the most important indication for the use of histamines. In the acute forms, although they evidently accelerate the regression of symptoms, it is difficult to draw certain conclusions because the symptoms are in themselves rapidly reversible. In chronic urticaria an improvement is generally noted, even when the allergic nature has not been demonstrated. Although the lesions in some cases persist, their effect on pruritus as a rule is evident.

Angioneurotic edema. Antihistamines here are most effective provided they are administered rapidly and preferably parenterally. In serum sickness they will improve pruritus and the blotches will be less voluminous but other therapeutic measures will be necessary to entirely relieve the cutaneous symptoms. In glottis edema, they are completely ineffective.

Contact dermatitis. The results obtained by different authors show great divergencies. According to our own experience and in agreement with the results of *Cerrarini* and *Riccardi,* they are of no proven value.

Locally they may alleviate pruritus to some extent, but their effect is difficult to evaluate. Moreover it should be emphasized that they may themselves, or the excipient in which they are contained, give rise to hypersensitivity reactions.

They show more efficiency in cases of drug dermatitis due to antibiotics, vitamines, hepatic extracts etc., in dermatitis caused by sunlight and accidents caused by jellyfish stings.

Atopic eczema. In this condition the expected improvements have not been realized. According to our own statistics they amounted only to 22.5 per cent, 20 per cent being found by *Bassas Grau;* this is notably in contrast with the results of certain American authors who give figures as high as 62 per cent.

Various indications: In blood transfusions, pentaerythritol and heparin have been added to the blood in order to diminish secondary reactions. They have been employed with great effectiveness in intestinal worms in adults and children. Their use in migraine, common colds, nephritis, purpura, disorders of the genito-urinary and intestinal tract and collagen diseases has on the whole been disappointing.

Side-effects and toxic symptoms. The various secondary effects have been listed by *Wyngaarden* and *Seevers.*

I. Nervous system.

A. Central.

1. Stimulation.
   Insomnia,
   Nervousness,
   Vagal stimulation,
   Tachycardia and hypertension,
   Muscular twitchings,
   Hyperreflexia,
   Tremor,
   Convulsions.

2. Depression.
   Drowsiness,
   Somnolence,
   Narcolepsy,
   Weakness,
   Ataxia,
   Delirium,
   Coma.

3. Neuropsychiatric.
   Nightmares,
   Impaired judgement,
   Delusions,
   Hallucinations,
   Mental depression,
   Reduced mental efficiency,
   Confusion,
   Toxic psychosis.

4. Miscellaneous.
   Dizziness,
   Headache,
   Syncope,
   Fever,
   Hyperthermia,
   Cerebral edema,
   Electroencephalographic changes.

B. Peripheral.
   Toxic neuritis,
   Parathesias,
   Areflexia.

C. Special sense organs.

1. Ears.
   Tinnitus,
   Vertigo,
   Labyrinthitus.

2. Eyes.
   Dilated pupils,
   Blurring of vision.

II. Gastrointestinal system.
Anorexia, nausea and vomiting,
Heartburn,
Cardiospasm,
Diarrhea,
Constipation.

III. Cardiovascular system.
Hypotension,
Vasovagal phenomena,
Syncope,
Shocklike state,
Palpitation,
Tachycardia,
Hypertension,
Cerebral edema,
Electrocardiographic changes.

IV. Respiratory system.
Asthma.

V. Genito-urinary system.
Irritative symptoms,
Spasmogenic retention,
Upper nephron nephrosis.

VI. Skin and mucous membranes.
Dry mouth,
Dermatitis,
Urticaria.

VII. Hematological system.
Neutropenia,
Agranulocytosis,
Hemolytic anemia.

Intoxication.

Intoxication by antihistamines is characterized by symptoms of cerebral excitation with convulsions or state of depression with coma and psychic disturbances. Young children are particularly sensitive to intoxication.

The excitation syndrome. This is characterized by convulsive crises following a phase of excitation. The pupils are dilated; cyanosis of the lips and stertorous respiration are frequently noted. The intervals between the convulsive crises become shorter and shorter.

Coma. Coma may follow or it may occur without any previous convulsions. Tachycardia, oliguria and a considerable fall in blood pressure are generally present. The symptoms may disappear within 10 to 24 hours without sequelae; in rare cases does the patient die from vascular paralysis.

Psychic disturbances, such as mental confusion, delirium, etc. may accompany the other symptoms. *Samper* has described a fatal accident in an infant fifteen months old, who by mistake took some Benadryl tablets; after a few hours he passed into a state of coma and died shortly after.

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PSYCHOSOMATIC ASPECTS AND PSYCHOTHERAPY IN ALLERGIC DISEASES

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Leyden

CONTENTS

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[1] The author wishes to record his indebtedness to his co-worker A. J. Welman, M.D., for the considerable share which he had in compiling the survey of the literature, and in the catamnestic investigation.

I. Theoretical Viewpoints

A. *General introduction.*

Without lapsing into an exhaustive historical introduction, it may be remarked that the psychosomatic significance of allergic affections, notably of bronchial asthma, was already known in antiquity.

As early as the 4th century B. C. Hippocrates pointed to the relation between asthma and emotion, and utilized this link in the treatment of this affection. In later times, too, the influence of emotions in the causation and treatment of allergic affections, and particularly of asthma, has not been lost sight of. One example of this was Willisius, according to whom "... violent motion of the body or the mind led to asthmatic attacks" (1682). Again, Corvisart, Helmont, Laënnec, and Trousseau make mention of psychic influences in asthmatics; Henry Hyde Salter (about 1850) and John Ch. T. Throwgood (about 1860) have communicated their experiences of the favourable effect of a conversation in similar diseases.

I would here postulate, in principle, that the old rift that used to exist between the allergologist on the one side, and the psychologically oriented physician on the other side has now, to all intents and purposes, been closed. Under the spell of the Cartesian doctrine of diaschizis, the concept according to which physical and mental phenomena must be regarded as distinctly separate things, held sway for hundreds of years. But in the light of modern studies of man as a physico-mental totality it is now well-nigh unthinkable to speak of a "purely bodily" or a "purely psychic" illness; and equally, in our view, the term "psychogenic" has become obsolete. It is both safer and more in accordance with present-day conceptions to drop the

concept of monocausality in disease, and better to speak of pluriform conditionality. In conformity with this, we shall, in discussing emotional influences use the term "psychic determination".

In the Leyden Psychosomatic Centre we consider psychosomatic diseases to be those affections whose existence is evinced on the physical plane, and in whose appearance the patient's emotional experiences in the present or in the past are mixed up as co-determinants. Taking this definition as starting point, we may in many cases attribute a psychosomatic significance to allergic diseases; a circumstance which in that case should be taken into consideration not only with respect to the genesis and outward manifestation of the affection, but also in the therapy. This significance varies all according to the mode in which the emotion is experienced by the patient. The modus of experience naturally depends first and foremost on the personality structure (the reaction-type) of the individual; next, on the aggregate of factors in the patient's inner and outer world that gave rise to the emotion in question.

The psychosomatic aspect of the affection becomes more strongly prominent as the emotional experience appears to have a greater psychotraumatic significance for the individual. This means that not every affection that is regarded as psychosomatic—and therefore, not every allergic disease—is bound, in every case, to have a psychosomatic character. Now this cannot invariably be concluded one way or the other from the biographical anamnesis (longitudinal section of the person's life history, better: the individual's reaction-history); it requires a thorough and detailed psychosomatic examination. In our Psychosomatic Centre we institute for this purpose, apart from the somatic (internal and purely organic) examination, a biographic or autobiographic, a psycho-diagnostic, a physio-psychologic, and a psycho-social investigation (see under III, Ba). Our experience with allergic diseases has taught us that not all cases, by a long way, are eligible to being classed as psychosomatic! And this applies, apart from asthma, also to urticaria, eczema, Quincke's edema, vasomotor rhinitis, and various forms of headache known as being allergically conditioned. We shall revert to this point further on.

B. *Psychic determination in the problem of allergy.*

In considering the significance of psychic determination in the problem of allergy the first question to ask oneself is why, and to what extent emotional influences should have given rise precisely to allergic affections. This question touches upon the problem so important in psychosomatics—of specificity. Without wishing to go

deeply into this problem as such (244), the following points require examination with respect to allergy:

1. Are the contents of emotional experiences, in fact, of significance in allergic diseases?
2. Do there exist specific, emotional experience contents capable of giving rise to an allergic disease?
3. Does there exist a specific personality structure which may lead to an allergic disease?
4. Is it necessary for a specific, emotional experience-content to act upon a specific personality structure in order to give rise to an allergic disease?
5. Or need neither the experience-contents, nor the personality-structure be specific for this to happen?
6. Were the experience-contents the primary cause of the allergy, or is the latter primary, and does the psychic determinant which, as such, led to the syndrome, act secondarily on an already present, not psychically determined allergy?

In the following we shall discuss the various points of view as they appear from the literature and also state our own inferences. On reviewing the literature, however, one finds that many authors do not touch upon some of the above questions.

(1). *The significance of emotional experience-contents, as such, in allergic diseases.*

It is generally agreed that events (or rather, experiences) of an emotional nature are very often involved in the outward manifestation of allergic diseases. This also tallies with our own experiences; but whether one would be justified in speaking of specific, emotive influences is doubted by many, including ourselves; although in certain cases of allergic manifestations one may admittedly come across roughly corresponding conflict situations (see under C below).

We here give a few data from the literature, that throw a light on the significance of conflict situations in general as determinant factors in allergic diseases. The reader will find elsewhere some more or less complete summaries of the relevant literature (H. A. Abramson (3;5). Fr. Alexander and T. M. French (10). M. Bleuler (21), Flanders Dunbar (58), Milton L. Miller (148), I. H. Schultz (212), Oswald Schwarz (217), P. F. D. Seitz (220), Erich Stern (234; 235), B. Stokvis and A. J. Welman (250), H. Völkel (266), E. D. Wittkower and Brian Russell (282).

In one of his very readable works, Erich Stern (234) points to the significance of life-conflicts in general in the genesis of disease, and deals with the various

allergic affections, in which he ascribes considerable importance to psychic influences.

F. W. Clarke (40) made a catamnestic investigation of children who had been treated by an allergy specialist. He found that a large number of allergic children had formerly shown psychic disturbances. S. S. Stevenson (238) came to the same conclusion, and made therapeutic use of it. We have had similar experiences ourselves. Again, T. L. Squier (233) and M. Ziwar (296) have pointed to the significance of psychic traumas in allergic affections. Of the non-allergic factors, S. C. Dees (46) regards the psychic one as the most frequent in the genesis of allergic affections. In the course of an investigation into the family relationships of 400 children he found an abnormal parent-child relation in the majority of cases.—To this corresponds also the investigation made by J. H. Mitchell, C. A. Curran and R. N. Meyers (151, 152). These authors studied the action of what they term "psychogenic factors" in allergic diseases. They made a subdivision into two groups: the first showed positive skin reactions in an allergic test, while the second group did not. Especially in the second group, these authors consider psychic factors to be very important.

The same authors compared 12 adults suffering from "allergic nasal disorders" with 12 vasomotor rhinitis patients, and found that personality problems and negatively resolved emotions had a greater causal (better: conditioning) significance in the former than in the latter group.

Medard Boss (27), in his important study on the problem of allergy, comes to the insight that a psychic factor (anxiety) is one of the causes of these affections. He regards them as a defence mechanism against the outer world (die leibliche Austragungsform einer existentiellen Abwehrhaltung).

The significance of emotional factors in *bronchial asthma* has been discussed by us in an earlier publication (250).

E. Wittkower (281) who, in collaboration with H. Petow and H. Pollnow (176), investigated cases of asthmatic patients already many years ago, stressed the fact that in most cases of bronchial asthma psychic factors play a part as well as somatic ones. The same conclusion was arrived at by E. Billings (20), E. A. Brown and P. L. Goitein (33), S. Gunnarson (89), E. B. Kris (119), and J. Naber (167).

Some investigators carry their conceptions about the psychic character of asthma very far indeed. S. J. van Pelt (172) considers spasmodic asthma to be a symptom of "underlying nervous disorder" only. J. Groen and co-workers (49; 87) hold that there exists a purely psychogenic form of asthma, in which allergic factors do not play an important part. Our own view on this question is given under C, below.

A number of investigators have made a special study of *allergic skin diseases*. We may here mention Erich Stern's excellent article (235), in which he gives a survey of the problem of the relevancy of psychosomatic medicine to dermatoses, and discusses, *inter alia*, eczematous affections, neurodermatitis and urticaria. Emotional experiences, especially in family relationships, were found to be a factor of importance in allergic skin diseases (G. A. van Balen (13), F. E. Cormia (42–44)).

The last-named author also found disturbed family relationships in all his patients with chronic constitutional *eczema*. A. J. Mitchell, L. Frost and J. R. Marx (150) had corresponding experiences.

E. Wittkower and P. G. Edgell (280) found reason to refer most of 90 eczematous patients, examined by them, to a psychiatrist: conservative treatment had been unsuccessful, while in some cases the patient made a strange impression. They found that the skin disease bore some relation to recent happenings, in addition to which the patients felt emotionally insecure. The authors pass over the point why emotional experiences should precisely seek their way out through the skin. Similar findings are those of M. J. Rosenthal (191) and I. B. Sheddon (222).—*Urticaria* was investigated by L. Kaywin (112); an emotional cause could be demonstrated in between 10 and 18 per cent. of his urticaria patients.

We should finally mention *migraine*. As experience teaches, considerable importance is here attached in many cases to emotional factors. This is confirmed by a great many authors (e.g. A. Garma (78), F. Kennedy (114), J. S. Lewis and C. J. Rowe (129), F. Reichmann (186)).

We may here add a few words concerning the link between *allergic diseases and the psychoses.*

To investigate the possibility of this connexion, R. M. McAllister and A. O. Hecker (11) examined 1875 psychiatric patients and 757 individuals from a control group for allergic symptoms, i.e. by ascertaining their sensitivity to an allergen that represented a daily milieu factor for all of them. It was striking that the psychiatric patients turned out to be more sensitive to the allergen than the control group. The same conclusion was arrived at by H. C. Leavitt (122) and K. B. McInnes (102). But it is contradicted again by W. D. Ross and coworkers (193) and by M. Zeller and J. V. Edlin (294), all of which does not bring one much further.—A remarkable observation was made by D. H. Funkenstein (75). In 6 psychotic patients with bronchial asthma he found an alternation of psychotic symptoms and asthmatic attacks. J. C. Sabbath and R. A. Luce (197) found that the two affections at times alternated, at times coincided. It appeared to them that asthma is not bound up with certain psychoses; but that the degree of asthmatic severity is lessened according as the patient's personality is more deeply involved in the psychosis. Our own experience does not suffice to decide whether, and to what extent, there exists an unqualified connexion between asthma and psychosis. D. Leigh and J. W. L. Doust (124) deny its existence.

In our Psychosomatic Centre we have observed various examples of asthma as a manifestation of a form of somato-psychosis (243) ("Organ-psychose" in the sense of H. Meng (137)). Also E. Stern (235) is of the opinion that asthma in some cases may be conceived as an "organ-psychosis".

Viewed from this angle, a link definitely does exist between the appearance of allergic manifestations and psychosis (cf. under I C below).

(2). *Specificity of the emotional experience-content (conflict).*

We here postulate at once that our experiences with allergic patients do *not* justify our assuming the existence of a genuinely specific conflict-situation. A distinction should be made between "conflict" in the psychoanalytical sense and "life-conflict". In both respects we could not state any specificity. But the literature contains the names of many authors who feel justified in admitting specificity of the emotive experience-content in sufferers from allergy.

Thus, F. Alexander (9) (who in some cases, as in migraine, does not entirely reject the specificity of the personality (see point (2) above) attaches importance to the specificity of the conflict facing the patient. In his profound study on patients with allergic diseases this leading investigator refers to the patient's relation, which has remained immature, to the mother-imago. According to the author this immaturity causes the individual to react inadequately to specific difficulties in his life (conflict-situation); for here, after all, a call is made on the patient's independence. L. J. Saul (200), in collaboration with John W. Lyons (202; 203), found that, in allergic patients, any threat to the bond with the mother creates a yearning for help or protection that expresses itself in various disturbances (as in the respiratory system and in the skin).

H. Miller and D. W. Baruch (141) studied the allergic symptoms in 22 patients. They believe that the production of these symptoms must be conceived as an endeavour to win the love of others, to express feelings of hostility, or to mask a feeling of guilt or anxiety. In another article (142) the same authors describe their experiences with 63 allergically reacting children and 37 non-allergically reacting control children. In 62 out of the 63 cases the children felt they were being rejected by the mother, while in the control group this feeling was found in only 9 out of the 37. In a subsequent investigation (144) the authors ascertained the influence of feelings of hostility which the examined children had with respect to their milieu. It was found that the allergic children, far more than those of the control group, showed a tendency to block their feelings of hostility and direct them toward themselves. The examined children included sufferers from asthma, hay fever, and eczema.

L. J. Saul (199) (see above) determined corresponding findings in sufferers from *hay fever.* The study of three patients led him to the hypothesis that one of the factors responsible for this affection was the presence of repression of libidinous desire. We, too, came to the same conclusion. Again, Fl. Dunbar (59) raised the question of emotional factors in hay fever.—The connexion between psychosexual development and the appearance of hay fever has been further studied by G. W. Wilson (275); that is, on the basis of 7 psychoanalytically treated patients. It was assumed that their hypersensitivity to pollen was caused by the patients having been insufficiently able to gratify their sexual curiosity olfactorily. Naturally, such a pronouncement calls for confirmation. One author who has devoted his attention particularly to rhinitis is S. G. Wolf Jr. (283), who is of the opinion that feelings of anxiety, hostility, guilt and disappointment are coupled with nasal hyperfunction.

A very large number of investigators have occupied themselves with tracing the connexion between the genesis of *bronchial asthma* and certain conflict situations. One of the first to elucidate this problem profoundly was F. Alexander, in collaboration with Th. M. French (72). These two authors believe that heredity is an important factor. Next to this they regard emotional determinants as essential; sufferers from asthma have a great need for love and fond care. In this the authors put their focal point in the patient's separation from the mother.

As long ago as 1922, E. Weiss (269, 270) pointed to the unconscious longing for the mother, coupled with the feeling of being betrayed by her, and with castration anxiety. According to French and Alexander (72) the basic conflict in asthma is one between the urge to cling and the temptation to separate. In a later publication, French (70, 71) underlined these findings: "... fear of estrangement from a mother and inhibition of crying". According to them, the nuclear conflict is the ambivalent disposition with respect to the mother. This was also pointed out by Mitscherlich (153). Already long before this, we ourselves had observed that asthmatic children cannot achieve a bond of mutual confidence with their mothers. Harris (99), too, refers to this.

The connexion between asthma and the modus in which the patient experiences the separation from a mother-imago is also referred to by M. Ziwar (295; 296), and by J. Delay and M. Ziwar (50). H. Miller and D. W. Baruch (146), and also P. M. Symonds (259) put maternal rejection in the key position. A. E. Scheflen (207) found, in a woman with bronchial asthma, who had a strong positive transference to the therapist, that she reacted with an attack of asthma whenever she felt rejected or slighted.

L. W. Sontag (229), too, lays emphasis on the presence of dependency needs. The investigations of A. Dührssen (56), P. G. Edgell (62) and of Th. F. Freuting and H. S. Ripley (74) also revealed a strong need in these patients for love and protection by one of their parents, and a retarded development in their emotional life. The resulting immaturity causes them to be inadequate in their relationship towards their fellow-men. According to Edgell, many parents of asthmatic children lapse, on the contrary, into an over-anxious and over-protective attitude towards them. This view has also been put forward by C. Swanton (257) and by J. A. Gendrot (80).

F. Alexander and Th. M. French (10) further assume that there is a connexion between the appearance of asthma and the suppressed crying for the mother. Ziwar (295; 296), too, regards the asthmatic attack as an equivalent of "suppressed tears of fright". In conformity with this, J. A. Gendrot (80), A. Hanse (96), K. Egen (63), B. Knick (116), G. Schwöbel (219) and F. Mohr (159) call the allergic reaction, in some cases, an equivalent of anxiety. (The same view was already expressed earlier by Freud). I. D. Harris and co-workers (99), whose findings correspond to those of Alexander and French, reported that asthmatic children find it harder to cry than normal ones. In our own clinical material we have reports of asthmatic patients who had stated spontaneously that they were able to cry about

their grief when free from attacks, but not during periods in which attacks occurred.

Other conflicts in asthmatic cases have also been described. D. Leigh (123), H. Miller and D. W. Baruch (147) lay stress on the presence of anger.

J. Bastiaans (19), in an important article, states on the ground of his extensive psychoanalytical experience that he found the asthmatic respiratory symptoms to correlate, on the psychological plane, with pronounced greediness (inspiratory introjection), difficulty in giving up property or an object of love (respiratory constipation), and "laryngo-respiratory vaginismus".

Both Alexander and French, moreover, have referred to the link that appears to exist between sexual problems and asthma. One of our own cases was a 23-year-old student, who had attacks, usually during week-ends, when he was without his fiancée, with whom he had regular intercourse; an example of the asthmatic attack as the equivalent of sexual distress. To the existence of this phenomenon, Fritz Mohr, in an excellent article (158), drew attention as long ago as 1937. Furthermore, P. Federn, O. Fenichel, I. H. Schultz, E. Weiss (see Völkel 266), and A. V. Magee (135) have pointed to the significance of sexual conflicts in asthmatics.

It will doubtless be clear from the above that psychosocial work (case-work), and the patients' elimination from their domestic milieu may sometimes be of considerable therapeutic importance. Our own experiences in this respect are also confirmed by J. Groen, D. Hallowitz, N. Kühne and M. M. Pestikin (see Völkel (266)).

On reviewing the many data that may be found in the literature, one will find that the majority of authors report the presence, in asthmatic patients, of an unsatisfied longing for warm-hearted friendliness, solicitude, and contact with their milieu (mother); often coupled with a compensatory attitude of reserve; and further, either an incapacity to express aggressive tendencies towards their milieu, or an extreme self-control in this respect. It is not so difficult to select, from these many situations, a few that one might put forward as being "specific". We shall refrain from doing so; we have here to do with conflict situations of a general nature well-known in the theory and experience of neurosis.

Now to what extent has a specificity of conflict-situations in cases of *allergic skin diseases* been demonstrated? In answering this question various difficulties arise. With regard to eczema there exists a widely ranging literature; on the subject of angioneurotic edema, on the contrary, the published investigations are far fewer in number.

F. Alexander (9) is of the opinion that attempts at generalization have, in fact, failed in the study of the allergic dermatoses. According to him, the patient makes use of his physical being for the purpose of getting attention and winning love and privileges (exhibitionism). This, however, calls forth feelings of guilt. The skin being, in this case, the cause of the feeling of guilt, it also becomes the

organ in which the punishment for the patient's own, unaccepted feelings is expressed, namely in the form of painful sensation. Scratching appears to be of importance in this respect; it enables the patient, under the influence of his feeling of guilt, to direct his hostility towards himself.

As regards *angioneurotic edema,* hardly anything is to be found in the existing handbooks by Alexander, Dunbar, English, and Weiss. B. Mittelman (155) refers to its somatic nature. L. J. Saul and C. Bernstein (201) believe they observed, in their patients with *urticaria,* a link between this skin disease and a repressed desire to cry. Alexander came to similar findings in his own cases, and averred that these patients, in common with asthmatics, feel a need for a dependency-relation with a parent imago. He found another similarity to bronchial asthma in the phenomenon that also urticaria patients find it hard to cry.

Various forms of *eczema* have been closely studied psychologically. In patients with eczema on the hands the conflict appeared to consist in the being rejected by the mother, by the family, or by the financé(e) (F. E. Cormia (41), S. H. Zaidens (293)). According to the latter author, the localization is a symbolic expression of prayer (?!). R. M. B. McKenna and I. Macalpine (134), as well as E. Pichon-Rivière (174) believed they could observe in their patients a central conflict in the form of the need on the part of the patient to be dependent. H. M. Stone (253), in an investigation on eczema in children, came to corresponding findings. E. Schneider (210) concluded from his investigation that the emphasis should rather be on feelings of anxiety and guilt, following from outbursts of hostility and agression. Interesting psychoanalytic experiences are those which Gisela Krichhauff (118), and J. R. Prakken and H. Musaph (179) had with eczema patients. Cormia (41) neatly expresses the psychosomatic link between conflict situation and skin as follows: the skin reflects the load of life in the psychomatic personality.

As against those authors who assume a psychic determination of eczema, there are others who deny the existence of any link between the appearance of eczema and the presence of conflict situations. This is the view held, for example, by H. W. Siemens of Leyden; this prominent dermatologist attaches no belief to emotional influences as a causal factor in allergic eczema (224), a view which he bases on clinical-experimental observations according to which an automatic regularity was found to exist in recovery and relapse on admission and discharge of clinical patients of all ages (H. W. Siemens and G. G. Jagtman (225)). On these grounds Siemens rejects the term neurodermatitis. (In the case of warts, and in psoriasis Siemens (226), does not deny the significance of psychic influences).

We should not like to go as far as Siemens; but we do guard ourselves against onesided views and speculations that might discredit legitimate claims of psychosomatic medicine in the eyes of the allergy specialist and dermatologist.

The above also applies to *urticaria.* L. Kaywin (112) mentions a number of emotional factors that might be of significance in the case of urticaria patients; notably anxiety, diffidence, and frustration. Also H. Musaph (165) points to the significance of anxiety, and to the defense mechanism of anger and rancorous feelings in thirty patients with chronic urticaria examined by him.

G. F. van Balen's careful, calmly reasoned discussion (13) contains a useful survey of the literature.

Foster Kennedy and co-workers (113) described a patient who reacted with urticaria under the influence of a sudden serious fright. These authors conclude that what they call "fright-urticaria" is, in fact, based on a lability in the endocrinic metabolism with a vegetative-nervous constitution of the psycho-physical totality (114); they contend that this in itself already sets up an antiphylactory hypersensitivity to sudden fear. F. F. Wagner (268) describes a female patient with emotional problems in relation to her mother and sister. The complaints disappeared when both died.—Emotional factors due to the military situation may give rise, in some individuals predisposed to this, to the appearance of urticaria (Sullivan and Bereston (256)).

We see that little agreement seems to prevail also here; all one can say is that emotional influences are evidently of significance in the appearance of urticaria.

Let us now turn to *migraine,* passing over, for the moment, the question whether or not this affection is of an allergic nature. In the following survey of the relevant literature we shall cite only those authors who believe—as we ourselves do—that migraine must, in some cases, be regarded as an allergic reaction, be it only in a certain sense.

Alexander (9) refers to the experiences of psychoanalysts who, thanks to their frequent and intensive contact with their patients, have occasion to witness attacks of migraine right through. The central conflict in those cases invariably proved to be a state of repressed anger. According to Alexander an attack of migraine can be caused via the action of some imaginary fancy on the vegetative nervous system. Edward Weiss (270) confirms the opinion of the Chicago school when he writes that migraine ". . . seems more closely related to the character structure and personality trends observed in patients with essential hypertension, having to do with the amount and disposition of "hostile impulses" ".

These two authors' remarks tally with our own observations inasmuch as we have also observed, both in sufferers from essential hypertension and from migraine, a blocking of aggressive tendencies.

Summarizing, we repeat that *the most extreme caution is imperative with respect to the generalization of conclusions from observations, however carefully made, in a few patients;* there may be different psychic determinants that influence unmistakably the appearance of allergic affections.

(3). *Specificity of the personality structure.*

Already from remote times the opinion has been widely adhered to, on the ground of clinical observations, that certain diseases particularly affect persons with a certain physical habitus.

Thus, we know that individuals of slender stature, with narrow thorax and glossy hair more readily tend to develop pulmonary tuberculosis than those differently built. With this correlation as starting point, some connexion was presumed to exist also between manifestations of the personality and certain diseases. For instance, it had for a long time been noticeable that persons with a morbid receptiveness to the experience of anxiety are predisposed towards cardiac diseases. A number of authors, as W. C. Alvarez (12) and G. Draper (55) and before that, L. Braun (29), have attempted closer study of these correlations; some years ago we ourselves went deeper into the question of these correlations in a separate monograph (240).

The first to investigate this problem systematically, *inter alia* in allergic diseases, was Flanders Dunbar (57;58;60), who drew up a number of personality profiles. According to her there exist correlations between personality types and certain diseases, and this she holds, applies especially to psychosomatic affections, to which may also be reckoned certain cases of those diseases which have an allergic basis. Different investigators have tested these findings by their own experiences.

Before giving a survey of the relevant literature, we would remark at once that our own experiences with allergic patients have *not* made us acquainted with any specific structure of the personality. No general agreement can be found among the various authors. Dunbar's investigations have been criticized by F. Alexander (9), W. Bräutigam (30), E. Funk, and W. Schwidder (see No. 266).

E. Schneider (209) endeavoured to come to a subdivision of allergic patients on the basis of the typology according to Jaensch. Another investigator who considered it possible to give a description of the allergic patient's personality, and notably of that of the *bronchial asthma* patient, was U. Pipkorn (175). I. G. Rhodes (187) found, in children with allergic diseases, certain rapidly changing character qualities. E. A. Brown and G. L. Goitein (32) concluded, on the ground of an investigation into the temperament and instinctive drives in 100 individuals, that "... the asthmatic subject is of a cyclothymic disposition, associated with paranoid features, repressed hostility, and self-punishment motives". According to these authors, moreover, the asthmatic patient often has a fixation to the oral or anal stage of development, with the result that oral-erotic and anal-sadistic traits play an important part in the formation of his personality. Another personality characteristic, supposed to have proved of importance, is an inclination to homosexuality (Fl. Dunbar (57, 58), F. Mohr (159)), while E. Jolowicz (105) stated in 1934 that sufferers from asthma were self-assured and ambitious.

F. Reichmann (185, 215) regards bronchial asthma as a neurosis of the respiratory tract, viz. as an expression of a psychopathic constitution. According to her, every asthma patient shows certain psychopathic traits that act partly causally, partly secondarily. In common with K. Hansen (98) she points to the occurrence of manic-depressive symptoms in asthmatics. It was especially when Hansen's patients were passing through a depressive period that he found their asthmatic attacks to increase. From the psychoanalytic literature we know, *inter alia* from the writings of O. Fenichel (67) that there exists a relation between manic-depressive symptoms and bronchial asthma.

On the basis of Hansen's views, G. Schwobel (219) examined 129 asthmatics with the aid of the biographical anamnesis, an allo anamnesis of the patient's relatives, and by the application of the Wartegg test, the Rorschach test, and by graphological methods, apart, of course, from the customary physical examination. With the aid of this method he drew up a characterological profile of the asthmatic patient. A. A. Pontius-Müller (177), in order to draw up a character structure of the asthma patient, performed a graphological investigation in 80 patients. According to her, the asthmatic is a person who is sensitive, passive, and self-assured; his emotional life is dominated by anxiety, i.e. by fear of bronchial spasm and existential anxiety, as a consequence of an inadequate maturation of the personality.

H. H. J. Jaspar, J. J. G. Prick and K. J. M. van de Loo (104), in their important publication dealing with asthma, put forward the—in our own view, correct proposition that the personality structure varies in different asthmatic patients, but that it has one common feature: hypersensitivity to the experience of the loss of dependency, of being unprotected, or of separation.

Another allergic complaint in which endeavours have been made to discover a definite type of personality common to the respective patients, is *migraine*.

G. A. Touraine and G. Draper (261) reported finding in these patients an immature emotional development together with a well developed intelligence. According to these authors, attacks do not come on until the patients are compelled to leave the milieu with which they are familiar and have to shoulder the responsibility for themselves. Olga Knopf (117) found, in 30 migraine patients examined by her, that they were excessively ambitious, reserved, dignified, sentimental, and lacking a sense of humour. H. G. Wolff (286) reports finding in these patients the propensities of a compulsive character with extreme ambition, rigidity, and inability to carry responsibility; they chronically felt insulted and were impossible to please. He considers this attitude to be due to the patients' inner awareness that they have failed to satisfy the demands they once set themselves. A. R. Furmanski (76) studied the character patterns of 100 migraine patients (65 women and 35 men). He found distinctly narcissistic character traits and a strongly developed aggressive disposition. These patients, he found, had been frustrated, when young, in their strong affective longings, and this caused them to develop ambivalent feelings. In a most readable article M. Sperling (232) relates his psychoanalytic experiences with 14 adults and 9 children, all suffering from migraine. All these persons appeared to have a marked oral fixation, and showed anal-sadistic features. In common with the authors already cited, he too was struck with the narcissistic and over-sensitive attitude to life of these patients.

This much is clear: not much agreement can be found in the literature; neither could we ourselves get as far as drawing up a generally valid personality profile in our patients suffering from migraine.

E. Wittkower (278), who has been especially occupied with investigations in patients with *skin diseases*, described character traits in urticaria patients that could be traced back to repressed aggressivity, a masochistic disposition, repressed exhibitionist tendencies, and denial of infantile dermal eroticism. According to him, urticaria is an expression of infantile rage; a compromise between the unconscious desire to draw the mother's attention to the skin, and the need to punish oneself for having this desire (cf. Fr. Alexander's (9, 10) conception, mentioned under (1) above, concerning allergic dermatoses). B. Woodhead (288), in investigations made in 29 adolescents, found the presence of an aggressive, egoistical, sensitive disposition. This author regards as fundamental a constitutional disposition towards allergic manifestations, and an inharmonious child-parent relationship.

H. Häfner and H. Freyberger (91) feel justified in concluding from their clinical observations that sufferers from "skin allergoses" (urticaria and Quincke's edema) have certain essential personality characteristics in common. Here, too, G. F. van Balen (13) quite rightly advises caution.

For further reviews of the Anglo-American literature in this field we refer the reader to the eminently commendable writings of P. F. D. Seitz (220), and of E. Wittkower and Brian Russell (282). An excellent survey of the further European literature is that by Erich Stern (235). Milton L. Miller (148), in his "Allergy and Emotions: a Review", gives a good survey of the literature on the psychosomatic aspects of urticaria and atopic dermatitis. A considerable volume of literature on psychosomatic conceptions concerning allergic disorders of the respiratory tract is cited by H. Völkel (266) in an excellent survey. With regard to asthma itself we refer the reader to B. Stokvis and A. J. Welman (250).

Summarizing, we may say that, also with respect to the personality structure in allergic patients, no such thing as a general agreement can be gleaned from the literature. In short, *a specific "allergic personality", to judge from our experience, does not exist.*

(4). *Specific emotional experience-content coupled with a specific personality structure.*

A number of investigators believe that a given conflict situation alone is not sufficient to give rise to a given disease. They incline to the opinion that there exist certain traits in the personality of the patients examined by them, but that these traits by themselves would also be insufficient to determine the outbreak of a particular disease. They believe that a given emotional experience would only then be of causal significance in the case of an individual who, owing to his or her disturbed development, shows certain personality traits.

This, in our own view, is most exaggerated; we are reluctantly reminded—sit venia verbo—of a certain type of armchair science, and of wishful thinking on the part of those physicians who might adhere to this artificial conception in its extreme form. Examples of this are found in the summarizing papers cited under (3) above (148; 220; 234; 235; 266).

This reproach definitely does not apply to Eduardo Weiss. This prominent clinician holds that, speaking generally, neuroses and allergic diseases occur so frequently that both may be found in many cases coincidently in one and the same patient. But a more thorough examination of such patients reveals the fact that this coincidence is nevertheless not entirely accidental, but that it stems from one and the same inner disposition on the part of the patient. With this

we completely agree; after all, we regard allergic psychosomatic affections as somato-neuroses. Weiss further states that, next to the neurotic character structure, certain very definite affects occur typically. He particularly mentions, in asthmatics and sufferers from allergic skin diseases, the bond with the mother, while he considers aggressive impulses, next to a neurotically reacting character structure, to be jointly responsible for attacks of migraine. In a subsequent publication, E. Weiss (270) declared that such patients often have a psychopathic character structure. H. A. Abramson (6) had the impression from patients examined and treated by him that this type of person, with their infantile personality structure, responds with allergic affections to any threatening daily situation in their lives.

Neither Weiss nor Abramson, therefore, can be said to be representative of the conception: specific emotional experience-content with specific personality structure. Indeed, the fact that patients with allergy of a psychosomatic nature have an infantile personality structure already follows from their being somato-neurotic.

The number of authors who regard the appearance of allergic diseases as being determined both by a specificity of the emotional experience-content (conflict situation) *and* by a specificity of the personality structure, is only small.

(5). *Aspecificity of both experience-content and structure.*

Many authors, including ourselves, have come to the insight that *in the manifestation of diseases of an allergic nature, neither the personality structure nor the emotional content of the conflict can be called specific.*

Linford Rees (184), in a recent, well documented publication, puts forward this, *in our view the only correct, conclusion.* Also J. J. Lopez Ibor (133) writes on the ground of great experience: "I have not found any definite personality type in asthmatics". B. Knick, Mainz, expresses himself in the same sense. Again, F. Mohr (160), in a recent essay on allergic dermatoses, emphasizes that the notion of specificity must be rejected.—As W. J. Quarles van Ufford (181) and Denis Leigh (123) rightly remark, the conflict situation itself is often not important, but the patient only uses his attack of asthma to draw attention to himself.

(6). *Primacy to the experience-content, or to the allergy?*

The question whether to consider the psychic factor (experience-content) or the allergy as primary would in our opinion be settled satisfactorily once and for all if one could look on allergy as A.

Mitscherlich (153) does - as being a coincidental psychosomatic process; in that case the patient's hypersensitivity would have been acquired in both a somatic and a psychic respect; in other words, his allergic susceptibility would be both primarily somatic and primarily psychic. Not having been able, however, to prove the truth of this hypothesis, we feel compelled to hold aloof from it in the following considerations; and to adhere to the conception that the allergy itself is primarily somatically determined.

A number of investigators have studied the question of the influence of psychic determinants in the appearance of allergy as such. In this, the following possibilities present themselves:

a. *Somatic determination of allergy.*

This conception implies that allergy may be either primarily inherent in the constitution, or generated through sensitization. This aspect of the problem naturally falls outside the scope of the present discussion, and we may refer the reader to the relevant chapters in this book, and to existing handbooks on allergy.

b. *Psychic determination of allergy.*

Some authors, as S. Rothman and S. A. Walker (194), veer over to the other angle, and ascribe to psychic factors the very greatest importance in the genesis of eczema and urticaria; even to the point of regarding as dubious the significance of allergic factors altogether. Such one-sidedness, we are convinced, is carrying things much too far, and can only discredit the significance, as such so important, of psychic influences.

Other investigators are of the opinion that an emotional experience-content alone may already be sufficient to give rise to an allergic condition. We doubt whether a causality of this kind can be proved to exist.

In investigating this problem various difficulties arise that render the results of anamnestic, catamnestic and experimental examination unreliable. For, it appears, there occurs a number of "allergic" affections (e.g. asthma, eczema, urticaria and migraine) without the patient in question showing any allergic reaction at all. We already cited Rothman and Walker in this connexion.

F. M. Rackmann (182) declared that allergy is a young people's disease. According to him, asthma in individuals over forty is not of an allergic nature. Also H. A. Abramson (1) found, among the allergic patients examined by him, a number with migraine or asthma in whom it proved practically impossible ". . . to demonstrate immunologic asthma". Side by side with these, he came across a number

of persons in whom the allergic symptoms were too violent in relation to their existing allergy. When, therefore, one finds in a patient who has never before shown any signs of allergy, an allergic manifestation after a psycho-trauma, it remains a difficult question to answer whether this manifestation, as such, is merely accompanied by allergy (positive skin test, eosinophilia, etc.), or whether the patient was already allergic before, without its being revealed in the form of clinical symptoms. The latter alternative is the more difficult of the two to ascertain objectively.

J. Groen and co-workers (49; 87), and M. L. Miller (148) here speak of 'psychogenesis' (see under 1 above); E. Wittkower (176; 276; 281) and I. H. Schultz (213) regard psychogenesis as unproven. F. C. Metzger (140) is of the same opinion. We give our own views below (p. 372 et seq.).

For that matter, the psychosomatic therapist should prefer, in our opinion, to speak in this connexion of conversion-hysterical phenomena, thus distinguishing these from allergically determined affections.

c. *Latent, somatically determined allergy, becoming manifest owing to a psychic factor.*

According to this conception somatically determined allergy was present in latent form, becoming manifest through a psychic cause and so expressing itself in the form of an allergic affection. It was in conformity with this view that K. Hansen, E. Moos, J. and R. Naber, I. H. Schultz, E. Wittkower (see No. 266), and, later, F. Mohr (158; 159) argued that, under the influence of experience-contents, a previously existing, latent allergic condition becomes reactive and may thereby give rise to an allergic affection.

"The physical disposition to asthma is the point of attack for unsolved psychic difficulties", writes Richard Siebeck (223) in his fine work: Medizin in Bewegung. Again, "Asthma allergens can be considered as substances to which the patients have become conditioned during a contact coincident with a state of conditional tension, which was subjectively experienced as a feeling of oppression", write J. Bastiaans and J. Groen (87; 88).

A similar opinion is held by H. Häfner (90). This investigator justifies his conception on the ground of his observation of two patients with urticaria and Quincke's edema (angioneurotic edema). According to him, the tendency to react allergically is dependent upon the irritability threshold of the diencephalon; the existing allergy becomes manifest via the action of an emotion on the vegetative nervous system and the diencephalon.—S. S. Leopold (127) takes up the same standpoint; he, too, is of the opinion that emotions can aggravate allergic symptoms, and ascribes this to their effect on the adrenal cortex and the hypophysis.

The nature of the psychic factor able to render the allergy manifest has been

further elucidated in an extensive investigation by H. Miller and D. W. Baruch (145), who assume that the relation between the mother and the allergic child (in the sense of "maternal rejection") is an influence in making the allergy manifest. Out of 100 allergic children, 97 proved to be "rejected". The chance that an allergic child lives in a milieu with an element of "maternal rejection" in the domestic atmosphere is greater than in the case of a non-allergic child.

d. *Side-by-side occurrence of an allergic component and a psychic factor.*

This situation concerns patients known to be allergic, but in whom allergic manifestations occur either through a somatic cause (allergen, infection, etc.), or owing to an emotional experience-content. The two above mentioned authors E. Wittkower and H. Petow (281), who do not deny possibilities referred to (under a, b and c) none the less consider, in common with V. Schatia (206), the existence side by side of interacting allergic and neurotic components to be more credible.

An important finding in this connection is that of S. Gunnarson (89), who examined 58 asthmatic children, all of whom showed a positive allergic skin test. He found that in more than 53 per cent, a psychic component came into play, which revealed itself in the form of anorexia, pavor nocturnus and suchlike. Also J. A. Blue (22), F. C. Metzger (140) and M. M. Salazar (198) are of the opinion that a psychoneurosis, or emotionally charged experience-contents can complicate an already existing allergy. E. Wittkower (276) and H. A. Abramson (2) also uphold a dual genesis, especially in the case of bronchial asthma, just as F. Morel (161) does with regard to urticaria. The same conclusion is arrived at by H. Ruhland (196) in his small but valuable book "Ganzheitsmedizin und Psychosomatik"; i.e. the presence of somatic, psychic and allergic influences.

e. *Primary presence of allergy, affecting the psychic condition.*

Obviously, allergic diseases can exercise a great influence on the modus of experience and the behaviour of the sufferer. The asthmatic child finds himself ostracized from play and games; later on he cannot join camping excursions, etc. When applying for a job, asthmatics find themselves in an invidious position. Children with chronic eczema, already while still babies, experience being tied up to prevent them from scratching. As toodlers they have to go without certain tid-bits. In contact with others they come up against aversion. Especially in a young girl in the period of puberty, this is bound to set up a grave conflict, or a feeling of frustration. Contacts with the opposite sex, school trips and holidays are preceded by a long anxious wait to see what the condition of the skin is going to be under certain circumstances. Owing to irregular school attendance, the affection also forms a hindrance to the child's proper education, as well

as causing difficulties later on when applying for a job. Conversely, these problems may give rise to tensions that, in their turn, unfavourably affect the complaint.

F. W. Clarke (40) rightly pointed out that many so-called problem-children with allergic diseases, given adequate anti-allergic treatment, can grow into quite manageable individuals. This is in conformity with a large number of observations made by P. J. van der Werff and W. van der Bijl (273) in their Clinic for Allergic Diseases in Amsterdam, as well as by ourselves. Similar experiences are reported by F. Deutsch and R. Nadell (53).

We were able to observe in many allergic patients an unfavourable influence on their emotional condition from their allergically determined ailments (asthma, eczema). In some cases this circumstance alone renders psychotherapeutic treatment necessary.

C. *The line of thought here followed.*

We shall begin by inquiring to what extent one is justified in conceiving the problem of allergy as a psychosomatic one, and in how far different principles ought to be held valid for the group of allergic somato-neurotic affections, from those applicable to non-allergic somato-neurotic diseases of the respiratory tract, the skin, and the circulatory organs.

Many of the authors cited in the above speak of skin diseases without making any distinction between allergically and non-allergically determined affections. And the same applies to bronchial asthma. Yet, in the majority of these complaints psychological factors, after all, are in one way or another of significance (C. T. Prout (180), W. Bräutigam (30)).

As long ago as 1938, I. H. Schultz rightly remarked that in allergic syndromes several determinants may invariably be observed, such as inflammations, vasomotor reactions, psychic conflicts, etc. Here one involuntarily reflects that this plural conditionality might well apply also to affections of a non-allergic nature. For that matter, psychic influences very often appear to come into play in all sorts of diseases; in this, Alexander (9) goes as far as to consider *all* ailments as being psychosomatic, because psychological factors, after all, invariably play a role in one way or another. But then the term "psychosomatic" loses its *raison d'être*. A delimination of the concept "psychosomatic" is definitely necessary.

A number of British investigators, with J. L. Halliday (93) as their representative, reserved the name "psychosocial affection" for a number of known, specific complaints, including asthma. Many investigators, as E. Wittkower (279) and F. Deutsch (51–53), Viktor

von Weizsäcker (271), A. Mitscherlich (154) as well as ourselves, use—as already mentioned—the term "psychosomatic" for those affections in which emotional factors act in considerable measure as determinants. Their influence may either stem from the past or originate in the present; however that may be, they are active *now*, either consciously or unconsciously, all according to the nature of the check on them (control, restraint, inhibition, suppression, repression).

Of the theoretical insights, the psycho-analytical view is, to our mind, the most important. To it we owe the concept of conversion (physical manifestation of the mental conflict), and of the symbolic significance of the "organ-language".—In the light of the modern conception of man as a psycho-physical totality, spiritually free, we would regard psychosomatic affections as results of a prolonged sequence of physiological processes that appear in the form of simultaneously occurring, secondary phenomena in cases of chronically acting emotions and conflicts. In this, man is thought of as being a psychosomatic entity, anchored to his milieu, and exposed to countless morbific influences. Added to this, the individual is exposed to the "life-stress situation", of which the conflict-situations are only a component part. The "stress" theory has been elaborated by the endocrinologist Hans Selye (221).

In this state of "stress", emotive influences form an important component. In common with Alexander we emphasize, in sufferers from psychosomatic affections, the occurrence of conflicts in the sense of frustrations in the matter of feelings of dependency, of sexuality and in the form of blocked agressivity. We should remark in this connexion that very many people, in their daily lives, are under constant pressure from such conflicts without ever falling ill. Every human being, after all, reacts to influences from the outer world, or from his (or her) own spiritual inner world, according to his own individual disposition. The fact that this entails the occurrence of certain corresponding behaviour-patterns in different individuals, should not, in our opinion, be (mis)taken for "specificity"! As already mentioned, we (244) were unable to prove that particular conflicts or particular life-conflict-situations belong to particular psychosomatic diseases; in other words, we did not find any *specificity with respect to these conflicts.* Asthma, after all, must be considered a somato-neurosis; and its occurrence is therefore conditioned by all sorts of psychic agents (fixations, infantile emotional bonds, conditioned reflexes, identification, feelings of guilt, other affective influences [fear and anxiety, hate, rage]).

As referred to in the above (under B), a number of American investigators, including Flanders Dunbar and J. Ruesch (195), hold

that specificity must be assumed to exist also with respect to the personality of psychosomatic patients. Admittedly, certain similar personality traits may be observed in a number of patients suffering from one and the same affection. But that, in our view, is not enough to justify our generalizing and speaking of a specific structure. As will be clear from what follows (under II B), in which we discuss the results of our test-investigations, our experimental researches have *failed to demonstrate any specificity with respect to the personality structure* either in psychosomatic patients in general, or in persons with allergic affections in particular.

However, although we are of the opinion that there exists no specificity in psychosomatics, we might none the less ask ourselves whether the sick human being is not (unconsciously) trying to avail himself of his allergic symptoms in order to express something or other.

It is to this question that the Heidelberg school (Christian, Mitscherlich, von Weizsäcker) endeavours to give an answer. These investigators regard the psychosomatic affection as an expression of being human; the sick person is "a human being" passing through a crisis. Mitscherlich (154), in an important article on allergy, refers to the allergic asthma attack as a possible equivalent of a cry of distress or a call for help. In this sense, allergy may be conceived as a form of defense against the outer world. Our own experiences point in the same direction.

From these various insights there grows the conception that psychosomatic syndromes (or allergic affections) are really an expression of two fundamental problems that the fact of being human entails, namely, the problem of erotic desire and that of dependency, or selfishness. They are the same problems as emerge from the symptomatology of psycho-neurotic conditions. Also in somato-neurotic conditions, therefore, we find these problems represented. In psychoneurosis we recognize the struggle of the human being insufficiently able to fulfil his human task. In the somato-neuroses (a better term, to our mind, than psychosomatic diseases (39)) he appears as being engaged in the same fight; but he betrays this through different means of expression.

The question why, in one case, the effected person reacts psychoneurotically, and in another case somato-neurotically, and why, in the latter case, different organic systems are involved, can in our opinion be answered only hypothetically for the time being. And the same applies to that important question: what is the situation of the human psychosomatic totality which gives rise to the production of allergens? To reply to this question would not, we believe, be scientifically justifiable at present either.

The various factors that may co-operate in the selection of a given organ ("organ-choice") are, *inter alia,* the inferiority of the organ; the organ-language; psycho-infection (imitation (185); pseudo-heredity [E. Speer (230; 231)]; "wirksame Bilder [="active images"]); identification, fixation to sustained somatic affections; psycho-traumatic experiences in the past or in the present, and conditioned reflexes that have become chronic in the sense of Pavlov (K. M. Bykow (35), B. Freedman (69), N. Metalnikow (138)). Here we must also point to the—so important—psycho-physical constitution, as evinced by investigations with "neuropathic" children. Deeper insight into the concept of "constitution" in general, and with respect to allergics (95) in particular, is urgently required, if the true significance of the concept of "overstressing" is to be validly assessed.

Next to overstressing, the sudden cessation of a burdening factor, too, is of importance in the genesis of a number of complaints. A crucial point is whether the individual is capable of adapting himself; that is, not only in a psychic sense, but also physically: the body, too, is liable to acquire habits formed by drilling. Looked at in this way, allergy itself might be viewed as a form of adaptation. But one ought to be careful with this idea of "stress": the same thing that, for one person, means an element of stress may be the very thing that gives relief to somebody else. The man or woman who, under pressure from neurotic feelings of guilt, works unduly hard, experiences the compulsory sunday rest as irritating and disagreeable ("sunday neurosis"). In our opinion, the concept of "stress" only acquires significance when viewed jointly with the individual's personality and life-situation; that is, in any given case, with the affected person's experience-modus. What matters in the last instance is whether or not the "homeostasis" in the sense of W. B. Cannon (36) (a condition of equilibrium which may vary, but which is relatively constant) is being disturbed.

Of great importance in giving rise to somato-neurosis is the psycho-traumatic effect of various disappointments and deprivations (frustrations) as a determinant factor. This situation, however, is often viewed too one-sidedly. For it is precisely these frustrations that warn a person to develop his latent powers, i.e. by stimulating his capacity for active adaptation. Viewed from this angle, frustrations *qua tales* are indispensable. Up to a point, indeed, man creates frustrations for himself as unconsciously felt possibilities for development and regulative control. This regulative capacity is closely related to both the constitution and the momentary situation; that is to say, with the individual's disposition at the moment that certain morbidly conditioning factors act upon him. The number of people who go short of affectionate kindness; who find no gratification of

their ambitious desires; who need safety and protection, is beyond counting. Not all of them suffer thereform the kind of injury that manifests itself in the form of a psychosomatic disorder. By "disposition" we here mean — next to the susceptibility to morbid complaints dependent upon constitution and circumstances — the temporary receptivity to the action (or, as the case may be, the experience) of those factors which make a special demand on the individual's capacity for adaptation. Probably a particular significance should be ascribed to the concepts "being sensitized" and "being allergic" respectively, relatively to patient's reacting either psycho- or somato-neurotically. We shall here refrain from pursuing this point.

Now to summarize our own views, as discussed so far, we feel unable to make any clear distinction between somato-neuroses of an allergic and a non-allergic nature. For we failed to find any unqualified indications that might justify our assuming the existence of any specificity of either conflict situations or personality structures. That which the human being *with* a somato-neurosis is said to have in him specifically may often be found also in people *without* any somato-neurotic complaints whatsoever. What did admittedly strike us was that all patients examined by us had an immature, underdeveloped personality structure; especially in allergics, we frequently noted an ambivalent attitude towards the object of their love, experienced by them as the mother-imago. An intense feeling of dependency was a prominent feature in the majority of our patients, in addition to which strongly aggressive tendencies towards the outer world were found to be active. The patient disapproves of this aggressivity on the ground of a highly-pitched Ideal-Ego function; represses it from the consciousness, and instead, directs his aggressive impulses—by way of self-punishment—towards himself.

Let us now briefly discuss our experiences with patients suffering from various allergic diseases. As regards *bronchial asthma* the following transpired. Experiences in our Psychosomatic Centre demonstrated that, in bronchial asthma, the morbific agents generally include a somato-neurotic and in a few cases a somato-psychotic affection. In the latter cases we have to do with an "organ-psychosis" in the sense of H. Meng (137), already referred to under I B 1. A telling example of this was described by us elsewhere (243).

In those asthmatic patients who may be regarded as somato-neurotics we observed the influence of many different conflict-situations as co-determinants: conflicts in their marriage, in their employment, in matters of religion, and/or (less often) in their sexual life. In many cases considerable significance must be attached to the anxiety

factor. A striking feature was, every now and then, the patient's ambivalent attitude towards the—often dominating—mother-figure, so often pointed to in the literature; the fear of being separated from the mother, and the asthmatic attack as the symbolic expression of crying for the mother: "crying inward". In some cases the asthmatic attack seemed to us an equivalent of a sexual experience; but this link does not, in our experience, occur so often (so-called "sexual emergency"). As we remarked before, our findings do not justify us to speak of any specific asthma-conflict, even admitting that the above mentioned conflict-situations do occur now and then.

As we already stated under 3, the personality structure of our asthmatic patients, too, could not prove to us the existence of a generally valid specificity in that respect either. What springs to the eye time and again is the infantile, immature personality, with the arrested development of its emotional life and the narcissistic bond with the individual's own psycho-physical being; but this, after all, is the same in every neurotic and, *ipso facto* therefore, also in the somato-neurotic asthma patient.

What is argued for the asthmatic applies equally to other allergic patients suffering from disorders of the respiratory tract (vasomotor rhinitis, hay fever), and to a certain extent for allergic migraine and allergic dermatoses (eczema, urticaria, angioneurotic edema, Quincke's edema). There, however, it is not so much the need, frustrated in infancy, for the mother's care and being cherished and fondled by her that stands in the forefront, but rather the surge of aggressive tendencies, coupled with the blocking of any possibility to discharge the pent-up emotions.

We were genuinely unable to ascertain the presence of a specificity common to these widely different situations.

We may finally remark that, in some cases, the psycho-neurotic condition was seen to become exacerbated according as his somato-neurotic complaint (i.e. asthma) improved. Similar findings are reported by W. Dogs (54) and V. von Weizsäcker (271).—*Mutatis mutandis,* J. Swartz and E. V. Semrad (258) have pointed out that psychotherapy can become dangerous in some cases of asthma, because it might further an earlier outbreak of psychosis. We ourselves have not gathered any such experience.

To conclude the first part of this chapter, let us endeavour to summarize schematically the views we have set out above.

The distinction between "somatogenic" and "psychogenic" allergic disease we reject on principle. In practically all cases allergic affections are, we believe, conditioned pluriformaly. In some cases the somatic factors are prominent, a corresponding somato-therapy is

then indicated; in other cases, on the contrary, psychic factors predominate, the somato-therapy must then be aided by some form of psychotherapy.

We are of the opinion that *allergy is primarily somatically determined, but that, in the actualization of allergic symptoms (organ-choice), psychic determinants may come into play.* In some cases it is the psychic influences that determine the degree in which the allergic factors can become manifest. This conception finds support in observations such as those of M. W. Gerard (81), according to which psychoanalytic treatment admittedly failed to remove the patient's sensitivity to allergens, but had nevertheless eliminated any further attacks of asthma when the patients so treated were again exposed to the allergens.

Schematically represented, it may be said that

Allergic symptom = expression of primarily somatically determined allergy + expression of a psychic component.

In some cases the significance of the psychic component is extremely slight and that of the allergy very considerable. In such cases one gets the "purely" allergic symptoms that have no psychosomatic importance. We then get the equation:

allergic symptom = expression of allergy + 0.

In other extreme cases the significance of the allergic component may be practically nil, while the psychic factor is the determinant element *kat exochen.* One then has to do with neurotic (conversion-hysterical) phenomena. We must pass over the question of the extent to which, also in those cases, a part of the allergic factor still remains present, so that in asthma too, in the sense of conversion-hysterical reaction-forms, an allergic component is playing its part. That is, naturally, a matter of hypothetical speculation. According to the experiences in our Psychomatic Centre, allergy is invariably present in "genuine" asthmatic attacks however prominent the psychic determinant may be (cf. also the findings of E. Hanhart (95), who ascertained the absence of sensitivity to allergens in only 8 per cent out of 1,200 asthmatic patients) . . . Again, I. H. Schultz (213) and E. Wittkower (276) consider any "pure psychogenesis" of asthma unproven. Maybe the term "allergiform syndrome" would be more apposite here; we would rather not use the expression "psychogenic asthma". Here, therefore, we get:

allergic symptom = 0 (?) + expression of psychic component.

The allergologist generally refers this type of patient to the psychiatrist without further ado. In the majority of cases, however, both factors should be assigned a measure of significance, and the allergologist will accordingly treat the patient in co-operation with the psychosomatic therapist.

It will bear repeating: *not every allergic affection should, in our view, be called psychosomatic.*

II. Experimental Medico-Psychological Viewpoint

The experimental medico-psychological aspects of the problem of allergy—leaving aside the study of animal psychology and experimental neuro-physiological studies—may be approached from one of three angles:

A. Psycho-diagnostic examination.
B. Physio-psychological examination.
C. Experimental clinical psychological examination.

A. *Psycho-diagnostic examination.*

Since this chapter is intended for allergologists, we do not propose to present anything like a complete survey of the literature dealing with the psycho-diagnostic examination of the allergic patient's personality. None the less, it would not be right to pass by this examination in silence, because the question of the specificity of the personality structure, which so repeatedly came up for discussion (under I), is closely bound up with the results of the psycho-diagnostic examination. Let us briefly introduce the subject-matter.

1. *Introduction.*

The following aspects may be distinguished in the personality of the individual: (a) intelligence; (b) character; (c) instinctive impulses (*Triebleben*); (d) temperament; (e) psychomotoricity. To test these various aspect there exist many different methods.

In our Experimental Medico-Psychological Laboratory we apply the following methods, which are in general use, to all patients by way of routine examination, and in the form of this test-battery: Wechsler-Bellevue test (intelligence); Rorschach (character, temperament); Szondi (instinctive impulses). Drawing tests: Wartegg-Zeichen test (WZT); House-Tree-Person test (HTP) (character, temperament, conflict situation); Thematic Apperception test (TAT) and Four Picture test (FPT) to inquire into the conflict situations.—In common with H. Enke and Hildegard Hiltmann (64), we attach considerable value to the projective test methods for psychosomatic patients. For a discussion of the significance of psychological tests in psychosomatic research we refer the reader to the notably interesting article by J. T. Barendregt (15).

2. *Literature.*

From the literature dealing with psycho-diagnosis we mention the following: A. Kaldegg (108) reports his results with the Wechsler-Bellevue test in 20 suf-

ferers from migraine. His findings suggest that migraine can be found at all intelligence levels. J. A. Mansman (136) found the same for asthmatics. We too found that our patients had average intelligence. In common with ourselves, Kaldegg found that "... no personality profile of a consistent sort was shown". Various investigators have examined allergic patients with the Rorschach test: J. T. Barendregt (14, 16), J. Groen (84), Maryse Israel (103), H. H. J. Jaspar, J. J. G. Prick and K. J. M. van de Loo (104), M. Schachter (204), V. Schatia (205), S. J. Vles and J. Groen (265), E. Wellisch (272). Schwöbel's investigation (218) has already been referred to. The majority of these authors were able in their records to report the presence, demonstrated with the aid of the Rorschach test, of the familiar neurotic tendencies in sufferers from asthma; while a number of them believe in the existence of typically asthmatic psychic characteristics. Barendregt emphasizes the fairly frequent occurrence, in asthmatics, of content-indications pointing to a state of psychic oppression.—In the case of neuro-dermatitis patients, too, the Rorschach test is supposed by S. Borelli (24, 26) and by R. J. Lévy (128) to reveal specific characteristics. (alias: "Neurodermitikertyp"; "... marked signs of repressed hostility"), whereas Kaldegg (108), whom we have already cited, could not, on the contrary, demonstrate a typical Rorschach picture. Flanders Dunbar (58), on the other hand, does hold that specific syndromes may be revealed through the Rorschach test. This we are unable to confirm. Mansmann (136) rightly points to the prognostic significance of the Rorschach test in asthmatics.

Important investigations in sufferers from skin diseases, including those of an allergic nature, were made by P. de Graciansky and Erich Stern (83, 234) with the aid of the projective Thematic Apperception test, for the purpose of discovering the presence and nature of conflict situations. Mansmann (136) is inclined to regard the projective tests for asthmatics as being of equally great significance as the skin tests. This may perhaps be true in some few cases. We furthermore refer the reader to the summarizing article, already cited, by E. Stern: "Psychosomatische Medizin und Hauterkrankungen" (1956) (235), which contains an extensive account of other investigators' psycho-diagnostic results.

With regard to the Human Figure Drawings, A. H. Modell and H. W. Potter (157) found little homogeneity in asthmatics; the drawings showed nothing but signs of immaturity. Our own relevant findings are in conformity with this.

We would finally mention the graphological examinations of asthmatic patients made by A. A. Pontius (177), introduced by A. Jores (107), which are supposed to indicate the presence of character traits typical of the asthmatic. H. Musaph (166) advises, for sufferers from skin diseases of a psychosomatic nature being psychologically examined, the use of the directive method, involving a questionnaire technique. Generally speaking we have no special leaning towards the use of that type of method.

3. *Our own investigations.*

For the purpose of testing empirically the hypothesis of the specificity of the personality structure of allergic patients, we compared, on the basis of material relating to *circa* 100 allergic patients, the data yielded by the structure-analytical examination with the corresponding results obtained in 125 psychosomatic "patients-in-general" who were examined in our Medico-Psychological Laboratory.

In all patients concerned, the above-mentioned test-battery was

applied. As will be seen from the range covered by the diagnoses of the diseases from which the 125 psychosomatic control patients suffer, they include also a certain percentage of persons with allergic complaints. In order to keep the comparable material perfectly pure, we were compelled to make up a second group for comparison: the number of 125 psychosomatic patients was accordingly reduced by the number of patients with allergic ailments.

Let us now subject the results of the separate tests to a closer scrutiny. For an exhaustive account of the precise data we refer the reader to a separate publication (251); we shall here confine ourselves to our conclusions from the data obtained in the three groups, viz. (1) the allergic patients; (2) the psychosomatic "patients-in-general", and (3) the psychosomatic, non-allergic patients[1].

a. *Wechsler-Bellevue test.* – We shall outline the results of our examinations of 87 allergic patients. As is known, the W. B. test consists of 11 sub-tests. For each of the sub-tests the "weighted score" for the 87 patients' average was calculated, and an average psychogram drawn up. The same was done with the two control groups, three different psychograms being obtained in this way. Each curve represents the psychogram of the imaginary average patient from each group respectively.

Comparison of these three curves shows that they have a certain similarity and that their respective courses are not widely divergent; all three show the characteristics considered some years ago by D. Rapaport (183) as typical of the neurotic. That should not surprise anybody; for all three groups consist of selected psychomatic—i.e. somato-neurotic—patients, who are *ipso facto* bound to show the characteristics of the sufferer from neurosis.

It is obvious that, in this respect, it would be wrong to suggest the presence of specificity.

b. *Rorschach test.* – In order to ascertain whether, and to what extent, the results of the Rorschach test might yield a particular picture in allergic patients, we *examined* 88 allergic patients with the aid of this test, and here *too,* drew up an average psychogram, in which the various data relating to the location, the determinants, the content, the experience-balance, and the approach have been elaborated. Such psychograms were also drawn up for the two control groups. No significant differences were found among the various series of figures[2]. What we did observe, in the content, however, was

[1] The author here wishes to record the important share taken by the staff of the Medico-Psychological Laboratory of the Psychiatric University Clinic, Leyden, in particular by Mr. J. D. A. Doeglas, in the compilation of these results.

[2] The author here wishes to acknowledge his gratitude to Mr. P. van Weeren for his valuable assistance in the statistical elaboration of this part of the investigation.

the feature of "responses showing oppression" referred to by Barendregt in the case of asthmatics.

All our allergic and psychosomatic patients showed the characteristics typical of the neurotic syndrome. But we failed to discover any specific personality structures, either in allergic patients in general or in patients with certain allergic diseases in particular, with the aid of the Rorschach test.

c. *Szondi test.* This test was applied in 92 patients, from whom a total of 435 records were obtained. With the aid of a special technique, to describe which would mean going into undue detail, and for which we refer the reader to another publication (251), we were able to produce a roughly correct profile of the average allergic patient.

With this we arrive at an approximate average of S+-+ Po (or--) Sch-- C- +. According to Szondi (260) the average picture in the case of healthy persons is S+ + P+ - Sch-- Co+. Comparison of these two profiles shows that, in the allergic patients, the bond with, and/or dependence upon, the object of his love, experienced as the mother-imago, strongly predominates, while in addition, conscience-anxiety, guilt-anxiety, fear of punishment, and even, in the presence of a severely functioning conscience, a panic-like terror may be found to occur. Here too, therefore, the neurotic attitude to life, infantilism, arrested sexual development and immaturity of the personality figure in the picture yielded by the test.

The Szondi picture of the average allergic patient does not indicate the existence of specificity within the general picture of the average psychosomatic patient (244).

d. *Other tests.*—Neither do any of the other tests mentioned (the WZT, HTP, TAT, FPT) reveal any specific picture—and particularly, any specific conflict situations of the allergic patient. Various frustrations are found with regard to the need for love and tenderness, and the absence of care in youth; ambivalence with respect to the love-object experienced as mother-imago; at a later age, frustrations in the matter of employment, sex-life, marriage, or religion. The fact that the asthmatic suffers from anxiety due to the threat of suffocation is not at all surprising; whether, and to what extent, this anxiety is bound up with any pre-oedipal anxieties (e.g. the fear of being deserted by the mother) is a question demanding further study.

But all these conflicts overlap and intertwine; we on our part have become more and more firmly convinced that any delimitation of the conflicts to conform with the particular syndromes is nothing but armchair science, and that in practice one should content oneself with tracking down conflicts in the particular case under treatment, without being able to prove specificity even in that respect. And

quite in accordance with this conception are the mutually contradictory findings of a number of authors (some of whom we have cited under I B2 above) who in some cases reported having found quite different "specific" conflicts in their patients.

Summarizing, we find that *the psychodiagnostic examination of the allergic patients studied by us has revealed a predominantly neurotic picture.* This is consistent with our view that the psychosomatic patient in general, and the allergic patient (only in so far as he is psychosomatic) in particular, both belong to the group of somato-neurotics, with all the characteristics of the neurotic patient, including his incapacity to find an adequate solution of his life's problems.

B. *Physio-psychological examination.*

In our Psychosomatic Centre we attach much value to the physio-psychological examination of allergic patients. This concerns the manifestations of the affects in the vegetative organic systems. The organism responds as a whole to each separate emotion: the affect expresses itself, in our opinion, in "affect-experience" and "affect-manifestation", both of which occur simultaneously. In the light of this totality-view of the affect expressing itself psychosomatically we do not use the term "somatic symptoms as results of the emotion"; but we regard the accompanying psycho-physiological phenomena in the vegetative system as expressions of the affect itself. As W. H. von Wyss (291) rightly remarked, the (observable [St.]) reactions on the part of the vegetative organs are far poorer than the psychomotorial manifestations (facies, gesture) and what is expressed in the complexity of the person's individual experiences.

Various aids are at one's disposal for the study of reactions in the vegetative system. We may refer the reader to a previous publication (241); we here content ourselves with mentioning the investigations, with the aid of the psychogalvanometer, as an expression of an affect experienced by allergic patients (chiefly asthmatics); they showed that the persons concerned were in many cases of the sensitive type of character; very receptive to emotional stimuli—in other words, very emotional,—but deficient in the ability to mentally digest these emotions. This gives rise, in these people, to a conglomeration of affects that may lead to complex-formation. We hope to be able to extend these investigations with the aid of the polygraph recently constructed under the direction of the late J. van Gemert and ourselves, which permits simultaneous registration of the pulse (sphygmography), blood pressure (tensography), electric heart-muscle action currents (electro-cardiography) and cerebral cortex currents (elec-

tro-encephalography), the blood supply in the extremities, the respiration (pneumography), and psychogalvanography.

Relatively little is known in the *literature* concerning the physio-psychological examination of allergic patients.

What we are here considering is the study of changes in the vegetative means of expression under the influence of emotive experiences in allergic patients. As early as the end of the last century, W. Wundt and his co-workers were occupied in studying the respiratory curve in order to analyse a patient's feelings ("Eindrucks- und Ausdruckspsychologie"). There exists a very extensive literature dealing with the respiratory manifestation of emotional experiences (L. Braun (28), p. 217 et seq., Fl. Dunbar (59), p. 385 and 628, H. G. Wolff, S. G. Wolf and Cl. C. Hare (287)). Some years ago Golla and Römer (quoted by F. Mohr (158) endeavoured to make a far-reaching characterological analysis of allergic patients on the ground of the respiratory curve.

For the present purpose we are interested in this problem only so far as allergic patients are concerned. But with regard to this only relatively little is known. Some interesting pneumographic investigations were made around 1950 by Ian Stevenson (236) who, *inter alia,* demonstrated in an asthmatic patient that merely to think about his (hated) wife, or to talk about some brother caused great changes. In co-operation with Harold G. Wolff (237) he studied the effect of emotions on the secretion of bronchial mucus. H. N. Willard, R. C. Swan and G. A. Wolf (274) proved that spirometric deviations occur under the influence of life stress. From recent times, we may here mention the investigations of Th. H. Holmes and co-workers (101), and of Stewart G. Wolf, Thomas H. Holmes, Th. Freuting, H. Goodell, and Harold G. Wolff (285), who made an experimental study of the influence of a life situation engendering conflict and anxiety, in patients with hay fever and asthma, on the ground of distention and secretion of the nasal mucosa.

Other interesting empirical investigations are those by Stewart G. Wolf (284), who examined the function of the nasal mucosa in patients with vasomotor rhinitis during emotive situations. He found an abrupt increase in nasal function during an interview concerning serious personal conflicts. Again, W. B. Faulkner (66) ascertained the presence of objective changes in the respiratory tract during a conversation (contraction when faced with disagreeable subjects). A simple method for making physio-psychological examinations with the aid of the respiration was recently described by B. Ackner (8).

Investigations into the physical manifestations of affective experiences have also been made with the aid of electro-encephalography. Denis Leigh and D. A. Pond (126) studied the electro-encephalogram of patients with bronchial asthma. Their publication also contains a survey of the literature; it shows very little general agreement.

The last-named two authors found no difference in their findings as between adult asthmatics and neurotic patients. (This statement conforms to our own conception of considering sufferers from asthma as somato-neurotic patients, and with J. T. Barendregt's (14) pronouncement in his eminent dissertation dealing with the Rorschach test in asthmatics, to the effect that these patients are to be classed as psychoneurotics). Leigh (125), however, in common with Morley, holds the view that "...the physician who considers asthma as primarily an allergic disorder may well be mistaken". As will be clear from what has preceded, we hold a different opinion in this respect; in common with E. B. Strauss (254) we believe that the allergic diathesis is usually present, but that, also in those cases, there may be a significant psychic determinant. Attention was also called to this influence recently by R. S. Bruce Pearson (34).

S. C. Dees and H. Lowenbach (47) report that they found deviations in the electro-encephalogram of allergic children, irrespective altogether of their type of behaviour. In common with Wood and Clark (see No. 292), they ascertained that the electro-encephalogram taken during epileptic equivalents is practically identical with that taken during allergic attacks of scratching in eczematous patients. (Extensive data hereon are given in H. A. Abramson's (5) standard work on asthma). It would, indeed, appear as if the EEG does reveal non-specific anomalies in asthmatics.

We may further mention the physio-psychological investigations with the aid of skin temperature measurements in patients suffering from Raynaud's syndrome, performed by B. Mittelmann and H. G. Wolff (156); the well-known investigations by Felix Deutsch (51) into the respiratory type (spirogram) in asthmatics, and his experiments with the photo-electric plethysmograph (reactions of the dermal capillaries (52); further, the findings of Kramar (investigation of the capillary response to emotion); the spectroscopic study of asthmatics by D. Leigh and J. W. L. Doust (124); Daniel H. Funkensteyn's (75) findings, also in asthmatics; those of M. E. Obermayer (the cutaneous reaction to histamine introduced by iontophoresis; those of J. M. van der Valk and J. Groen (264) (cutaneous electrical resistance in the course of an experimentally provoked emotional stress situation).

These and similar exact investigations—still few and far between, unfortunately (S. Lambergeon (121))—are of very great importance for our knowledge of the physio-psychological mechanisms.

C. *Experimental clinical psychological examination.*

We are here concerned with the experimental psychological examination of allergic patients in the clinic, with the aid of which it is endeavoured to find out, on the basis of various experiments, what significance ought to be attributed to the psychic determinant in causing the complaint to arise. The experimental set-up is generally decided upon on the ground of the patient's biographical data (anamnesis).

Such experiments have mainly been made in relation to the psychic determination of the asthmatic attack. We may here cite, *inter alia*, the experimental work done by E. Dekker, J. Groen and H. E. Pelser (1955) (48; 49; 86), F. Mohr (158), I. H. Schultz (1939), B. Stokvis (1940) (246), Strübing (255), and E. Wittkower (1935) (276). Similar experimental – partly anecdotal findings, however, are already quite old; as L. Braun (28, p. 218) informs us in Oswald Schwarz's (217) fine handbook of psychosomatic medicine (1925), P. Morawitz described many years ago how a woman, who experienced asthmatic attacks whenever she smelt a rose, also had an attack when merely looking at a deceptive paper imitation of a rose. Similar experiments in a patient with attacks of hay fever were described by Stachelin (quoted by R. Siebeck (223)), F. C. Metzger (139) in 1947, and G. Katsch (1955) (110).

Other examples are found in Flanders Dunbar's standard work "Emotions and Bodily Changes" (59, p. 385); in K. Hansen (98), in I. H. Schultz's (214) "Das autogene Training" (by now a classic); in H. Schwartz's book on allergy; in Erich Stern's (234) admirable work of reference, and in E. Wittkower's (277) extremely sound experimental study "Einfluss der Gemütsbewegungen auf den Körper".

Attempts have also been made to convert conflict situations experimentally into dermal symptoms by hypnosis (S. Borelli (25), A. I. Kartamysev (109), J. G. Kepecs and co-workers (115), Philip F. Durham Seitz (61)).

The clinical experimental psychological examination is, in our considered opinion, of special significance for a better understanding of the genesis and symptomatology of allergic diseases.

III. Therapeutic Viewpoints

In the third part of this discussion of the psychic components of allergy we shall first briefly state our own conceptions regarding the therapy of allergic diseases, followed by a survey of the existing literature on the subject, and concluding with a statement of our own relevant therapeutic experiences.

A. *Psychosomatically directed therapy.*

In our approach to the problem of human illness we have, in the above, based our reasoning on the conception of man as a psychophysical totality. A number of different facets of the "being human" are involved when illness attacks a person; therefore, every disease, including allergic ailments, is multi-conditioned (pluriform-con-

ditionality concept). In conformity with this, the therapy should also be directed towards different aspects of the complaint in question.

One would naturally wish, in the case of allergic patients, to apply a special, psychosomatically-directed therapy which would reach the different aspects of the state of illness simultaneously. But so long as such a comprehensive therapy is lacking, one is compelled to have recourse to a combination of therapeutic measures directed somatically and psychically at the same time. The emphasis here is either on both together, or on one of the two aspects, and depends upon which of the two should be given a predominantly determinant significance in the genesis and outbreak of the disease.

Experience has taught us that a certain number of patients may be helped by an exclusively somatic therapy. For these patients the psychotherapist is not even consulted. But there are those sufferers from allergic ailments who, despite extensive medication find no mitigation of their complaints. These patients may well be helped if the allergic treatment is supported by some form or other of psychotherapy; indeed, in such cases the medicinal therapy may then be reduced, or even completely stopped, after a short time.

Obviously the present chapter does not purport to go into the many different forms of drug therapy. These are dealt with in detail elsewhere in this volume. We shall here confine ourselves to discussing the several methods of psychotherapeutic treatment.

B. *Determination of indicants.*

1. *Pluridimensional diagnosis.*

In instituting a somatic therapy for a predominantly organic affection, the indication must obviously be sharply determined. Exactly the same applies to psychotherapy.

Patients visiting our Psychosomatic Centre are first thoroughly examined somatically. In recording the biographical anamnesis an insight is obtained into the circumstances of the patient's life. The psycho-social examination conveys an impression of the social conditions (environmental factors) in which he spends his days. Further, in order to find out the degree to which the deeper strata of the personality may also act as determinants, the patient is examined psychodiagnostically. This medico-psychological examination is made with the aid of the various test methods that have already been referred to. All these data are supplemented by the results of the physio-psychological examination.

After the results of these several examinations have been combined and integrated, it is endeavoured, by team discussion, to arrive

at a diagnosis that shall be pluridimensional; i.e. not merely based on the symptoms, but also on the structure, the degree of development and the type of behaviour of the personality. Only after this is a definite form of psychotherapy decided upon.

2. *Forms of psychotherapy.*

The aim of this exhaustive psychosomatic examination is to obtain an insight into the factors that have acted psycho-traumatically on the "being human" of the patient, and have had their share in determining his "being ill". The purpose of the psychotherapy is to eliminate these—unconsciously operating—factors in one way or another.

This can be done in one of three ways:

a. The psychotherapist can endeavour, jointly with the patient, to make the unconscious traumatically active experiences emerge into the consciousness, so as to give him an insight into the link between these feelings and his complaint. This insight may have a liberating effect. What is attempted, therefore, is to expose the predominantly conditioning determinants with the aid of an *uncovering psychotherapy.*

Different forms are in use to achieve this. Good results may be obtained with the orthodox psychoanalysis according to Sigmund Freud; this method, in our opinion, is the therapy of choice in the thus indicated cases. Various modifications—or rather, derivates of this method are known.—Further, the methods of Alfred Adler, of C. G. Jung, and of Alphonse Maeder, as well as those of the present Vienna school (Igor Caruso and Viktor E. Frankl), too, are each of considerable value.—In view of the long time taken by a psychoanalytical treatment, another method has been developed by Franz Alexander and Th. M. French: the so-called short-term psychotherapy. In this, the cathartic element predominates, the patient being given an insight, in the course of only a few sessions, into the interdependence between certain emotions and his complaints. To some extent the effect of this method is due to suggestive factors; here, the role played by the therapist is obviously a far more active one than in classic psychoanalysis.—We may further mention the "non-directive therapy" according to Carl R. Rogers, which aims to influence the patient not directly but indirectly.—Catharsis is brought about either by hypnosis (hypno-catharsis) or with the aid of a narcotic (narco-analysis); after this, what has been revealed by catharsis is further examined epicritically in the course of a therapeutic conversation, and so integrated with the patient's actual emotional life.

b. A special form of uncovering therapy is that of Arthur Kron-

feld: the *psychagogical or re-educative treatment*. There, one endeavours to induce the patient, who has become fixed in some real contemporaneous problem in his life, which he (unconsciously) expresses in an allergic ailment, to find a new way of life. In some cases the physician gives guiding lines (suggestive-psychagogical treatment).—Here follows an example.

The patient, Miss Anna Dl. (Registration No. 172), was a woman of 36, who had been suffering from bronchial asthma for about 9 years. She is a daughter of a family with four children, in which a relatively harmonious atmosphere prevails. Patient has always felt more attracted towards her father than towards her mother. She has never been really ill. At the age of nineteen she became acquainted with a young man and became engaged. The couple planned to get married. Two years later the war broke out; her fiancé was called up for military service; he disappeared in the fight against the Germans, and was reported missing. In the middle of the war the patient received a Red Cross message to the effect that her fiancé was alive. After the war they saw each other again. They had been faithful to each other, and decided to get married. A few months later the man suddenly fell ill, and died within a few days without regaining consciousness. The last few days the patient sat by his bedside; he was unable to speak. After his death, the patient got into a dream-like state; on awakening from this some days later she had her first attack of constriction. Her trauma had given her a feeling of "having had the road of her life abruptly cut off".

With the aid of re-educative therapy it was endeavoured to lead this woman on the road towards a new direction of her life. Asthma, in this patient, appeared to be an equivalent of pent-up grief of losing her beloved, and of the impossibility of ever having children; a cry of distress; a "weeping inwardly". She eventually chose the profession of child nursing in a home for children, which gave her a feeling of independence. The patient has now been without any attacks of constriction for several years. The existing eosinophilia proved to have disappeared after the treatment.

c. In some cases the uncovering of the morbific experience must, for various reasons, be abandoned; for example, when the patient's introspective possibilities are inadequate because of insufficient intelligence, or, maybe, when integrant possibilities are lacking. In such cases, elimination of the morbific experience may be achieved by forcing it down still more deeply; in other words, by furthering repression.

In such cases the morbific determinant is "covered up" with the aid of a *covering psychotherapy*. This comprises all those forms of treatment that make use of the influence of suggestion. Extensive use can here be made of different forms of hypnosis, and of various *relaxation therapies* (242; 246). Of the latter we mention the autogenic training method according to I. H. Schultz; the fractionated, step-by-step active hypnosis of E. Kretschmer, and our own Leyden active relaxation method (tonus regulation).

Next to individually applied forms of treatment there are the dif-

ferent forms of *group therapy* (group discussion, activity groups, didactic groups, and "staged" group-psychotherapy [psycho- and socio-drama]). A place apart is held by the work done by the (usually female) social worker; the *case-work*, to which we assign great importance, especially in allergic affections, as supplementing and supporting the physician's therapeutic measures. In case-work a number of social measures are combined that aim at exercising a beneficial influence on the patient's social life (marriage, family, employment). In this, the case-worker has a leading function under the supervision of the psychotherapist.

3. *Criteria.*

The form of psychotherapy to be decided upon mainly depends upon the following criteria:

a. *The nature of the patient's personality structure.* All according to the patient's age, intelligence, regulative and integrant possibilities, character, etc., a choice is made between an uncovering, a covering, and a psychagogic treatment.

b. *The nature of the doctor's personality structure.* A therapist with compulsive character traits will be most attracted towards a method that takes its course along strict rules, as with certain relaxation therapies. Other physicians, on the other hand, may feel a greater affinity for a revelational method. It would be wrong to lay down that a given psychotherapeutic method is preferable to another; after all, the efficiency of any method depends on who applies it.

c. *The nature of the method to be applied.* Various circumstances (lack of time, work on hand, place of residence) may compel the choice of a particular method.

d. *The nature of the disease.* In contrast to the determination of indicants for treatment with drugs, the exact nature of the patient's ailment is, in psychotherapy, the last consideration; the other factors (under a, b and c above) are of primary importance.

C. *Psychotherapy in allergic diseases. Survey of the literature and case-reports.*

Following the above introduction on the determination of indicants and the significance of psychosomatic therapy in general, we will now pass in review the various conceptions relating to allergic diseases that are put forward in the literature. Since the majority of authors make no clear distinction between the different forms of therapy we shall only refer, in what follows, to the uncovering and the covering therapy. For the sake of surveyability we shall subdivide

the material according to those affections which are commonly regarded as allergic.

A number of authors treat of psychotherapy in *allergic diseases in general.*

D. W. Baruch and H. Miller (17) describe five patients who underwent both medicinal and individual therapy. Three of them were, in addition, treated by group-psychotherapy. The treatment had a favourable effect both on the allergic trouble and on the patients' personality problems. The same authors (145) were also successful with group-psychotherapy in allergic patients. E. A. Sirmay (227) points to the importance of analytical methods in allergic patients. W. Kaufman (111) discusses the psychic aspects of the treatment of patients with nutritional allergy.

With respect to psychotherapeutic experiences to aid the treatment of *vasomotor rhinitis* there exist only few publications compared to the number dealing with the other allergic affections. Brandenburg considers psychotherapy to be of value in cases of rhinitis.

A study of the literature dealing with *bronchial asthma* shows that the number of patients that have been treated psychotherapeutically for this disease is very great indeed. We already reviewed this subject with A. J. Welman in a previous publication (250). A number of authors, among whom we may mention J. Hirschmann (100), F. Reichmann (185), H. L. Rogers (189), N. Ross and Ch. P. Wilson (192), R. Siebeck (223, p. 142), and Th. F. Freuting and H. S. Ripley (74) rightly advise combining medicinal and psycho-therapy. In that respect some authors (H. A. Abramson (3; 4), E. A. Brown (31), Erik Fagerberg (65), J. Groen (85) and E. Weiss (270)) attach much value to combining A.C.T.H. with psychic treatment. This also tallies with our own experiences. Next to specific desensitization, we regard psychotherapy as an important adjuvant. In her publication of 1953, Sirmay (227), clearly elucidated the share that psychotherapy can take in the treatment of allergic patients in general.

Most authors, however, merely refer to psychotherapy, without stating either its form by name, or the somatotherapy, if any, that was combined with it.

Thus, E. Moos (162; 163) reports on a number of patients with bronchial asthma whom he treated psychotherapeutically, and in whom the eosinophil blood picture became normal. We have ourselves had similar experiences. J. Loewenstein (132) saw, out of a group of 48 patients, a definite improvement through psychotherapy in 60–70 per cent. He makes special reference to the psychoanalytic method.—The importance of psychotherapeutic treatment of asthmatics is also prominent in the experiences related by Fock (68), F. Gardey (77), Ph. M. Gottlieb (82), A. Kronfeld (120), H. Pollnow and co-workers (176), C. H. Rogerson (190) (in children), and L. Unger and B. F. Gordon (263).—E. J. Billings (20) discusses the treatment of 17 cases of what he calls "psychogenic asthma", in 6 of which psychotherapy proved successful. A. B. Scheibel (208) treated a 10-year-old boy by psychotherapy for 13 weeks, which resulted

in the complete remission of asthma, as well as an improvement of the patient's relationship with his milieu. J. Naber (168) describes his experiences with 23 patients. According to this author psychotherapy is the sole correct treatment of asthma. This pronouncement appears to us one-sided and exaggerated. Naber thinks it possible to cause an existing allergy or an allergic constitution to disappear by psychotherapeutic influence alone. With all our esteem for psychotherapy we would not dare to go as far as that. J. Peters (173) and later, H. Pozner (178) describe experiences similar to Naber's.

The significance of psychotherapy as such in the case of asthmatics has been elucidated by I. H. Schultz as long ago as 1929 (211), and demonstrated by him (213) in 1939. By means of tests in which the subjects were breathing according to a faulty respiratory technique, he came to the conclusion that healthy persons can have attacks of asthma in a purely psychogenic way. But even here, he rightly regards an existing disposition—i.e. the presence of allergic factors—as co-responsible. Asthma that is of an organic origin *can* be perpetuated by psychic factors, so that any exclusively somatic treatment must then fail in the first instance. It is precisely in those cases that it is indicated to forestall, and afterwards support, the medicinal treatment by psychotherapy.

Our own experiences more or less correspond to this; Schultz's remark that there must always be a certain asthmatic disposition on the patient's part is in conformity with our own opinion that the psychic factor can only be a co-responsable determinant. We incline more and more towards directing our attention also to the organic component, which unfortunately cannot always be exposed, and sometimes does not reveal itself until after a year or two (*cave:* pulmonary or bronchial carcinoma).

Many authors tend to decide upon a psychotherapeutic treatment which is more or less *analytically* oriented (H. A. Abramson (2), K. Hansen (98), E. L. Gaudet (79), E. A. Sirmay (227)). Good results can, in our own experience, be achieved with the so-called "short-term therapy" of *Alexander* and *French* (73) in patients with bronchial asthma. Then there are those investigators who attach great significance to a form of psychotherapy which gives prominence to catharsis (M. L. Miller (149) and M. C. Skands (228)). H. S. Ripley and S. Wolf (188) obtained good results with narcoanalysis.

As against those authors who prefer to treat bronchial asthma patients according to analytical insight there are a number of investigators who achieved their best results with a *covering form of psychotherapy.* Thus, I. H. Schultz and G. Schwöbel (218) apply the former's meaningful, admirably elaborated method called "autogenic training". H. Trautwein (262) treated 40 patients by this method, and observed signal results in 95 per cent. In 50 per cent of the patients the asthma completely disappeared. Our own experiences with this method are also quite good. A. Jores (106) applies a combined therapy of relaxation, breathing exercises and massage. We have further (245; 246) observed beneficial results from hypnosis. Various investigators (Brügelmann, N. Costa (45), Karl Egen (63), K. Hansen (97), Laudenheimer, I. H. Schultz), as well as ourselves, point to the mitigation and, in some cases, the total dis-

appearance, of asthmatic attacks through hypno-therapy, despite the presence of organic deviations. J. M. B. Morwood (164) describes a relaxation technique ("semi-hypnosis") with 65 asthmatics, applied with the aid of a gramophone!

Some of our own patients with organic deviations in the form of emphysema became more capable and efficient after a course of psychotherapy than they had been prior to the treatment. This favourable change in the patients' condition was due to the fact that, having previously been unable to mentally digest adequately their awareness of being ill, the treatment enabled them to adopt a fresh attitude toward life, or at any rate, to resign themselves to their condition.

J. Parow (171), who, in contrast to our conception as here described, refers to asthma as being a psychoneurosis, nevertheless points quite rightly to the importance of the right respiratory technique for asthmatic patients. In those cases where psychoanalysis was either impossible or unsuccessful he obtained good results with a covering psychotherapy. We prefer, wherever possible, to apply an uncovering form of treatment; but we believe it is wrong to apply—as Parow does—only the covering therapy, *per exclusionem*; after all, indications must also be heeded here.

J. A. Haiman (92) very rightly points out, next to the importance of psychotherapy, the great value of *social measures* and *case-work* in supplementing and supporting the treatment. To these we also attach very considerable value. D. Hallowitz (94) is of the same opinion: 50 per cent of the children treated by him completely lost their complaints after having been separated from their relations for some time, while another 35 per cent showed a distinct improvement through the same cause. But we ourselves would rather not resort to a radical measure of this kind, which causes the family life to fall apart; here, psychotherapy (to include the parents) is indicated first and foremost.

A number of investigators, among whom we mention H. Miller and D. W. Baruch (18; 147), discuss the favourable results achieved with patients treated by *group therapy*. We ourselves (249) feel inclined towards these methods (group discussion and psycho-drama) as supporting the individual treatment (B. Stokvis and A. J. Welman (248; 249)).

Angioneurotic edema has not been discussed separately by most authors, but usually together with bronchial asthma. In treating it, psychotherapy may be of importance. Sometimes angioneurotic edema precedes another somatic affection; the patient's mind becomes fixed on it and reacts correspondingly when faced with certain situations that are coupled with feelings of distress.

Allergic diseases of the skin, in which psychic factors play a part, were already referred to in the first section of the present chapter. The authors cited there naturally made use of psychotherapeutic measures; the value of these is also emphasized by M. E. Obermayer (170).

Urticaria, like angioneurotic edema, is usually dealt with in combination with other ailments, in particular with other skin diseases. We were able to determine distinctly on several occasions that psychic factors are here co-responsible. Solicitude and perseverance with the patient are imperative in these cases (Obermayer (170)). The following example from our own experience may serve to illustrate this.

Miss Betty C., a 16 year old girl, comes to the out patients' department on account of urticaria, which has been breaking out at intervals during the past few weeks. A thorough allergic examination fails to reveal any distinct hypersensitivity to any particular substance. Eosinophilia is demonstrable in the blood. As the eruptions appear especially on week-ends, some psychic determinant seems possible. Closer examination shows that the patient comes from a harmonious family with 5 children. The girl has never had any allergic complaints; neither do they occur, as far as is known, in the family. About her school years and youth; no particulars worth noting. The menarche commenced at 14; this meant no great shock for the child, although she had been insufficiently prepared for it.

She has a couple of close girl friends with whom she goes cycling or camping on week-ends. Some time previously she had met a young man, three years older than herself, who was interested in her. On the evening when she had her first kiss, nettle-rash appeared on her arms and chest, disappearing again after about 24 hours. One week later, when she again met the young man, the itching nettle-rash came on already before the meeting. After the week-ends (they met only on Saturdays and Sundays) the urticaria spots disappeared almost entirely apart from a few irritating vesicles.

From talking with the patient it transpired that she really thinks herself too young to have a male friend, and much prefers going out with her girl friends than "with one of those boys". Talking the matter over with the girl made her consciously aware of what she really meant by those words; and she left. During a second talk she informs us that she has broken off the association, and that no fresh eruptions have appeared since. One week later she had no more complaints whatever. A control-check six months later showed that she had been without complaints ever since.

It was unfortunately impossible to ascertain the precise significance which the urticarious eruptions had for this girl; maybe the nettle-rash was to restrain her from having further intimate relations. However that may be, the urticaria, in this case, was definitely predominantly psychically determined.

According to C. S. Wright (289) special attention is due to feelings of anxiety in patients with urticaria. In our opinion that does not apply in very many cases; in fact, we are convinced that this author is wrong in regarding psychiatric treatment as invariably indicated in urticaria. In serious cases he saw results from electro-shock treatment; we consider this method, which is so very drastic, to be absolutely non-indicated. In milder cases he recommends psychoanalysis. This method has been discussed by J. Neumann and A. Welcker (169) for treating *eczema*. These authors found that the symptoms disappeared following dream-analysis; but the patients' neurotic problems of life were not entirely solved thereby. H. Volkmann and K. W. Eissing (267) incline more towards suggestive therapy; in patients with urticaria or eczema they successfully apply hypnosis. According to these investigators these two ailments must be regarded as "vasoneuroses". Again, J. Bonjour (23) advises suggestive treatment for eczema; either alone or in support of some other therapy. Similar experiences are described by A. I. Kartamysev (109), who saw lessening of the irritation in eczema and urticaria after 2–5 sessions. By an experiment with a patient with urticaria he endeavoured to demonstrate the psychic significance of the affection. A woman patient who was sensitive to quinine developed an eruption of nettle-rash on being given powdered sugar in a suggestive manner. Conversely, no urticaria appeared when, in a hypno-suggestive condition, she was given quinine that was announced as being sugar. We too sometimes obtained good results with hypnotherapy.

The psychotherapeutic significance in *migraine* is demonstrated with an illustrative case by L. S. Lewis and C. J. Rowe (130). It concerns a woman patient with persistent migraine, in whom all somatic measures without exception had failed (D.H.E., histamine, cortisone, ligation of the arteria meningea media). She was completely addicted to barbiturates. Superficial psychotherapy succeeded in freeing this woman from her complaints, and in inducing her to shoulder some degree of responsibility.—We have ourselves seen many examples of favourable results of psychotherapy in patients with headaches of an allergic nature.

As the above survey of the literature shows, numerous authors have stressed the significance of psychotherapy in allergic diseases. Here follows a brief account of our own experiences.

D. *Our own experiences: Catamnestic examinations following psychotherapy of allergic patients.*

In communicating our own cognate experiences, we shall make use of the catamnestic investigations which we made with A. J. Welman, in patients with allergic diseases treated in our Psychosomatic Centre[1].

Various catamnestic investigations relating to the results of psychotherapy are known from the literature. Not all of these, however, can stand the test of criticism. In a few other publications we have reviewed the findings of other authors, and stated the requirements which, in our opinion, such catamnestic examinations ought to satisfy (247; 252). For details concerning the results of psychosomatic therapy in psychosomatic patients treated by us we refer the reader to the relevant paper on the subject (252).

We are here concerned only with the results of psychosomatic therapy in allergic patients treated by us in our Psychosomatic Centre. For completeness' sake we once again point out that by "psychosomatic therapy" we mean: somatic therapy combined with such psychic treatment as is indicated.

Our (provisional) investigation covers 51 allergic patients, all of whom underwent a regular treatment; in other words, a somatic therapy combined with a form of psychic treatment. If necessary, the therapy was supplemented, both during the period of treatment and afterwards, by "case-work" by a woman social worker.

To enable ourselves to study the findings as objectively as possible, we did not confine ourselves to merely sending a questionnaire to

[1] The author here wishes to express his gratitude to Mr. T. Swelheim, M.B., for his valued assistance in carrying out this investigation.

the 51 patients alone, but included also their family doctors in the investigation. For, on the one hand the patients tend to give a flattering picture of their condition in order to please the therapist (non-liquidated positive transfer situation); but on the other hand the interviewees sometimes greatly exaggerate the seriousness of their condition, i.e. when the transference of negative infantile feelings is not properly liquidated.

As regards the subjective findings, we received 40 replies to the 51 letters sent to the patients; the objective findings were taken from 33 replies we received to the 51 letters sent to the family doctors. Our control periods vary between six months and over two years. It is, of course, intended eventually to repeat and extend the investigation.

Table 1 shows the nature of the diagnosis; this was chiefly concerned with asthmatic patients. All had been thoroughly treated somatically before being passed on to the Psychosomatic Centre. This somatic treatment extended over periods varying from a few months to more than twenty years. In many cases somatic measures could be stopped soon after psychotherapy was instituted, only the latter being continued; in other cases psychotherapy did not make any difference to the patient's condition.

The somatically applied therapy was carried out in accordance with prevailing principles (see elsewhere in this volume); the forms of psychotherapy applied by us are described under C (III) above. As already stated, not only individual psychotherapy was applied, but also combinations of it with group-therapy (group discussion, psycho- and socio-drama, socio-therapy [Carp (37; 38)]). We hope at some future time to publish a catamnestic investigation in allergic patients who were treated exclusively somatically.

Now for the *results*.

In addition to the diagnoses, Table 1 also shows the results obtained with the patients who replied to the list of questions sent them. Under "Number", column 1 shows the number of replies per diagnosis received from the P(atient) and the D(octor) respectively. In the following five columns, under the criterion of appreciation, the number of respective diagnoses is stated on which a reply was received by us.

As will be seen, the asthma group predominates to such an extent that, with respect to the results, any diagnostical differentiation would have been pointless. The fact that the material examined is so heterogeneously distributed is naturally due to the extent to which patients are passed on to our Centre.

The results are summarized in Table 2.

(a) Table 2a gives a comparison between the results that were

obtained respectively with covering and uncovering therapy. (The psychotherapy was applied in conjunction with somatotherapy). In this table the comparison has been determined on the basis of the (subjective) judgment of the patient him- or herself.

TABLE 1
Results of catamnestic investigation in allergic patients.

Diagnoses	Number		+++		++		+		±		−		0	
	P.	D.	P.	D.	P.	D.	P.	D.	P.	D.	P.	D.	P.	D.
Asthma	35	30	9	5	8	6	6	10	7	7	4	2	1	–
Headache	1	–	–	–	–	–	1	–	–	–	–	–	–	–
Eczema	2	1	–	–	1	1	–	–	1	–	–	–	–	–
Migraine	2	2	–	–	1	–	–	1	–	–	1	1	–	–
	40	33												

Meaning of symbols	Patients	Doctor
+++	I have no complaints and am working as usual	Very satisfactory
++	I have occasional complaints, but am carrying on as usual	Satisfactory
+	I am troubled pretty often, but manage to do some work	Barely good enough
±	I keep getting the complaints and have to stop working every now and then	Doubtful
—	I feel very ill and can't do any work at all	Not good enough
0	No comment	

It will be seen that, just as in our catamnestic investigation of psychosomatic patients generally, who were treated both somatically and by psychotherapy, there is evidently *no statiscally significant noteworthy difference between the results respectively obtained with covering and uncovering psychotherapy.* Now this finding seems surprising at first sight. But what really matters in actual practice, in the case of these somato-neurotic patients (Carp and Stokvis (39)), is that the symptoms must be made to disappear. That, at any rate, is the criterion one sets in judging the results of the therapy. The extent to which the patient's neurotic attitude toward life which

one tries to influence especially when applying a prolonged, uncovering therapy changes or improves, utterly escapes the therapist's judgment during the examination. One should not, therefore, conclude from our own findings that a time-devouring, but insight-giving form of treatment might just as well be replaced by a brief and summary covering one!

TABLE 2

Summary of results of psychosomatic therapy in allergic patients.

a. *Evaluation by the patient (40).*

Evaluation	Covering psychotherapy and Somatotherapy (14)		Uncovering therapy and Somatotherapy (26)	
	Number	Per cent (14)	Number	Per cent (26)
+++	2	14.3	7	26.9
++	4	28.6	6	23.1
+	2	14.3	5	19.2
±	3	21.4	5	19.2
—	3	21.4	2	7.7
0	–	–	1	3.9

b. *Evaluation by patient and doctor.*

Evaluation	by patient (40)		by doctor (33)	
	Number	Per cent (40)	Number	Per cent (33)
+++	9	22.5	5	15.2
++	10	25.–	7	21.2
+	7	17.5	11	33.3
±	8	20.–	7	21.2
—	5	12.5	3	9.1
0	1	2.5	–	–
no reply	11	–	18	–

c. *Duration of control-check as criterion (40).*

Evaluation	Control-check during less than 1 year (23)		Control-check during more than 1 year (17)	
	Number	Per cent (23)	Number	Per cent (17)
+++	6	26.1	3	17.7
++	6	26.1	4	23.5
+	3	13.–	4	23.5
±	3	13.–	5	29.4
—	4	17.4	1	5.9
0	1	4.4	–	–

As the tables show, the (+++) and (++) modes of reaction total about 40–50 per cent. This is encouraging, if not yet good enough for rejoicing. We would stress the point that we were unfortunately unable to extend our investigation beyond the total of 40 replies received from patients. But *impressions*, rather than statistics, were the object we had in view.

b. The middle table (2b) shows a comparison between the evaluation by the patient and by the doctor. One should not conclude from this table that the patients cherished a more favourable opinion about their condition than the physicians: we are here dealing with two groups of different patients. At most one might say that, out of a group of 40 allergic patients treated with psycho- and somatotherapy, *improvement in about 45 per cent* was reported by the patients themselves (Σ [+++] and [++] = 22.5 + 25), while in another group of 33 similar patients, the family doctors found *improvement in about 35 per cent,* (Σ [+++] and [++] = 15.2 + 21.2).

c. From the bottom table (2c) it appears that *the effect of the treatment does not weaken in the long run* in the patients examined by us. Of those that were control-checked for less than twelve months, 12/23 = 52.2 per cent reacted favourably; out of those checked for longer, 7.17 = 41.2 per cent. These differences are not significant; naturally, the investigations need to be supplemented. But here again, we have to do with two groups of different patients, and the numbers are unfortunately small. Here also, what matters is the *general impression.*

One might wonder, after all, whether the improvements recorded are, in fact, to be credited to the treatment; since the tables omit to mention how the patients would have classified themselves before the treatment. But to get the patient to pick a place for himself in a particular category of morbidity did not always prove practically possible. In order, therefore, to ascertain whether and to what extent the patients did, in fact, attribute improvement in their condition to the treatment they had received, they were sent, together with the criteria already mentioned, also the following three statements to select from:

I hereby inform you that your treatment has
- made me no better
- made me better
- made me worse

Out of the 51 allergic patients who received this form, 40—as already stated—filled it in. Their answers may be divided as follows:

TABLE 3

Results of the psychotherapy, as judged by the allergic patient.

Evaluation	Number	Per cent (40)	Per cent (51)
Made me better	25	62.5	49.
Made no difference	9	22.5	17.7
Made me worse	2	5	3.9
Don't know	4	10	7.8
No reply	11	.....	21.6

As this table shows, the percentage of allergic patients who felt they have been helped was 62.5. That this percentage is higher than that of the allergic patients who found in themselves a distinct improvement (45 per cent) may be explained by the fact that, according to our experience, many a patient in whom the allergic symptom showed hardly any improvement (or none at all) nevertheless felt that he had been helped, either thanks to a positive transference situation created during the sessions, or, maybe, thanks to his having gained more insight and better control of his affective condition, and thereby learned how to deal more distantly with his life's problems.

Our investigation has given us the impression that the combined application of somato- and psychotherapy in allergic patients is justified and promising. Our results with psychotherapy are not unsatisfying, but they enjoin modesty. Once more we emphasize that not all cases of bronchial asthma, or of allergic diseases in general, should be taken to be, *qua tales,* psychosomatic diseases: in some cases the psychic determinants in these affections are practically negligible, at any rate from a psychotherapeutic angle.

After all in actual practice the allergic patient does not go to a psychiatrist but to an allergy specialist. In many cases the somatologist's approach to the patient in a human relationship based on mutual confidence will be sufficient to back up his medicinal hygienic therapy (G. A. Lindenboom (131)). But when the problems of life confront the patient with apparently unsolvable difficulties, the assistance of the psychotherapist, probably together with that of the case-worker, will prove indispensable.

Summary.

The psychosomatic approach to allergic diseases more than merits the attention of the allergologist. It forms a link between the old, exclusively somatic conception on the one side, and the psychogenic view tending to exaggeration, which we consider obsolete; and might

enable the realization of the long cherished wish to come to a co-ordination of the study of organ allergy and neuropsychiatric allergy (7).

Without lapsing into exaggeration ourselves, and overestimating the significance of psychic determinants, we feel justified in concluding that, in many cases, emotional influences from the past and/or from the present play a part either in the conditioning or in the outward manifestation of the allergic disease, or in both. Understanding of the personality of the sufferer and of his milieu, and of his physio-psychological behaviour may be a valuable auxiliary in the allergologic examination, for the purpose of giving the patient—*only if and when indicated*—psychotherapeutic treatment in addition to somatological treatment. For, not every case of allergy can, as such, be considered a psychosomatic affection: in some cases the significance of the psychic component is practically nil. But when, in certain cases, psychotherapy is indeed indicated, our experience has shown that the patient very often benefits from it, although the results, *qua tales,* are still conducive to modesty.

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ALLERGIC DISEASES OF THE SKIN

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Diseases of allergic origin, so diverse in their clinical aspects, have nevertheless some common characteristics which are also found in cutaneous allergy. Here too, they proceed from the individual, not from the nature or dose of the allergen; they follow the same irregular capricious course, heal without leaving sequelae and always show a tendency to recur as long as the offending cause has not been eliminated.

A distinction must be made between diseases arising from a humoral and those due to a tissue allergy. The former are best known to allergologists because they are often associated with other manifestations of the same type such as asthma, rhinitis, and migraine. In addition, whatever their form, urticaria, edema, purpura, eczema, they can easily be differentiated from the tissue allergies by certain characteristic features in their etiology and pathogenesis:

presence of circulating antibodies,
positive Prausnitz-Küstner reaction,
the allergen is generally an inhaled or ingested protein (food, pollen, drug),
the allergic reaction takes place in the superficial derm,
the practicable tests are the scratch or intracutaneous tests,
the skin reaction is of the immediate, urticarial type,
a hereditary factor and blood eosinophilia are almost always present.

In tissue allergy, on the contrary, where the clinical picture is more uniform as it is always an eczema:

circulating antibodies have never been found,
the Prausnitz-Küstner reaction is negative,
the allergen is external; the reaction is produced by contact and takes place in the epidermis,
the practicable tests are the patch tests,

the skin reaction is delayed and eczematous,
no hereditary factor or blood eosinophilia are present.

Although at present little is known about their pathogeny, recovery from tissue allergies is rapid and certain, as there are no other diseases of hypersensitivity where the allergen can more easily be detected. However, the rapid development of modern industry, the common use of very complex cosmetics, even the progress in pharmacology, contribute to increase their frequency.

Skin Allergies of Humoral Origin

Among the cutaneous syndromes arising from a humoral allergy, a distinction must be made between:

1) The urticarial dermatoses:

urticaria,
angioneurotic edema,
prurigo infantilis,
polymorphous erythema,
allergic purpura,
fixed drug eruptions.

2) The eczematous dermatoses:

diathetic eczema or atopic dermatitis.

As some of these are dealt with in other chapters, they will only be briefly mentioned here.

A. *Urticarial Dermatoses.*

I. *Urticaria and Angioneurotic Edema (Quincke's Edema).*

These dermatoses have the same etiology and the same pathogenesis. They can coexist or alternate in the same patient. Their allergic origin, already conjectured by Wolf Eisner and later by Hirsberg and von Pirquet, was accepted earlier and more readily than was the case with eczema. This is perhaps due to the fact that these patients frequently have a personal and familial history of rhinitis, asthma or gastro-intestinal allergy.

In *urticaria,* the eruption consists of urticarial elements, essentially pruriginous, appearing suddenly and disappearing, without leaving any trace, within a few minutes or hours. The outbreaks, however, often recur at short intervals, sometimes returning daily for several months.

Angioneurotic edema (Quincke's edema), a form of giant urti-

caria, is a white, elastic and non-pruriginous edema; its appearance is likewise sudden and transient. It is localized most frequently at the face (lips, eyelids), sometimes in the larynx—a very serious localization—or at the genitals. The acute, transitory forms are mostly encountered in children, whereas the chronic, continually recurrent forms mainly affect adults, particularly women.

Numerous and varying etiological factors may be implicated in these reactions. Formerly, efforts were made to prove an alimentary origin (milk, chocolate, shellfish), but with the increase of pharmaceutical products, investigations were directed toward a medicinal etiology. One must always keep in mind the ingestion of aspirin, pyramidon, quinine, salicylate, derivatives of barbituric acid, sulphonamides, and injections of penicillin, bismuth, mercury, arsenic, endocrine extracts etc.

Certain inhalations may also, although exceptionally, be the cause: dust, feathers, wool, cotton, silk—Sulzberger, in 1954, reported that silk can be absorbed this way in sufficient quantities to produce urticaria—also inhalations of flowers, cereals, tobacco, pollens have been incriminated.

Even physical agents such as heat, cold, sun's rays, rubbing, pressure (dermographism), may play a determining role. A short exposure to cold air, a cold bath, a jet of ethylchloride, or, on the other hand, exposure to the sun, contact with hot water, or simply the warmth of a bed, may instantaneously provoke the reactions.

The role of bacterial agents is much more difficult to estimate. Although improvement is frequently observed following the elimination of foci of infection in the tonsils, teeth etc., microbial allergy has never been proved.

On the other hand, there is no doubt that endocrine or neurogenic factors may play a role in certain cases of urticaria, particularly in the chronic forms. Indeed, urticarial dermatoses frequently make their appearance during pregnancy, menstrual periods, menopause, or in cases of dysfunction of the thyroid, ovaria or hypophysis. It frequently happens that sudden fear or intense emotion produces or aggravates an eruption.

How can we discover, among all these numerous agents, the one responsible? Epidermal tests are known to be of no value in these cases, and neither are the scratch or intradermal tests very helpful, as too often urticarial reactions are obtained which have no clinical value, since elimination of these substances does not give rise to improvement or a new exposure to an exacerbation. Recurrence of symptoms after re-exposure of the organism to the antigen or their disappearance after successive elimination of the suspected factors, are the only tests which may enlighten the etiological investigation.

Finally, a positive Prausnitz-Küstner reaction provides conclusive evidence for the etiological diagnosis.

II. *Prurigo Strophulus or Brocq's Prurigo Simplex.*

Whereas angioneurotic edema and chronic urticaria generally only affect adults, prurigo strophulus, an eruptive recurrent dermatosis, often called urticaria papulosa, is a disease of infancy.

The illness generally appears in spring or summer, and begins as in urticaria with small urticarial spots, whose centre reveals a salient, acuminate papule. While the urticarial spot rapidly diminishes, the papule becomes more distinct and covered with a vesicle, usually excoriated by scratching. These elements are very pruriginous; they are scattered all over the body and are often mixed with urticarial wheals and bullous lesions. The evolution of this entity is paroxysmal; the duration of a paroxysm generally does not exceed a fortnight, however, recurrences may continue over a long period of time.

The etiology is difficult to specify. One most always finds a familial predisposition—antecedents of asthma, eczema or urticaria —and provoking factors: certain foods such as eggs, chocolate, fish, horsemeat and pork, or simply overeating or teething.

Treatment generally is disappointing; it consists primarily in finding and possibly in eliminating the provoking factor. It is necessary of course to watch the diet of the child which should be well adjusted and not too restricted. Antihistamines are not more effective in these cases than in urticaria and one often has to resort to nonspecific therapy.

III. *Polymorphous Erythema.*

Although opinions differ as to which dermatosis should be named "polymorphous erythema", it is certain that beside the infectious seasonal disease, there exists another form, closely related to and frequently accompanied by urticaria, which is often caused by a food or drug intolerance (arsenic, bismuth, sulphonamides, vaccines).

The eruption consists of erythemato-papillary spots, whitish and irregular, often flattened in the centre and in some severe cases bullous or hemorrhagic. The eruptions are more or less profuse and develop in outbursts of a duration never exceeding one or two weeks; they are mainly located on the extremities (hands and forearms), face and neck.

The clinical aspect as well as certain histological signs plead in favor of a sensitization process. However, a certain threshold of the antigen has to be reached before the lesions are produced. In a pa-

tient, for instance, after recovery from a polymorphous erythema due to the ingestion of sulphonamides, we could only reproduce the lesions by giving him an identical dose, namely six tablets.

Treatment is generally unnecessary; it is only of some interest in the chronic and recurrent forms, in which it is the same as in urticaria.

IV. *Allergic Purpura.*

A large number of cases of purpura, apparently primary or secondary to an infectious, medicinal (barbiturates, Sedormid, butazolidine), alimentary or so-called toxic origin, involve a phenomenon of intolerance.

The small purpuric spots are frequently associated with angioneurotic edema, urticarial wheals or a polymorphous erythema. They can also alternate with other allergic manifestations such as migraine or asthma. The pathogenic process and consequently the treatment are the same as in urticaria.

V. *Allergic Drug Eruptions.*

Counterpart of the progress in chemotherapy, eruptions due to drugs constitute today some of the most common dermatologic diseases. Their clinical aspects are manifold, and, as always, it is not the drug which determines the symptoms, but the sensitized individual. Sensitivity to barbiturates, salicylates, bromides, antipyrine, belladonna, penicillin, arsenic compounds, may provoke an urticarial dermatitis, polymorphous erythema or purpura. Some of these drugs (penicillin, arsenic compounds) and others such as quinine, mercurial compounds, sulphonamides, anesthetics can also provoke an eczema. In this case, however, the patient must have had a previous contact with the drug which was followed by no abnormal symptoms. Finally, some individuals may present after the ingestion of a drug, fixed eruptions which are evocative of an allergy to phenolphthalein, antipyrine, pyramidon, phenacetin or barbiturates, sometimes quinine or salicylates. These eruptions are oval, distinctly marked, erythematous, more or less edematous or even bullous, always pruriginous. Their medicinal origin being often unrecognized, they may persist for a long period of time without showing any tendency to extend or disappear. They also may vanish to recur again after a variable length of time in the same area with identical limits and characteristics, the rhythm of the recurrences being determined by the discontinuous administration of the drug. Following the elimination of the latter, the lesions disappear leaving a brown or even black pigmentation which may persist for a long period of time.

A characteristic feature of these pigmented fixed erythemas is their topographic and etiologic specificity. Thus, an individual sensitized to two different drugs will present two distinct reaction zones, both responding in a specific manner to the action of one drug or the other. Sulzberger reported the observation of a patient who presented on the hand a zone sensitive to the ingestion of barbiturates, and another on the thigh where the reaction only occurred after taking phenolphthalein. This abnormal sensitivity of a cutaneous area is frequently congenital and permanent; we have seen a dental surgeon who showed a fixed pigmented reaction following the ingestion of an Allonal tablet, and who presented four years later, upon taking the same drug, patches on the skin and mucous membranes having exactly the same topography as at the time of the first attack.

Whatever the nature of the drug eruption, it always differs completely from the toxic reaction caused by the same substance. A toxic dose of arsenic will determine an erythemato-squamous dermatitis, whereas an allergic process will result in an urticarial reaction. Moreover, in intolerance to drugs, a minute dose is generally sufficient to produce a severe reaction.

Although certain drugs are known to possess a great sensitizing property, each can act as an antigen. In these circumstances how can the causal agent be determined?

By patch tests, if the eruption is eczematous. It is, for instance, not uncommon to obtain a positive reaction with sulphonamides and anesthetics. In the case of antibiotics (penicillin, streptomycin) the simple patch test is often insufficient and one must resort to the scratch method.

By intradermal or scratch tests, if the dermatosis is of the urticarial type, but the tests are rarely positive. In addition, one has to be careful, as even in the absence of a local response, a simple intradermal test may provoke a dramatic general reaction.

Finally, in the case of fixed eruptions, it is by the history and not by means of skin reactions that the offending antigen can be detected. Eventually a reingestion of the drug will prove the diagnosis to a sceptical patient. Recovery is rapid, the dermatitis disappears as soon as the antigen has been eliminated, whereas it is not infrequent to see some urticarias due to drugs (aspirin, penicillin) persist for several weeks.

B. *Diathetic Eczema or Atopic Dermatitis.*

Humoral allergy can also manifest itself in the form of a diathetic eczema or Besnier's disease, called by American authors since 1933 "atopic dermatitis". Coca and Sulzberger define the illness in the

following terms, "Atopic dermatitis includes those inflammatory dermatoses which, in the majority of cases, are intimately and characteristically associated with other stigmates in the affected person and/or in his family".

This affection, which includes not only infantile eczematous dermatitis and papular dermatitis in childhood, but particularly the lichenoid callous dermatitis in adults, is most frequently associated and alternates with other diathetic manifestations.

Clinical manifestations.

Atopic dermatitis may manifest itself at all ages. It is generally preceded in childhood by an oozing, very pruriginous, often impetigenous eczema, chiefly located on the face, which appears around six months of age and disappears at the age of two. When relapsing, the illness takes the form of a sometimes papular, more often a lichenoid dermatitis, very pruriginous, and located on the flexor surfaces. Recovery may take place around ten or twelve years of age, unless the dermatitis reappears at puberty and persists chronically and recurrently until the age of 25 or 30. Cases in which the disease persists or in which it starts after this age, have, as a rule, a less favourable prognosis; the disease shows no tendency towards spontaneous recovery and may last throughout life.

The lesions are characterized by a considerable lichenification. The epidermis is dry, callous, of brownish grey color. No vesicles are found on clinical or histological examination. During the intervals between recrudescences, only the flexor surfaces are generally affected (neck, elbows and knees), but in the acute paroxysms the lesions spread over the face (forehead, eyelids), scalp, dorsum of hands and feet, and sometimes even over the entire extremities. Pruritus, a predominant symptom, frequently causes insomnia, and is partially responsible for the lichenification of the skin; furthermore it always results in lesions produced by scratching whose abundance is often out of proportion to the rather unimportant clinical lesions caused by the dermatitis. At times, the excoriations are superficially infected without concomitant adenopathy.

Associated symptoms.

A certain number of secondary symptoms are associated with these clinical signs:

Rugosity of the skin surrounding the dermatitis which is thick, dry, almost ichthyotic, and frequently the site of a follicular hyperkeratosis.

Presence of "white" dermographism, a whitish line, which ap-

pears after pressure and is due to vasoconstriction. Although it is not specific of atopic dermatitis, it is encountered much more frequently here than in any other form of dermatitis. The intradermal injection of histamine produces a larvate histaminic reaction, i.e. an absence of urticarial reaction around the injected area.

Disturbances of the superficial circulation: peripheral vasoconstriction (the patient is more apt to feel cold and the rapidity with which the extremities recover their warmth is diminished). Experiments have shown, that in these patients the temperature of the extremities is lower than in normal subjects having the same basal metabolism rate, and that they are apt to develop hypotension (Sulzberger, Baer).

Ocular disorders, occurring in severe cases, particularly atopic cataract, capsular and central cataract, are encountered in young patients and their evolution is more rapid than in the older age group. It is therefore always necessary to carry out an ophthalmologic examination in patients suffering from atopic dermatitis.

Disturbed perspiratory function, to which great importance should be attached. Pruritus often starts when increased perspiration is called for, e.g. in case of a change in temperature or an emotion. Obstruction of the sweat pores by a histologically established parakeratosis impedes normal elimination of perspiration; after its passage through the ducts of the sweat glands, it penetrates into the subcutaneous tissues and simultaneously provokes a severe pruritus and an urticarial reaction. Sulzberger is of the opinion that in extremely sensitive patients a foodstuff, inhalant or any other allergen may penetrate the cutaneous tissues through perspiration, and if rest seems to be beneficial it is because perspiration is reduced when isolated from all external influences.

Obstruction of the sweat pores may also explain certain climatic influences. It is well known that patients with atopic dermatitis experience seasonal outbreaks, that the majority of them feel worse during winter and improve in summer, that some benefit by a humid climate while others by a warm dry atmosphere. According to Sulzberger, this obstruction can be due either to a hyperkeratotic cone, composed of hard dry keratin or to a parakeratosis consisting in a swelling of the horny layer and edema of the peripheral tissues. In the first case hydration, by softening the keratin, would free the excretory ducts and facilitate perspiration; a humid climate is then indicated. In the latter, a warm dry climate which diminishes the edema, is more favourable. It is therefore indicated to classify atopic dermatitis into dry keratotic dermatitis, improved by a humid climate, and edematous dermatitis which improves in a dry atmosphere.

What other factors influence atopic dermatitis and provoke outbreaks?

certain foods, particularly: eggs, fish, chocolate, acid foods,

some inhalants such as dust, pollen, wool, silk,

infections which sometimes provoke a temporary remission as long as the temperature is high, but often exacerbates the dermatitis afterwards,

changes in genital function (menstruations, pregnancy) may be responsible for outbreaks as well as for temporary remission,

fatty substances which have only slight effect on a lichenified epithelium may worsen the dermatitis. Likewise, every irritation by a detergent or caustic product may constitute an aggravating factor,

finally, which role must be attributed to nervous factors? Some dermatologists are of the opinion that the psychic and emotional disorders, observed in patients with atopic dermatitis are not the cause of the disease, but merely the result of several years of pruritus, insomnia, and despair. Others, however, on the basis of psychological tests (52, 20 and 21) and electro-encephalographic changes, maintain that the majority of these patients not only present the psychological disturbances of neurotonic individuals, but also other psychic troubles, for instance epileptic crises, in which both autonomic and central nervous system are involved.

It is impossible to state if all these factors are causal or merely aggravating; nevertheless, they have to be taken into account and in every case a balance of the clinical, neurological and endocrinological factors should be made.

Can skin tests usefully contribute to these investigations? Although positive reactions are frequently obtained with foods and inhalants, these are generally of no clinical value, as their elimination or a re-exposure to them does not give rise to a change in the dermatitis.

Epidermal tests, on the other hand, are seldom positive, and even when they appear to be, histologic examination shows that it is most frequently a reaction due to irritation (e.g. to wool).

Finally, transfer of sensitization by the Prausnitz-Küstner test, does not present any interest on account of the polysensitization of these subjects.

In fact, all these tests are only of value in so far as they confirm the clinical history. It is the case history, the personal and familial antecedents, and the clinical examination, disclosing the aspect, localization, and evolution of the lesions which permit the establishment of the diagnosis of atopic dermatitis.

Treatment.

A detailed discussion of the treatment is here impossible; only the most important hygienic measures will be mentioned, which should be taken in all cases, as the causal allergen is only rarely discovered.

The patient should be advised:

to avoid dust, feathers, wool, silk; to wear linen or cotton clothing, to sleep on a rubber-foam mattress.

to avoid emotions, fatigue, and to use "tranquilizers".

to protect himself against secondary infections and contact with irritating substances (cleaning products, etc.).

When an alimentary allergy is involved, apart from less tolerated aliments (milk, eggs, lemon, spinach, fish, cod liver oil), it is only by clinical investigation, by the controlled effect of certain diets, that the regimen to be followed can be specified.

Nonspecific therapies may be tried (autohemotherapy); calcium gluconate and liver extract may be beneficial; if present, hormonal disorders or spasmophilia should be treated. In very severe conditions not responding to any of these treatments, corticoid hormones may be prescribed under control for short periods of time, in association with small doses of an antibiotic.

Local treatment has considerably improved in recent years by the adjunction to tar ointments of hydrocortisone lotions and ointments.

Tissue Allergies

Contrary to humoral allergies which are polymorphous, tissue allergies almost always manifest themselves in the form of an eczema. Although they may occasionally be due to ingestion or inhalation of an allergen or to infection, they generally are the result of a "contact"; for this reason they are called "contact dermatitis".

These forms of dermatitis, as already mentioned, become more and more frequent; they constitute a daily preoccupation for dermatologists as they actually represent 20 percent of all cases of dermatitis. They are, therefore, the object of constant investigation. Although their pathogenesis remains unknown, so that we only surmise that we are dealing with an epithelial allergy characterized by the presence of "fixed" antibodies in the epidermal cells, their etiology, on the other hand, has no secrets for the physician who performs a careful clinical study, a detailed history and makes use of epidermal tests.

What is the clinical aspect of a contact dermatitis? How can the offending cause be detected? Which allergens are most frequently encountered? What are the consequences of these sensitizations? These are the problems we will now approach.

I. *What is the clinical aspect of an allergic dermatitis of tissue origin?*

Most of the time it is a common eczema, sometimes acute, erythemato-edematous, vesicular or even bullous, oozing or covered by not too adherent crusts; at other times, chronic, exfoliating, crusty, occasionally fissured. The eruption is always accompanied and even preceded by pruritus which is one of the outstanding *quasi* constant symptoms in these forms of dermatitis caused by external sensitization. The clinical aspect of contact dermatitis, the detection of causative agents, the most frequently encountered allergens, as well as the consequences of these sensitizations are the problems which will be discussed at present.

Although the lesions are most frequently localized in the area in contact with the antigen, they may nevertheless appear at some distance. In addition, atypical aspects are not uncommonly encountered: the hands, for instance, by repeated contact with the offending agent, may reveal a fissured shrivelled aspect, reminiscent of a mycotic hyperkeratotic dermatitis; this is e.g. the case in dentists sensitized to anesthetics. At the lips, a sensitization to resin or to the ebonite of a denture is similar to an inflammation of the oral fissures. Other sensitizations may provoke only an erythematous dermatitis (vanilla, dinitrochlorobenzene) or an edematous dermatitis (mercaptobenzothiazole, manganese peroxide). In some cases of photosensitization, the lesions more closely resemble a burn than an eczema. Occasionally a pellagrous state is encountered with an ochre red, thin, tightly stretched, atrophic skin. Furthermore, dermatitis frequently reveals a pigmentary aspect, uniform or areolar, which clinically has nothing in common with an eczema.

Without taking into account superinfections and irritations by caustic products which frequently complicate the allergic dermatitis, although remaining eczematous, it may assume diverse appearances.

II. *On what basis can we establish the clinical and etiological diagnosis of contact dermatitis?*

history and skillfull clinical examination,
investigations by means of patch tests.

a) *History:*

History-taking is of utmost importance. First, one notes the absence of hereditary factors and of other allergic diseases. Furthermore the history will provide varied essential information concerning the onset, localization and exact nature of the initial lesions

which may have been different from those visible at the time of examination. Data will also be obtained concerning the course of the dermatitis in relation to professional activity (improvement during rest days, healing during prolonged holidays), as well as concerning its appearance in certain particular circumstances, such as the birth of a child (more frequent washings or daily contact with bleaches).

It is also helpful in detecting the causes by reviewing the patient's activities within the 48 hours preceding the attack such as application of fingernail polish or eyelash make-up, wearing of a new fur or dress, by ascertaining the seasonal influences (vegetables or flowers in season), by procuring information about previous therapies since the time of onset, about the cleaning products used, which, in addition to their rather mild sensitizing action, may favour the reactions to other substances by their traumatizing effect.

During this questioning one should not disregard those substances which have been tolerated for years, as sensitization may occur after a long period of tolerance; for instance, a woman, during her menopause, may become allergic to a dye she has been using for more than twenty years. Above all, patience, diplomacy and the cooperation of the patient are required.

Clinical examination: In the presence of an eczema, of limited extension with pronounced inflammatory reaction and unvariable localization during repeated outbreaks, a search for a contact antigen is indicated. The localization of the dermatitis will suggest the product responsible and make it possible to confine the investigation to a limited number of antigens.

Dermatitis of the eyelids will immediately suggest a certain number of possibilities: eyelash make-up if the dermatitis is transverse and ribbon-like along the free edge of the eyelid, a collyrium used for conjunctivitis or pupillary dilatation (anesthetic collyrium, containing an antibiotic, atropine), occasionally the plastic frame of eyeglasses, more often a nail polish which produces an erythematous, squamiform, pruriginous eczema at the inner angle of the upper eyelid, or a hair product, such as dyes and brillantine if the dermatitis is edematous. It may also be attributed to volatile substances: insecticides, paints, sawdust, fumes escaping from resin or plastic tubes, pollens, flowers (succulent plants, tulips ...). Dermatitis of the eyelids has also been encountered among workers handling oils, vanilla, flour, bakelite, dyed furs such as beaverette etc.

Dermatitis of the lips will suggest sensitization to lipstick, dentures or toothpaste; at the thighs a dermatitis caused by garters; while in case of an axillary localization a deodorant, toilet water, a depilatory or dye must be suspected. Dermatitis of the feet may be due to nylon stockings, the leather of shoes or an antimycotic product.

TABLE I

Antigens to be Suspected According to the Localization of the Dermatitis.

Eyelids	Eye drops, ophthalmic salves, make-up, nail polish, soaps, beauty products. Substances found in suspension in the atmosphere such as soot, insecticides, flowers or pollens.	Axillary region	Clothing or bacteria. Dress shields, cosmetics, deodorants, perfumes, soaps.
Forehead	Leather of hats, brillantine, frontal mirror supports, motorcycle goggles in plexiglass.	Lumbar region	Rubber belts, massage instruments, underwear.
Peribuccal region	Lipstick, ointment for chapped skin, toothpaste, cigarette holders, candy and even fruit juice, particularly orange and tangerine.	Peri-anal region	Anesthetic creams, anti-hemorrhoid ointments, suppositories, soaps, etc.
Perinasal region	Antiseptic substances: inhalation, pulverization, aerosol, or salves. Scented handkerchiefs.	Genitals	Therapeutic causes: antiseptic products, ointments, anti-parasitical or anti-venereal substances, preservatives.
Retro-auricular region	Brillantine, frame of glasses, telephone receiver, scarves or furs, perfumes. Auricular eczema has generally a bacterial origin.	Thighs	Coloured clothing (in the region of the fork), garters. In men, objects kept in pockets, matches, wallets, keys.
Neck	Clothing: collars of dyed clothes, lumber-jackets, collar-studs, shirt collars, woolens, jewels, necklaces, pendants, especially jewelry of plastic material, perfumes, nail polish.	Legs	Nylon stockings, depilatories, massage creams, cosmetics, plants.
		Feet	Stockings, socks, shoes, rubber sandals and boots: anti-mycotic products, sulfonamide powders, orthopedic appliances.

An eczema on the dorsum of hands or inner side of wrists is suggestive of an occupational origin: a bleach, cement, chemical products, carbon paper, leather, glue etc., as well as of so-called protective agents, barrier-creams and particularly rubber gloves when the upper limit of the dermatitis coincides with the upper edge of the glove. An eczema in a hairdresser involving only two or three fingers (index, middle finger) suggests sensitization to a hair-dye because of the gestures necessary for the waving of dyed hair. The aspect of the nails should also be taken into account as certain deformations reveal the presence of an associated caustic action.

Finally, a localization on the face, neck and hands, with a clear-cut-demarcation at the neckline of the dress and at the wrists, makes photosensitization evident and should draw attention to sensitization to sulphonamides, anesthetics, antihistamines, or other photocatalyzing substances (furocoumarines).

Henceforth, a thorough history and a careful clinical examination will make it possible to limit the problem, to confine the possibilities to two or three substances, and to make profitable use of epidermal tests. These will provide conclusive proof of the external origin of the dermatitis as they constitute the only means of reproducing experimentally the original circumstances of the clinical manifestation.

b) *Investigation by tests:*

1) Before making tests a certain number of precautions should be taken.

Choice of products to be tested: whenever possible, the same product which has been employed by the patient should be used for the test. If it is an unknown substance, its causticity must be investigated beforehand, as certain irritants (turpentine, detergents) may not remain in contact with the skin for 48 hours. The testing material should then be diluted to a concentration producing a reaction only in sensitized individuals, in order to avoid the "collective effect" produced by primary irritants, which should not be mistaken for a positive reaction.

Choice of time, testing area and preparation of the skin: tests should never be performed during outbreaks, as one runs the risk of provoking a violent exacerbation of the dermatitis and of obtaining a positive reaction without clinical value. The patient is first treated locally and asked to immediately eliminate all suspected antigens; by improving his condition one gains his confidence and also his cooperation which is often of great importance in the detection of the offending agent. Before the tests, one should never fail to inform him that a positive reaction may provoke a slight temporary recurrence of the dermatitis, as well as to advise him to remove the

patch in case of severe itching. For the sake of convenience the tests are generally performed on the back. However, in case of sensitization to lipstick for instance, an area with a thinner epidermis (eyelids, thorax) may be preferable, whereas in the case of a circumscribed localization, an area in its proximity may be chosen. Finally, in certain cases of stomatitis or glossitis caused by contact (dentures, amalgam) the investigation of the sensitivity of the mucous membrane may be performed by local contact tests using dentures or rubber caps; their interpretation, however, is difficult. As a rule, preparation of the skin is unnecessary. It may be useful nevertheless in order to simulate more closely certain particular clinical conditions (applications of sulphonamides to an ulcer of the leg, effect of cement upon an abraded skin) to degrease, pumice, alcalinize or scarify the skin beforehand.

2) Technique: The epidermal tests consist in bringing the product to be investigated into contact with the skin and covering it with a special, hypoallergic adhesive plaster (e.g. neodermotest) coated with a disc of cellophane in order to isolate a possible reaction from one which might be produced by the adhesive plaster itself.

As a rule, the tests are read after 48 hours. There are exceptions, however, in case of a very pronounced sensitization a distinct reaction may appear already on the first day while some delayed positive reactions may only become evident 3 or 4 days later.

3) In skin testing it is the interpretation which offers greatest difficulties. The following precautions should always be taken: after the adhesive plaster has been removed and the skin has been cleaned with ether, one should wait for an hour in order to eliminate the traumatic effect of the adhesive plaster. This is characterized by erythema, dermographism, or in hot weather by folliculitis. These manifestations, however, disappear rapidly in the case of an ordinary irritation, but they persist and assume an eczematous aspect when they are caused by sensitization. By replacing the rubber and the natural resins in the adhesive plaster by high-polymerized derivatives of aliphatic or aromatic hydrocarbons, it has been possible to obtain hypoallergic adhesive plasters which eliminate these hampering manifestations.

When a modification of the skin is noted, the test may be positive. In this instance, and notwithstanding the degree of the reaction, a pathognomonic symptom is always present, namely pruritus. Alone it would suffice to prove the positivity of a test, even if it was not confirmed by all the signs of an eczematous reaction with its erythema, edema, vesiculation, and the sharp or blurred outline which may project widely beyond the site of application of the test.

However, one must distinguish these positive reactions from the "collective effects" or false positive reactions. When a caustic product is applied to the skin, it always produces an irritation which varies according to the tested substance and which is encountered with insignificant differences in every individual. One can observe a simple "soap effect" characterized by an erythema localized at the site of contact, the skin being fissured, shrivelled, thin, hollow; or a more marked erythema with edema extending slightly beyond the site of contact, the "shampoo effect". The erythemato-edematous reaction may also be more intense and covered by follicular lesions having a suppurating aspect or even by small vesicles, the "croton oil effect". At times the "caustic effect" is characterized by an eschar with epidermic detachment. Pruritus never accompanies these various cutaneous modifications.

A diagnostic distinction between a "positive reaction" and the "collective effect" must be made whenever tests are performed with irritating substances such as detergents, sulphonated aliphatic alcohols, shampoos, ointments with penetrating excipients. In this case the manifestations may present some of the characteristics of both the caustic and intolerance type of lesions. The differentiation is made as previously mentioned, by eliminating the caustic effect by diluting the product and by examining the tests on the following days; in case of intolerance the lesion always develops into a true eczematization. In some cases it is not possible to arrive at a definite conclusion without a histological examination which always permits the differentiation between the two kinds of reactions. Finally, a positive reaction constitutes only a presumptive evidence concerning the causative factor. In fact, the individual may be sensitive to several substances of the same or of different groups. It is the cure of the patient following the elimination of the antigen which will provide a decisive answer.

If the reaction is negative i.e. if the skin is undamaged after the reaction to the adhesive plaster has disappeared, it is of course possible that the dermatitis is not caused by an external agent. However, before reaching this conclusion, one should resume the case history in order to make sure that the experiment has been carried out under the same conditions as those which existed when the dermatitis made its first appearance and that all the products handled by the patient have been tested. If necessary, one should not hesitate to extend the investigation. It was through a visit to the patient's home and workshop that we were able to detect a sensitization to an oilcloth, an artichoke stem, to vapors hardly perceptible by the patient, to intermediate substances in the process of manufacturing. Other investigations at the place of work enabled us to observe the

irritating action of repeated traumas or microtraumas which incited us to perform tests after pumicing the skin, after repeated alkalizations or applications of soap. Sometimes, it is even necessary to make scarifications prior to the test, when the antigen has been applied to a scar or an excoriation.

In certain cases of dermatitis due to cosmetics, a "summation" method should be resorted to, i.e. repeated applications of the antigen on the same area for several consecutive days. Contributory factors such as light and sun should be taken into consideration, particularly in certain sensitizations to dyes or perfumes, which can only be detected by means of ultra-violet rays. In clothing dermatitis, whose site of predilection is known to be the axilla, the tests may become positive only if the suspected material is impregnated with perspiration; in drug dermatitis, an association of two medicaments may be required to obtain a positive reaction. Finally, with cosmetics, since make-up is frequently superimposed on the face in several coats (powder, cream, rouge), "composite tests" may be compulsory, two or three products being brought together into contact with the skin. Is this merely a question of easier penetration of the antigen? Does the irritation and desiccation caused by soap facilitate sensitization to another chemical product? Or does the association of two products give rise to the formation of a new sensitizing chemical compound? At any rate, the use of combined tests has made it possible for us to evidence the causal factor in a certain number of cases of dermatitis whose origin had not been revealed by patch tests with each product separately.

Nevertheless, it still happens, in spite of all meticulous care and the *quasi* certitude that the dermatitis is produced by an external agent, that we are unable to disclose the allergen. Daily practice, however, shows that patch tests have made it possible to reduce markedly the number of cases of unexplained origin.

The practical interest of these tests is therefore indisputable. Furthermore, they have promoted very useful investigations concerning the threshold of sensitization, group sensitization, the comparative study of various derivatives of aniline, the etiology of dermatitis with atypical localization e.g. dermatitis caused by nail polish or following injections of spleen extract (anesthetic included in the solution). They also make it possible to determine which particular product will be tolerated by a patient sensitized to a product used collectively.

Is it possible to modify a test? Negativation of epidermal tests has been the subject of many investigation. It would indeed be of great interest to find a general or local treatment which would induce negativation of these reactions and therefore make it possible for an

individual to use a product to which he is sensitized. One of the most recent investigations on this subject by A. Haxthausen has shown the negativating action of certain chemical compounds (As_2O_3, salts of heavy metals) upon epidermal reactions performed by electrophoresis. Nevertheless, this action is always either very weak or is associated with a caustic effect, and it seems that no substance (male hormone, vitamin F, antihistamines and even adrenocorticosteroids by local or internal administration) is able to negativate a large positive reaction. Only by local injection of hydrocortisone have we been able to inhibit even strong positive epidermal reactions. The inhibition, however, remains localized at the site of injection, while the eczematous response manifests itself at the periphery of the injected area. Furthermore, this effect is only temporary; several months after the crystals of hydrocortisone acetate have been reabsorbed, application of the antigen at the same place induces again a positive reaction.

Drug Dermatitis

These forms of intolerance dermatitis arise from the application of a pharmaceutical product, to which the individual is sensitized, to a pre-existing lesion (dermatitis, infection, burn, rheumatic pain). Exceptionally, they may appear on a healthy skin, for instance following the use of atropine for pupillary dilatations or novocain for dental anesthesia.

In 1952, at the Congress in London, Pillsbury drew attention to the increasing use of sensitizing products in medical practice. These forms of allergic dermatitis of therapeutic origin, which constitute today the most frequent types of contact dermatitis, was the sole topic discussed at the Congress in Marseilles in 1954.

Less than 20 years ago, however, only a few isolated cases were known, generally provoked by a small number of products dispensed by pharmacists without prescription, (Peruvian balsam or yellow mercuric oxide ointment, arnica tincture, etc.); they were easy to disclose and their consequences were limited. The sulphonamides, followed by the antibiotics, and later the development of chemotherapy, have marked a new epoch in therapy, rich in results, but characterized also by an enormous increase in intolerance reactions.

How can the multiplicity of these reactions, often with unfortunate consequences, be explained? Various causes can be incriminated:

Systematic commercialization of new medicaments in three forms: oral, parenteral and topical.

Excessive publicity which promotes the sale, without medical

prescription, of ointments used without real necessity and for too long periods of time, whereas they are only of interest in certain well-defined diseases.

Application of these sensitizing drugs to an injured and often eczematous skin.

The fact that the eczematogenic action of certain substances is enhanced by their association with other products - (tri-antibiotics, penicillin-sulphonamides, sulphonamides-Dakin).

Finally, the use of new excipients, although superior to the classical preparations, makes them more sensitizing not only to themselves but also, to a considerable extent, to the active therapeutic elements they contain. In performing tests with the same substance incorporated in various excipients, we have been able to disclose the influence of this penetrating capacity on the sensitizing action. The results have been very different depending whether a solution, an ointment with vaseline, or propylene glycol was used. In the study of an antihistaminic ointment, we were impressed by the considerable number of reactions provoked by the excipient itself, reactions of desiccation and irritation of the skin or true positive reactions with pruritus, edema, and vesicles. It is obvious that the association of such an excipient with a product possessing a high sensitizing property as promethazine (Phenergan) would result in a particularly eczematogenic synergism.

The principal causes of contact eczemas of therapeutic origin.

A complete list of products responsible for these eczemas would be very long; we shall only mention:

Sulphonamides, which in 1949 caused 41 % of the total cases. This very high percentage was at that time explained by the fact that a large number of patients were treated locally or by oral administration with this drug in a pure state, in the form of micro-crystals whose traumatizing action highly favours sensitization. Experience has nowadays limited their use, and, therefore their consequences.

Anesthetic ointments used topically for the relief of pruritus. Local anesthetics give rise to numerous intolerance reactions; since their immediate sedative effect is greatly appreciated by patients, they have been included in the composition of numerous eye-lotions, suppositories, injectable ampoules. These reactions are particularly frequent with novocaine, anesthesine, scuroforme, dunacaine, less common with cocaine, ethyl chloride or stovaine. As we shall see later, sulphonamides and anesthetics can moreover cause accidents by photosensitization.

Antibiotics, likewise, differ in their sensitizing property; Aureo-

mycin in particular is much less sensitizing than penicillin, streptomycin, neomycin or tifomycin. The fact, however, that all these products are marketed in the form of ointments and eye lotions multiplies the accidents due to intolerance. Patch tests are often difficult to interpret as responses are generally weak. Here, as in the case of sulphonamides, it is sometimes necessary to combine the ordinary patch test with a scarification test. The intradermal test can give rise to a violent general reaction and should be avoided.

Antihistamines have, in 1953, been the cause of 50 % of our cases of drug dermatitis, mostly promethazine (Phenergan). Their localization may at times recall a photosensitization and their frequency is due to the indiscriminate use of this drug, administered in all manners to patients having a background of allergy.

In the pathogenesis and the study of the remote consequences of these forms of dermatitis three factors seem to be of importance.

1) group sensitization.
2) photosensitization.
3) connection between a dermatitis of external origin and sensitization through internal route.

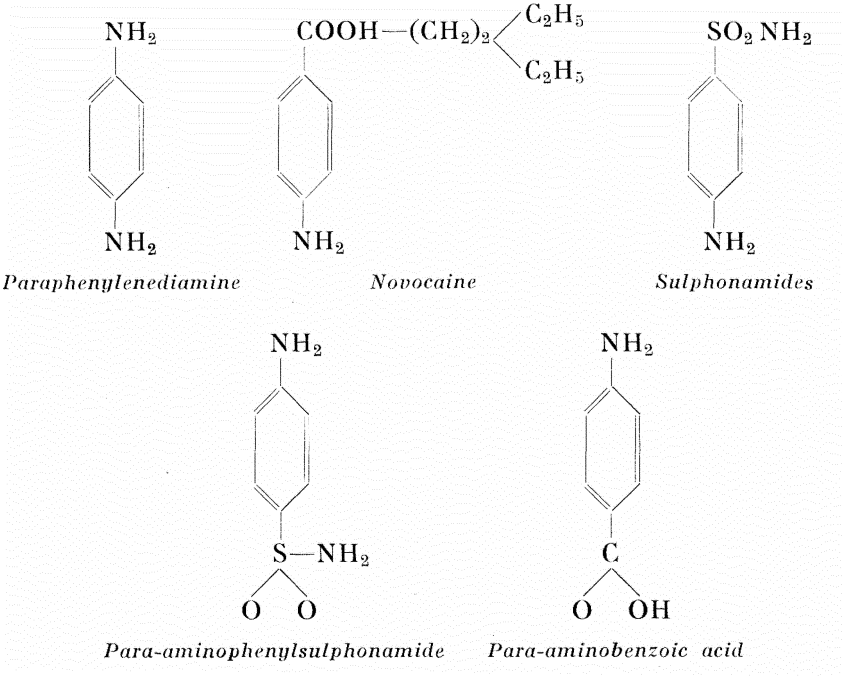
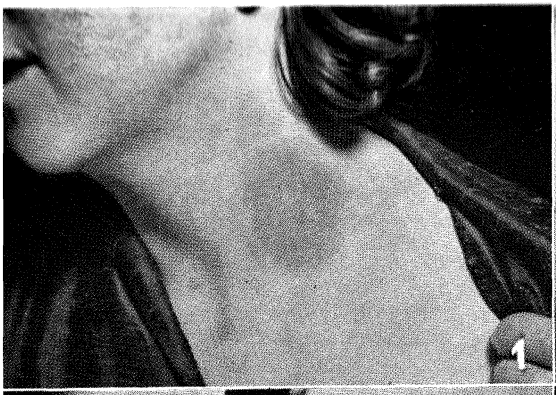


Fig. 14.
Substances of the para-group.

COLOUR PLATES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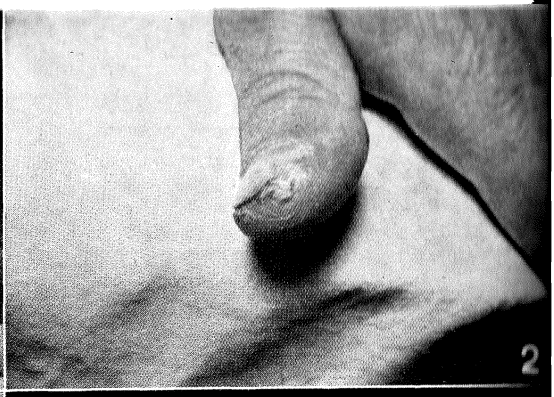
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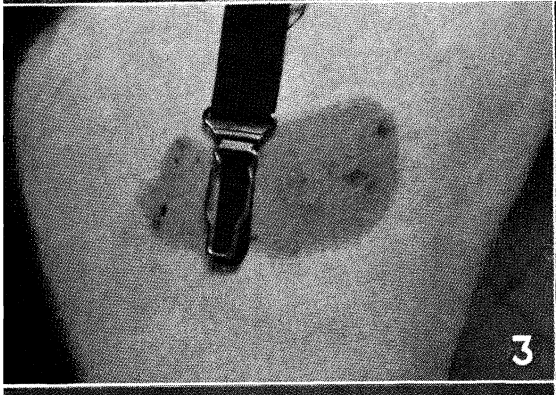
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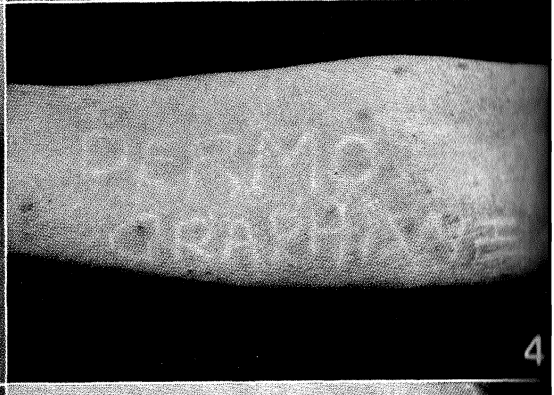
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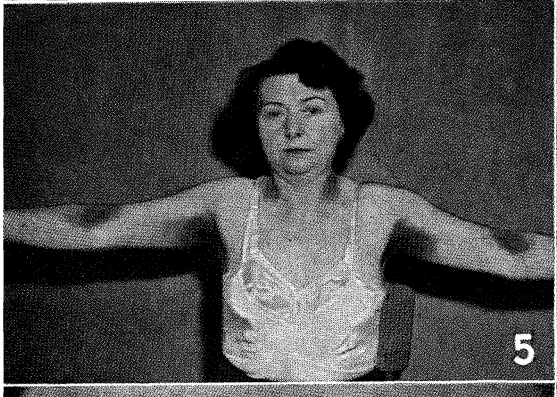
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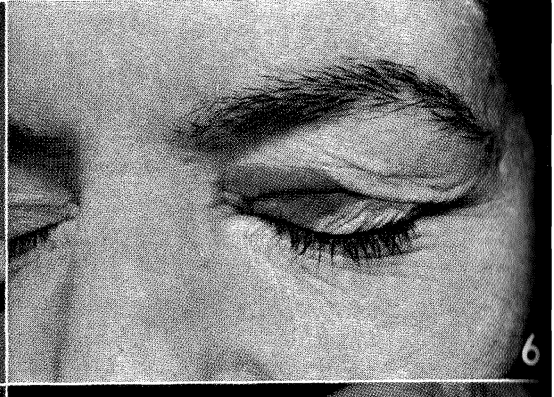
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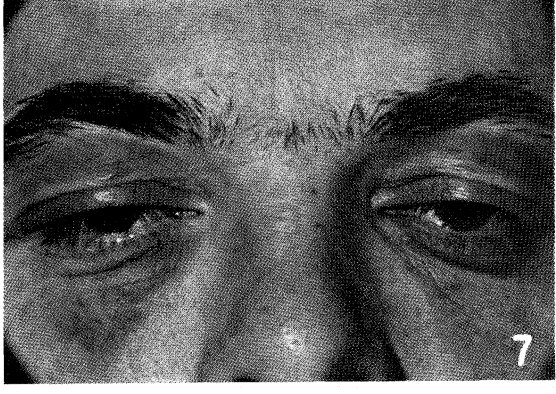
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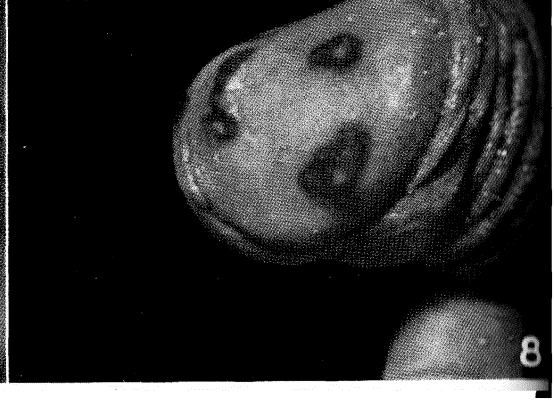
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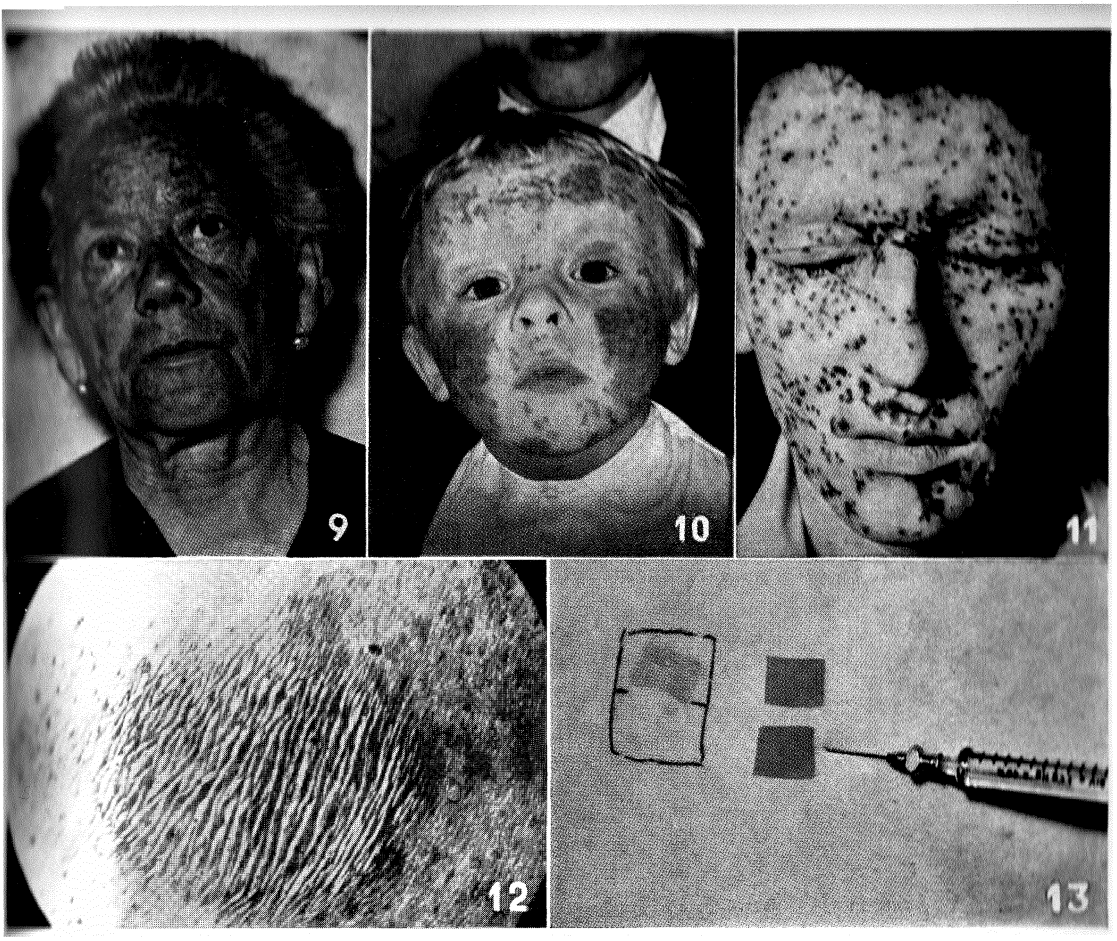


Fig. 1. Fixed pigmented dermatitis of the neck caused by ingestion of phenolphthalein.
Fig. 2. Dermatitis due to streptomycin.
Fig. 3. Eczema caused by a garter.
Fig. 4. White dermographism in a patient with atopic dermatitis.
Fig. 5. Clothing dermatitis localized on the neck, axillary regions and folds of elbows.
Fig. 6. Eczema of the eyelids due to nail polish.
Fig. 7. Eczema of the eyelids in a patient working with Bakelite, due to vapours to which he was exposed during work.
Fig. 8. Polymorphous erythema of glans caused by the use of bismuth suppositories.
Fig. 9. Riehl's melanosis.
Fig. 10. Infantile eczema in a two year old child.
Fig. 11. Atopic dermatitis of the face, with excoriations and superinfection caused by scratching.
Fig. 12. Soap effect. The skin is thin, wrinkled without vesicles; there is no pruritus. Histologically there is only a detachment of the horny layer.
Fig. 13. Local injection of hydrocortisone prevents the reaction. The upper test is positive to rubber, the lower remains negative because of a previous local injection of hydrocortisone.

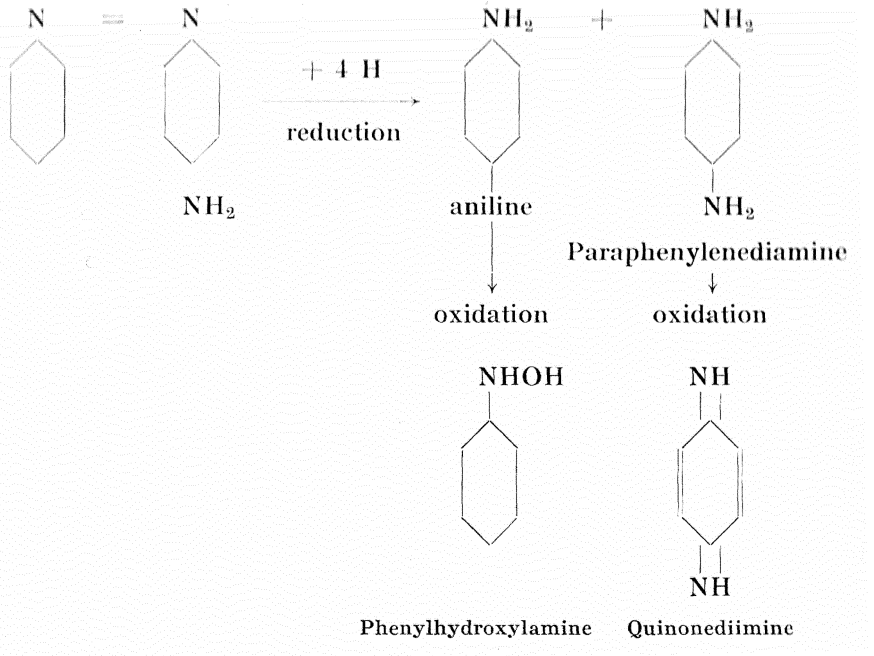


Fig. 15.
The mechanism of chemical transformation of an azo-dye, such as aminoazobenzene, in contact with the skin. (R. Mayer).

1) *Group sensitization.*

The possibility for an individual, sensitized to a primary antigen to react also to a secondary antigen, is the result of certain similarities in the chemical formula of these compounds or of their degraded products.

a) *The "para group"*. Bruno Bloch in 1911 was the first to draw attention, in connection with iodoform, to the relationship which may exist between sensitization and the presence of a specific chemical radical, the methyl group. In 1928, R. L. Mayer found a common chemical basis for hypersensitiveness to the azo-dyes and paratoluenediamine. Subsequently numerous authors, Flandin, Rabeau, Ukrainczyk, Nitti, Bovet, Depierre, Tzanck and collaborators, and in the United States, Sulzberger, Baer and Kanof, reported numerous cutaneous accidents provoked by various substances, which all contained in their formula, "a primary amine radical substituted in the para-position". In fact, all substances belonging to the paraphenylenediamine group, derivatives of aniline, possess a benzene nucleus in which the hydrogen in position 1 is substituted by a primary amine radical NH_2. Some of these compounds are closely related,

namely the sulphonamides, paraphenylenediamine, paratoluenediamine, and anesthetics of the novocaine group.

Consequently a subject sensitized to paratoluenediamine may also be sensitive to sulphonamides and synthetic anesthetics. An eczema caused by a dye containing a para-compound will therefore most often become aggravated by the administration of sulphonamides or anesthetic ointments. Other products belonging to the group of para-compounds are: para-aminobenzoic acid, para-aminosalicylic acid (P.A.S.), certain preservatives of cosmetics and azo-dyes which change into substances with a formula related to paraphenylenediamine when brought into contact with the skin. Para-substituted amines are even found in certain manufactured elastics. These various substances, however, do not possess an identical sensitizing property and furthermore an individual sensitized to one of these elements is not necessarily sensitive to the others. One realizes nevertheless, the consequences of such a sensitization and the difficulties encountered by an individual allergic to the para-group to protect himself against any contact with the antigens in daily life as well as in medical treatments. For this reason we customarily provide our patients, sensitive to one or several of these substances, with a certificate listing the products to be avoided.

Precautions to be taken by individuals sensitive to the para-group.

The following should definitely be prohibited:

sulphonamides (ointments, powders, eye-drops),
Phenergan (ointment, tablets, syrup, solution),
anesthetics of the novocaine group (ointment or injection),
slow-acting penicillin with procaine,
hair dyes with a paratoluenediamine or paraphenylenediamine base.

To be avoided:

newly dyed clothing,
the sun's rays.

To be used with precaution because of a possible sensitization:

picric acid,
para-aminosalicylic acid,
para-aminobenzoic acid,
dyed nylon,
elastic.

b) *The thiazine group.*—To the para-group, at present the most important and best known, must be added other groups such as the antihistamines. We have already mentioned that these substances

give rise to dermatitis in the uncovered areas, and this will be discussed again in connection with photosensitization. Ointments containing these substances, for example Phenergan, exceed the sulphonamides in their capacity to sensitize, and in the etiology of drug dermatitis they are the most frequently incriminated among all medicaments. Moreover, clinical experience has shown that sensitization to Phenergan results in the majority of cases in sensitization to Multergan, another antihistamine of the phenothiazine group. On the other hand, it is very rare in France, to encounter positive skin reactions to Tephorine or Pyribenzamine, two antihistamines with a different chemical formula; these, however, give rise to dermatitis in other countries (Switzerland, U.S.A.) where they are used topically.

Another derivative of the phenothiazine group, chlorpromazine or Largactil, can induce sensitization not only in patients who use the drug, particularly those sensitive to Phenergan, but also in nurses and workers associated with its preparation. Of 11 patients sensitized to promethazine (Phenergan), three gave a positive reaction to chlorpromazine (Largactil) and the absorption of a tablet resulted in a flare-up of their dermatitis. It is preferable that Largactil should never be used locally, as one runs the risk of provoking a sensitization which may be even more serious than that to promethazine.

These cross-sensitizations to Phenergan, Multergan, Largactil, can easily be explained by the similarity in their chemical formula.

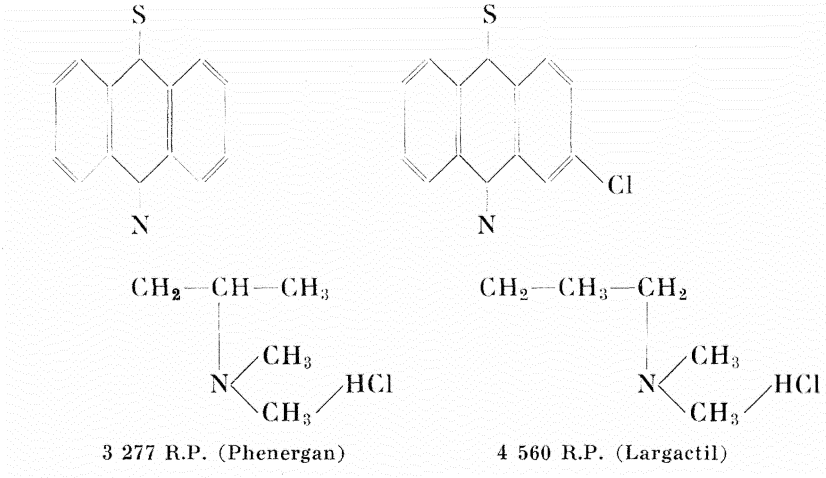


Fig. 16.
The only difference between Largactil and Phenergan consists in the addition of a chlorine atom and the position of the ethylamino-group at the third carbon atom instead of at the second.

In addition more than 30 % of the individuals sensitized to these antihistamines are also sensitized to paratoluenediamine and sometimes to synthetic anesthetics and sulphonamides. However, the phenomenon is not reversible: those sensitized to the para-group do not, necessarily, react to Phenergan. How can we account for this one-way co-sensitization when apparently there is no relation between the chemical formulas of these two substances? The assumption in all probability is that during the decomposition of Phenergan, substances related to the para-compound or to one of its breakdown products are formed, whereas the para-compound never can be transformed into a substance whose constitution bears the remotest resemblance to that of Phenergan.

c) *The neomycin-streptomycin group.*—The danger of group sensitization is even greater in the case of antibiotics, whose internal administration is sometimes indispensable in the treatment of diseases of vital prognosis. However, when a patient is sensitized to an antibiotic, its administration by internal route cannot be considered, no matter how serious the illness may be. Should the intolerance apply to a single antibiotic it may be replaced by another which is well tolerated. Unfortunately, group sensitizations occur which make it impossible for the patient to use a whole series of often irreplaceable antibiotics. In a large proportion of our cases we have demonstrated a cross-sensitization between neomycin and streptomycin. Eight patients sensitized to neomycin presented positive reactions to streptomycin, and, on the other hand, two nurses sensitized to streptomycin revealed an intolerance to neomycin. In studying the chemical formula of these two products we noticed a similarity between the two structures. We are thus dealing with a group sensitization which may have serious consequences because of the topical use on a large scale of neomycin, alone or in association with hydrocortisone, and because of the therapeutic importance of streptomycin. These facts call for careful consideration when substances which may reveal themselves irreplaceable in serious illnesses, are put on the market and generally used as ointments and eye-drops.

d) *The terpene group.*—There are other groups of sensitizing substances which are just as common, but less frought with consequences, as they include only few therapeutic products. In this regard, we shall only mention here one of the best known, the terpene group, which will be discussed later in connection with elastic and rubber dermatitis.

2) *Photosensitization.*

As is well known, subjects sensitized to the para-group or the thiazine group are furthermore exposed to accidents caused by

photosensitization, i.e. to eczemas localized on the uncovered areas (face, neck, hands, arms, and sometimes the lower third of legs) regardless of where the site of application of the antigen has been. This localization, which makes photosensitization obvious, is not always determined by a recent exposure to the sun; the lesions may appear at the site of an ancient photo-traumatism, reproducing for instance the neckline of a dress or a bathing suit worn several years previously. The evolution of these eczemas is of long duration; they may last for several years with alternating improvements and recurrences caused by new solar exposures. If the internal administration or local applications of the antigen are continued over a long period of time, the skin may become thin, atrophic and assume a parchment-like appearance reminding one more of a photodermia or a pellagra than an eczema. We have even seen patients in whom the dermatitis disappeared and was replaced by a lupus erythematosus.

In general, it is sufficient to discontinue the responsible medication, to apply a topical treatment as simple as possible, and, especially, to advise the patient to protect himself for a fortnight against exposure to daylight in order to obtain a rapid recovery. Later, a protection against the sun by means of creams or lotions will not always be sufficient to avoid relapses.

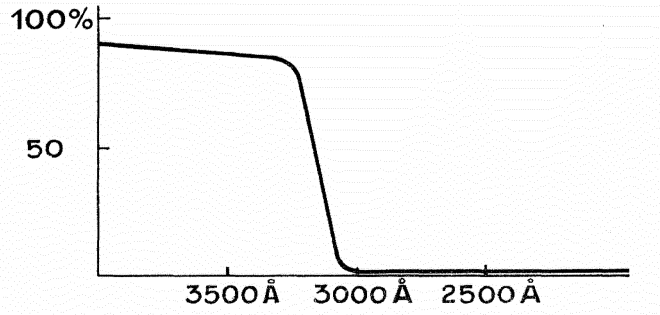
Even if these accidents seem to be produced by light, its antigenic role is only apparent, as it merely discloses in these patients a sensitization to substances which are at the same time antigens and photocatalysts.

Therapeutic products which are most frequently seen to be the origin of these accidents by photosensitization are the sulphonamides, the synthetic anesthetics and the antihistamines.

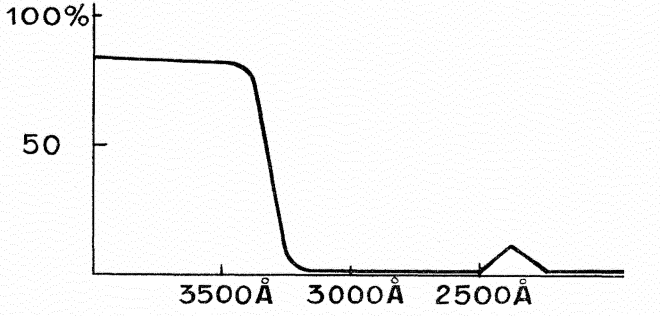
From 1945 until 1950, photosensitization to sulphonamides have, without doubt, been the most frequent and the most severe. Péterquin, in 1945, reported 75 cases of photosensitization in servicemen in North Africa treated with sulphonamide powders. Joulia, Fallot, l'Epée, Guichard des Ages, Dulong de Rosnay reported similar accidents. Guy Larue devoted his thesis to the same subject, and the present writers have reverted to it on several occasions since 1947.

The same type of lesions has also been observed following the use of other products belonging to the para-group, in particular the dermatitis in uncovered areas after application of anesthetic ointments and ingestion of P.A.S. This is not surprising, since substances of the para-group present analogies, not only in their chemical constitution, but also in their spectral or absorption curves established by spectrophotometry.

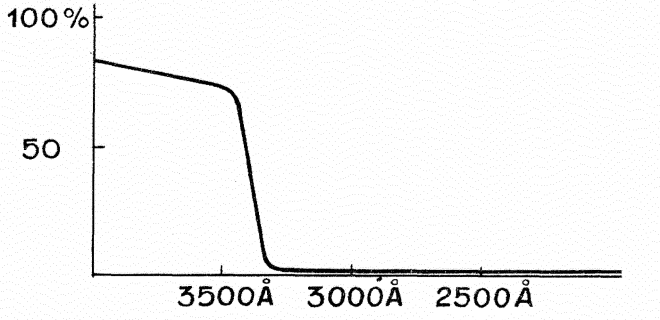
These curves show that sulphonamides, novocaine, and para-aminobenzoic acid behave as complete sun filters and that all have



Sulphonamide 1162 F (2.5 % in alcohol; thickness 0.05 mm).



Novocaine (2.5 % in alcohol; thickness 0.05 mm).



Para-aminobenzoic acid (water + alcohol).

Fig. 17.

Absorption curve of a sulphonamide, novocaine and para-aminobenzoic acid. Abscisissas indicate the wave lengths in Ångström units, ordinates the transmission in percent.

absorption bands for wave lengths below 3100 Å. It is obvious that such substances applied to the skin act as a screen or selective filter for certain wave lengths, whereas absorbed by the skin or taken internally, they may potentialize the absorbed radiation and then

act, not as a screen, but as catalysts or sensitizers for the absorbed wave lengths. Since administration of a photosensitizing substance is necessary for the production of the phenomenon, one may understand the risk involved by the incorporation of sensitizing products into irritating or penetrating excipients. This is unfortunately the case with certain antihistaminic ointments such as Phenergan; therefore, in the etiology of eczemas caused by photosensitization and of drug dermatitis in general, antihistamines, even more than sulphonamides, appear to be the main responsible agents. Of course, any internal administration may increase photosensitization and after recovery has been obtained, the ingestion of a tablet is often sufficient to reproduce the dermatitis in the uncovered or previously exposed areas.

The absorption curves of Phenergan and other substances of the phenothiazine group present the same characteristics as those of the para-group.

The only rational treatment, we repeat, consists in withdrawal of the patient from the light as completely as possible.

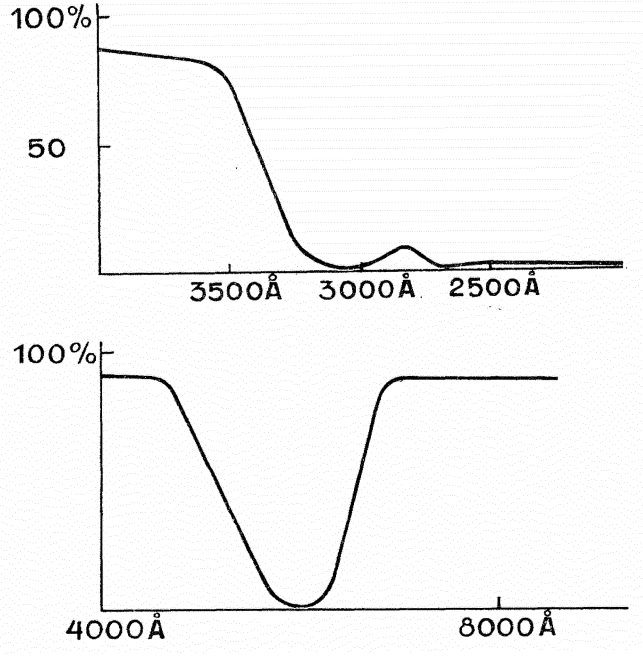


Fig. 18.
Absorption curve of Phenergan (alcohol 0.025 cc, thickness 0.05 mm). Abscissas indicate the wave lengths in Ångström units, ordinates the transmitted light in percent.

3) *Relation between dermatitis due to external causes and sensitization via the internal route.*

The majority of drugs responsible for intolerance dermatitis are marketed not only in the form of powders and ointments, but also as tablets and ampoules. However, a patient sensitized by local application of one of these products may at the same time become intolerant to its internal administration. This sensitization by internal way is frequently the consequence of the cutaneous intolerance, but the appearance of lesions seems, in some patients, to be connected with the notion of "threshold".

In 30 patients sensitized to sulphonamide powder, 17 presented a focal reactivation following the ingestion of a tablet. In 30 patients sensitized to Phenergan ointment, 15 presented, after taking the drug by mouth, either a reactivation or a generalization of the lesions accompanied by temperature, shivers, digestive troubles, and sometimes even syncope. Although a simple focal reactivation is most often the case, serious accidents are by no means rare. In addition, this internal sensitization does not apply only to the substance to which the patient is sensitized, but also to the other products of the same group. This must be considered as one of the causes of the periodic recurrences we observe. If it were necessary, we could find here another justification for the certificate we issue to our patients to be presented to the physician they may later consult. This has often made it possible to avoid serious, even fatal accidents.

Allergic Dermatitis of Occupational Origin

Dermatitis of occupational origin was the topic of the Congress in Lille, June 1955, and was again the subject of an important discussion at the International Dermatologic Congress in Stockholm, August 1957. *Birmingham* drew attention to the frequency of occupational diseases in the United States and to the high percentage of dermatoses, namely 65 %. Since more than half of these dermatoses are of an allergic origin, one can understand the importance of the problem of occupational eczemas from the medical and social point of view.

It is impossible to enumerate all the products capable of causing occupational dermatoses, nor to mention the trades in which they are mostly encountered, as every day industry produces new chemical products which possibly will become sensitizing agents.

One should always suspect an occupational dermatosis in the presence of an eczema which disappears when the work ceases and which recurs when it is resumed. At times the patient will point to

a definite product, but frequently he wrongly accuses all the caustic products which give him a burning and smarting sensation. By patch tests only can the provoking role of a particular product be established with certainty.

The importance of tests in the etiologic diagnosis of contact dermatitis has already been pointed out above. However, we wish to repeat that in the presence of occupational eczemas, perhaps even more than in other cases, the tests should be preceded by a thorough history-taking, and if necessary, by a local survey. Reproduction of the conditions for the appearance of the dermatitis should be carried out with maximum accuracy, in particular, one should never fail to reproduce the effects of primary irritation by degreasing, pumicing, alkalizing or scarifying the skin, or to dilute the industrial caustic or irritating substances in order to neutralize the caustic action, allowing only a possible sensitizing effect to remain. Finally, the habitual practice should be completed by "combined tests" which consist in associating several products with one another or with perspiration, "summation" tests in order to reproduce the daily action of the antigen upon the skin, and "completed" tests whereby the patient is placed under the exact conditions which are supposed to have provoked the dermatitis (resumption of work in the same surroundings). It is also the investigation by tests which enables one to examine the possible protective measures, to advise the sensitized individual on his future activities, to reclassify him in his profession.

Sensitization without doubt plays an important role in these occupational allergic dermatoses, however, the role of "irritation" is by no means negligible. In numerous cases the dermatitis is only secondary to an irritation which favours sensitization. According to our statistics, irritating factors play a predominant role in 50 to 60 % of cases and exert a less important influence in 30 %. A "primary irritant" is any substance which, applied to a healthy skin in sufficient concentration for a more or less prolonged period of time, produces cutaneous alterations in all individuals. Soaps, for instance, act mechanically by distorting the epidermic surface and dissociating the protective horny layer, and physically by reducing the superficial tension of the skin by "humidifying" it i.e. by rendering it more permeable. Pickling solutions and solvents, which exert a more brutal effect, induce deeper lesions, erythema, desiccation, hyperkeratosis and painful fissures.

It is on this already extremely complex cutaneous ground that an infinite variety of sensitizations are "grafted". As examples we may mention: the abrasive action of the very alkaline soap in paste form or of liquid cleaning fluids, which facilitate sensitization to chrome,

nickel, varnishes, enamels, paints ..., the irritation by detergents favouring sensitization to rubber gloves, the traumatizing role of cement in the sensitization to this product itself. Likewise, one cannot avoid being impressed by the number of hairdressers who become sensitive to the para-group after using cold permanent wave fluids, which cause, as is well known, a drying of the skin and an increase in its pH.

However, occupational eczemas due to pure sensitization are also encountered. They appear, evolve or become aggravated, and it is impossible to incriminate the slightest irritation; generally they heal very rapidly after stopping work. Among the most typical examples we may mention the eczemas of carpenters (sawdust) and of bakers (flour, vanilla) which do not affect the hands but are localized most frequently on the face and skin folds of joints, eczemas on the eyelids due to industrial vapours, or those among workers who handle substances with very little irritating effect such as cosmetic or pharmaceutical products.

The recovery from an occupational dermatitis, whatever the antigen may be, necessitates its elimination. However, when recovery has been obtained, the problem arises concerning the resumption of work. May these individuals resume work if they take certain precautionary measures, in other words, is it possible to protect them against the antigen? Rubber gloves would seem to be the answer, but as will be mentioned later, they are in themselves the cause of numerous intolerance reactions. The so-called protective ointments (barrier-creams, ointments with silicones) are equally not very helpful; in fact, patch tests have demonstrated that although they possess some effectiveness in protecting against primary irritants, they do not prevent the reaction after contact with the antigen. Rinsing with sodium chloride and hydrogen peroxide used in case of sensitization to paratoluenediamine may not only limit the intensity of the dermatitis to the para-group, but to a certain degree can also protect the sensitized individual. Its regular use before and after every contact with dyed hair has made it possible for us to allow some hairdressers sensitive to hair-dyes to resume their work:

Na Cl	15	parts
H_2O_2, 20 V	5	„
distilled water	100	„

As the preventive measures are only of slight effectiveness, one has to consider the professional and legislative regulations establishing the liability and the compensation for these forms of dermatitis. In France, at least, these are very illogical. Only certain occupational eczemas, such as those produced by intolerance to nickel,

chrome, trichloride, cement, paratoluenediamine, streptomycin, are indemnified as labour accidents. Several others, in particular sensitization to penicillin or chlorpromazine come under the Health Insurance Fund. On the other hand, legislation concerning labour accidents only takes in account the results of patch tests in eczemas due to streptomycin and paratoluenediamine. They have no medico-legal value in all other cases. It would be desirable, in France as well as in various other countries, if all occupational dermatoses with well established diagnosis, proved by positive patch tests and controlled by a specialist, were equitably compensated.

Dermatitis Due to Cosmetics

Intolerance reactions to cosmetics are the purest forms of allergic dermatitis. While drug dermatitis always follows the application of a pharmaceutical product to a pre-existing dermatitis, and occupational dermatitis appears on a skin irritated by detergents or traumas, cosmetic dermatitis is generally determined by the action of a product on a healthy skin. As a rule they are more benign and cure is easily obtained by elimination of the offending cosmetic.

They generally appear in the form of an eczema characterized by erythema, desquamation and especially by pruritus, which constitutes, as in every allergic dermatitis, the most important symptom. Their localization naturally depends on the responsible cosmetic; they are found most frequently on the face, which can be covered entirely or partially (eyelids, lips, cheeks) but sometimes also on other parts of the body, following contact with soaps, deodorants, depilatories, massage creams. Paradoxically, they can also be localized at some distance from the site of application. This is generally the case in eczema due to nail polish which, perhaps due to the rubbing of the fingers, affects the internal angle of upper eyelids, periphery of mouth, naso-buccal grooves, and neck. These forms of dermatitis are usually not severe, with the exception of hair-dressing products whose eczematogenic property is extremely variable. Shampoo, for instance, has often been the cause of a drying of the scalp with an increase of scales or of a simple local irritation accompanied by a burning sensation and pruritus; rarely does it cause eczema. Likewise, liquids used for cold permanent waving, which consist of ammonium thioglycolates, and possess a formula resembling that of depilatories, irritate and dehydrate the scalp. They can also break or burn the hairs when used incorrectly, for instance when excessive liquid has been applied to the scalp, the exposure has been prolonged, the rolling too tight or the neutralization insufficient; an eczema is, however, rarely produced. On the other hand

hair dyes, as already mentioned in connection with the "para group", frequently produce acute dermatitis, highly edematous and oozing, usually benign, but sometimes spreading over the entire face and neck and accompanied by general symptoms (lack of appetite, temperature, depression). For this reason the "touch test" has been made compulsory as a preventive measure prior to an application of a dye from paratoluenediamine.

Beside these benign or acute forms of dermatitis there are the *melanoses* consisting in uniform pigmentations in spots or in sharply limited stripes, called "breloque dermatitis". They are caused by an application of perfume or toilet water followed by exposure to the sun's rays. Sometimes these pigmentations become more diffuse, areolar, forming a fine slate-colored net which covers the entire face, while leaving a strip of healthy skin at the edge of the scalp; these are called "Riehl's melanoses". Their principal cause, in our opinion, is to be found in a sensitization to the synthetic essences contained in certain beauty products. Without denying that internal factors may play an important role, we consider that the local factor is the essential one; it is the action of the perfume contained in a cream, or more often in powder, which in association with solar radiation, causes these melanoses. The fact that the elimination of all perfumed cosmetics leads to a cure is without doubt the best proof.

In dermatitis due to cosmetics, as in all forms of contact dermatitis, patch tests will provide the proof as to which beauty product is responsible for it. Their interpretation is sometimes delicate as the reaction is often very weak. Even when the positivity is not evident although the clinical diagnosis of intolerance reaction to a certain cosmetic is indisputable, it may be desirable to make the test at the exact site where the product has been used or in an area where the skin is thinner (inner site of arms, anterior surface of neck, eyelids). Sometimes it is necessary also to resort to the "summation" effect, and in certain cases of sensitivity to lipstick, dyes or perfumes, to proceed to the irradiation of the tests. Finally, in melanosis, when several products have been superimposed on the face (powder + cream + rouge, or else shampoo + brilliantine), it is advisable to use the "combined tests". Very often in fact does the reaction remain negative if the cream or powder are tested separately, whereas their association brings proof of the sensitivity. This can be explained by an increased penetration of the antigen, the cream facilitating the penetration of the perfume contained in the powder.

Some cosmetic products can also provoke false positive reactions. Thus soap, shampoo, permanent wave fluids, toothpaste or brilliantine, when applied on the skin without occlusion for 48 hours, can

cause the "collective effect" mentioned previously, which must not be mistaken for a true positive test.

Furthermore, tests make it possible to determine amongst the components of the responsible cosmetic, the one which is eczematogenic for a particular patient and to establish the composition of the preparation for individual use.

Though cosmetic dermatitis most often occurs alone, it is sometimes associated with a drug dermatitis. It is then necessary to take each one into consideration as these intolerances to beauty products only remain benign if they are recognized and treated in a rational way.

Rubber Dermatitis

Apart from certain pharmaceutical products, rubber is the antigen which today provokes the greatest number of intolerance reactions. Around 1935, however, only rarely were accidents imputed to it. How can such a change be explained? Should one incriminate the synthetic rubber or the present-day method of preparation of natural rubber? It seems that the sensitizing power of synthetic rubber has been greatly exaggerated, since in the U.S.A. it is used to manufacture hypo-allergenic gloves. On the other hand, it has been observed that the number of cases of rubber dermatitis has considerably increased since the incorporation of new substances in the gum: plasticisers, dyes, sulphur, accelerators, antioxidants. There are thus reasons to believe that part of the responsibility may be attributed to the accelerators in vulcanization (mercaptobenzothiazole, diphenylguanidine) and to the antioxidants, among which there are various derivatives of paraphenylenediamine. Likewise, the molecular chains of isoprenes, which constitute unmanufactured rubber, can be the origin of intolerance reactions.

Rubber gloves are the most frequent cause of rubber dermatitis as in many professions (workmen, surgeons, nurses and particularly housewives) they are indispensible or worn as a form of protection. Ninety percent of cases occur in women and most often in those whose skin, previously traumatized by the drying and alkalization due to cleaning products, is particularly subject to sensitization. The aspect of this dermatitis is very evocative of its etiology as it affects the dorsum of hands and shows at the wrists a clear horizontal limit corresponding to the edge of the cuffs of the gloves. The positivity of the cutaneous tests is generally evident. In certain cases, however, a positive reaction is only obtained if the rubber has been previously impregnated with the patient's own sweat.

How can these patients be protected? When they are exclusively sensitive to rubber and do not present any intolerance to products

they handle during work, elimination of the gloves will bring a complete cure. For the greater majority, however, it is necessary to substitute the gloves for some other method of protection. Since it is known that the so-called "protective" creams do not possess any efficacy, the only solution is the use of hypoallergic gloves; their manufacture, at least in France, is still insufficiently developed.

Individuals sensitive to rubber are in a large proportion allergic to all rubber products. The following shows how to recognize this form of intolerance dermatitis:

Garters cause a dermatitis localized on the thighs, mostly on the anterior surface where contact is closer and rubbing more constant. It is clearly demarcated, seldom oozing, and has often a dry lichenified aspect. Only the rubber brace is responsible for the eczema, and it is often sufficient to replace it or cover it with a satin ribbon to avoid any reaction.

Rubber girdles cause dermatitis of the abdomen and lumbar region.

Brassières, because of rubber attachments on the straps, dress shields, men's suspenders, raincoats, rubber boots and shoes, elastic stockings and bandages, rubber sheets, hot water bottles ...

These patients can further show intolerance reactions to their dental equipment of vulcanite, manifested by glossitis, sores of the lip commisures, sometimes a peribuccal dermatitis or even eczematous lesions at a distance. In these cases the sensitivity can be evidenced by means of a special dental prothesis, which makes it possible to maintain the antigen in contact with the mucous membrane for 48 hours.

Finally, let us recall the frequency of sensitivity to adhesive plaster. Rubber is a polyterpene and adhesive plaster contains terpenic carbon combinations. Individuals sensitized to it risk becoming intolerant to the entire terpene group, which includes not only adhesive plaster, but also essence of lavender, violet, carnation, citronella, turpentine, revulsive salves and certain pectoral syrups.

Clothing Dermatitis

This form of dermatitis represents around 6 % of the cases of contact eczema seen in our out-patient department. Clothes and underwear are, through their composition, or more often through their dyeing or starching, a relatively frequent cause of cutaneous sensitivity.

They affect in particular the axillary area, but may also be found at the antecubital fossae, inguinal folds, or as a "necklace" around the neck. Their localization at the folds is due to the fact that fric-

tion, heat, humidity and primarily perspiration, play an important but not fully understood role in their pathogenesis. The question remains whether it is a matter of simple maceration, an increase in pH the acid perspiration becoming alkaline when its evaporation is hindered or whether the perspiration serves as a solvent or carrier of the allergen. The lesions, however, are not always located at the folds, they may sometimes reproduce more or less completely the shape of a clothing item, or even be located at a distance. This is the case with workers handling certain dyed furs (beaverette), who often present a dry eczema at the eyelids and around the nose.

Colored woolens, non-creasable fabrics and nylons are the most frequent causes of clothing dermatitis, but it is always to aniline or azo-dyes that one should first refer; in addition the fabric itself (woolens and nylon much more often than linen or cotton), mordants, antifungal products, insecticides, stain-removers or finishing products may also be held responsible for the intolerance. Particularly the so-called permanent finishings used in non-creasable fabrics, which are generally composed of resins of the urea-formic or melanine-formic type, appear to be very sensitizing. The action of perspiration or a damp ironing is sufficient to split these compounds and the formol group is liberated in its labile form.

Nylon stockings and socks provoke dermatitis at the popliteal surfaces and ankles; it is not due to the nylon itself, which is only an irritant, but to the azo-dyes used in the coloring or to the finishing products such as oils and sulphonated fats. Therefore it is sometimes sufficient to wash them before use in order to avoid any reaction.

Leather of any origin is not less sensitizing. Dermatitis may be caused by shoes, hats, clothing, wristwatch bands, wallets, suspenders. It is always violent and persists in spite of the fact that a piece of material has been placed between the leather and the skin.

Other forms of clothing dermatitis can be observed daily, the origin of which is not always easy to detect. Patch tests are most useful here also, but it must never be forgotten to moisten the antigenic product with the patient's sweat beforehand.

Conclusion

In the presence of a contact eczema the first concern of the physician will be the elimination of the provoking cause, as no treatment will be efficacious as long as the sensitized individual remains in contact with the responsible antigen.

As this cannot be discovered at the first consultation, the patient is requested to eliminate all suspected products for a few days and

at the same time a simple local treatment is prescribed, damp compresses of Evian water or of marshmallow root if the eczema is acute, compresses of boric acid or permanganate, eventually aqueous solutions of hexomedine or neomycine, whose antimicrobal action is remarkable, if the eczema is infected. Ointments containing hydrocortisone acetate, zinc, or olive oil, as well as solutions of crystal violet, eosine or silver nitrate will be prescribed if the eczema is subacute or chronic. In certain chronic cases, already lichenous, one can apply once a week trichloracetic acid at 33 %, whose calming effect on pruritus is excellent.

The general treatment should be limited to the usual sedatives (calcium bromide, phenobarbital, tranquilizers). In spite of their antipruriginous and hypnotic properties, antihistamines have been the cause of too many intolerance reaction to run the risk of prescribing them to patients with eczema.

It is essential to eliminate all sensitizing drugs and to search for the provoking cause, as cure will then most often be obtained and preventive measures be taken.

If the study of allergic dermatitis has today become an extensive field, it is for a large part due to the practice of skin tests. These do not present merely a practical interest, and it would be wrong to consider them only as a convenient clinical procedure. They are in addition a valuable instrument of research and an indispensible means of prevention, since we use them every day to determine the eczematogenic property of new products before their distribution.

Any substance may act as an antigen; although certain intolerances appear inevitable, it would be possible to take preventive measures against many others, provided a preliminary study is made of their properties, not only concerning their toxicity and causticity, but also in relation to their sensitizing property.

These methods of investigation should be practiced on a large scale, as the number of cases of allergic dermatitis increases with the constant progress in all branches of modern industry. Their consequences are such that chemists, forensic experts, medical officers, physicians supervising the processing of drugs and cosmetics should be familiar with all the problems they involve.

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URTICARIA AND QUINCKE'S OEDEMA

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I. CLINICAL FEATURES

When occuring in childhood, urticaria is frequently regarded as a more or less common children's disease; elevated itching patches appear occasionaly after eating strawberries, tomatoes, bananas, chocolate, pork, summer vegetables, etc. Usually only slight concern is given to these symptoms, the patches disappear fairly rapidly, and if the offending foods are eliminated, the lesions will not recur again.

Small and large itching patches appearing all over the body or localized in one area are also observed in adults. There is a sudden outcrop of lesions in some cases while others are marked by a gradual onset, following e.g. the injection of a preparation of ACTH (foreign protein), penicillin or another antibiotic, the injection of a contrast medium, procaine or other anesthetics by a dentist or surgeon, the ingestion of aspirin tablets, a bee-sting, mosquito or flea-bites, jelly-fish stings, as well as after eating chocolate, lobster, mussels or other foods, or the wearing of nylon or new woolen clothes.

In summer from time to time a swimmer has to be pulled out of the cool water, having turned a bluish colour, suffocating, nearly unconscious and occasionally covered with raised itching patches. Some workers, bicycling to their work, arrive with swollen itching hands and face. A soldier, returning after a long march or other strenous exercise, complains of oedematous, itching feet or even large itching patches all over the body.

Elevated iching patches may at times appear on the area covered by a tight belt, shoulder strap or garter. In some cases, the skin begins to itch, the patient feels a sensation of heat and burning, he starts scratching and long thick wheals appear. In others, a pinch or bump is sufficient to produce the lesions.

The elevated, itching patches present the following characteristics: firstly, a burning, itching, sometimes painful sensation of the skin

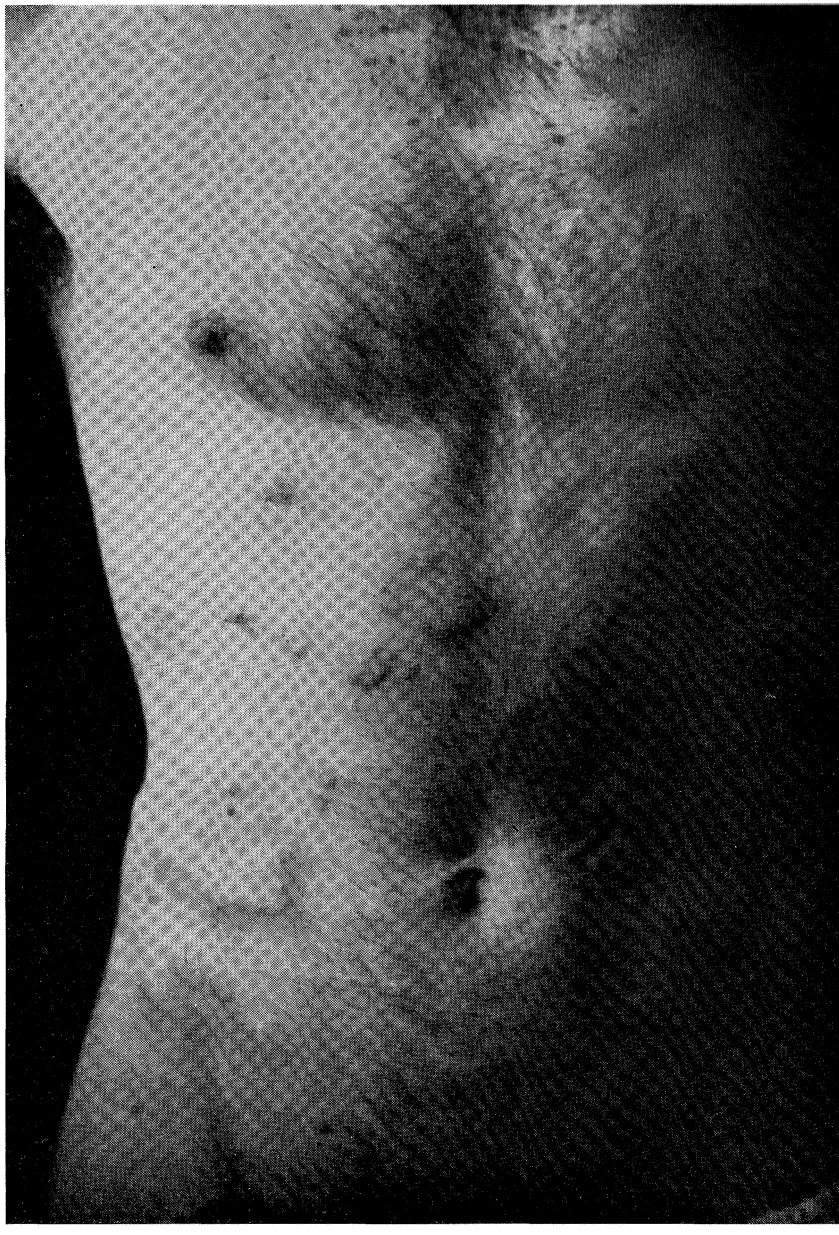

Fig. 1.
Urticarial wheals.

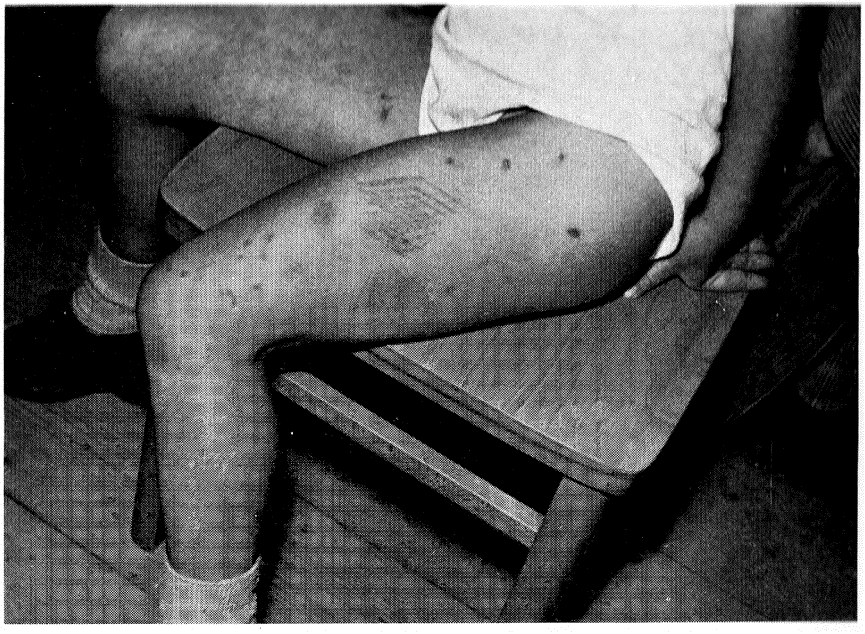

Fig. 2.
Strophulus.

is felt; this is followed by the appearance of a red elevated patch, to be succeeded usually by a more or less circumscribed white elevation surrounded by a red areola.

In certain cases, these patches and elevations seem to become confluent, forming large lesions, with less intense itching, but causing an unpleasant, at times painful sensation of tightness, or perhaps there may appear a swelling of the lip (often unilateral), cheek, eyelid, finger, hand, foot, tongue or glottis. The itching and intense redness disappear after an hour or more, followed by a gradual vanishing of the elevation or swelling, the site of which is still indicated by a slow red discolouration. The attack has now subsided, however, this often means only a brief respite for the patient. Every morning upon awakening, every night on going to bed or even suddenly during the day, the elevations will return, localized in some cases, dispersed in large numbers in others. The lesions may occur weekly, during each premenstrual period, throughout an entire season, or even for more prolonged periods. Beside the occasional and frequently recurring attacks, the condition may consist in persistent itching and a constant coming and going of the elevated patches and swellings.

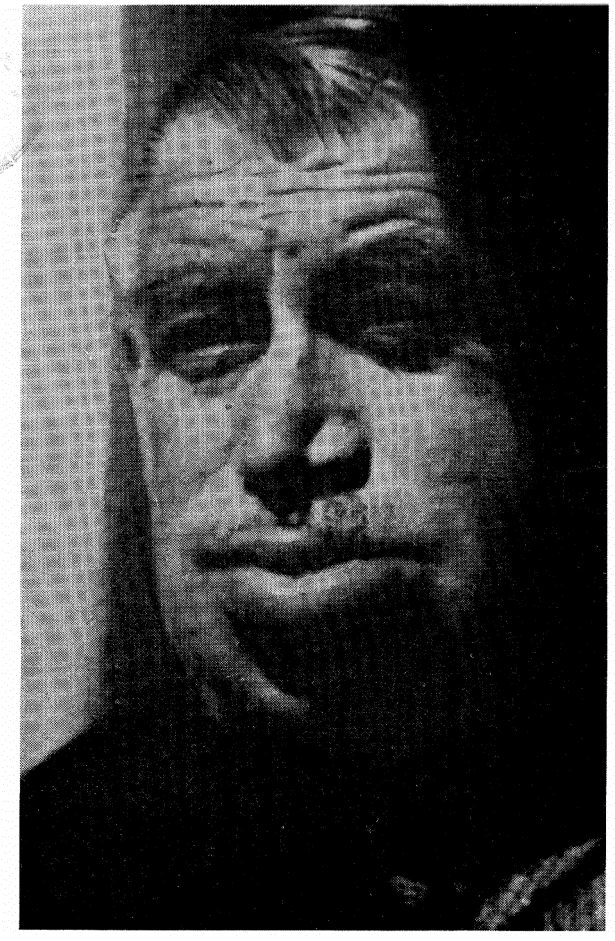

Fig. 3.
Quincke's oedema.

In addition to the skin symptoms, the oedema of the glottis frequently induces a sensation of suffocation, a rise in temperature, and a general malaise. An attack of this type may endure for hours or days, and then suddenly disappear again.

Other symptoms, especially in the more prolonged cases, may include an intense fatigue which cannot always be attributed to hypotension or a concomitant anemia, as well as marked mental restlessness induced by a constant itching or fear of the next attack.

The patient is frequently aware of the precipitating cause of the attack; he knew he was hypersensitive to aspirin but in error took a tab-

let containing salicylic acid to relieve his pain. In other cases, there is an obvious relationship with injections, the wearing of a particular garment, the ingestion of a certain kind of food, contact with flowers, exposure to cold or sun's rays, exercise, pressure, etc. Occasionally, other factors may be involved: the patient may be very tired, he had just undergone an operation or had an infectious disease, he has worked himself into a nervous state or has exerted himself to an unusual degree. In any of these events where the patient knows the causative factors, he will be capable of carrying out the necessary elimination treatment himself. Difficulty arises, however, when in spite of this, attacks continue to persist; usually in this case several causes are involved.

When a chronic patient subject to frequent attacks is questioned as to what he believes to be the cause of the attacks, it is surprising to hear that he is often able to state the cause precipating the onset of the initial attack, such as an injection, a jellyfish sting, an operation, a change in habits (emigration, repatriation), vaccinations, severe mental tension or excessive eating during holidays, whereas he is unable to identify the causes of the subsequent attacks.

Strophulus (urticaria papulosa, lichen urticatus) is a separate morbid entity; it is common in young children, especially in the spring and autumn, and is usually confined to the arms, legs and buttocks; it is marked by the appearance of itching vesicles or bullae surrounded by a red areola, from which a clear fluid may be discharged. Scratching may cause suppuration, in which case disinfectant treatment will be indicated.

De Lind van Wyngaarden has pointed out that hypersensitiveness to mosquito bites gives rise to strophulus-urticaria-like symptoms in children and occasionally in adults as well. The bite does not only induce a local reaction, but areas previously bitten also tend to react again. In addition, certain patients are hypersensitive to the bites or stings of mosquitoes, ants, flies, bees, wasps, etc., so that an intense local reaction results in the stung or bitten area, sometimes followed by a general reaction.

Besides the ordinary form of urticaria, Quincke's oedema is to be mentioned, which is regarded by some as an individual clinical picture, while as a special form of urticaria (angioneurotic oedema, giant urticaria) by others. The lesions in ordinary urticaria are confined to the skin, whereas in Quincke's oedema they appear subcutaneously or in the submucosa: swellings of the lips, cheeks, eyelids, fingers (often unilateral) or internal oedema of the glottis, brain, intestines etc.

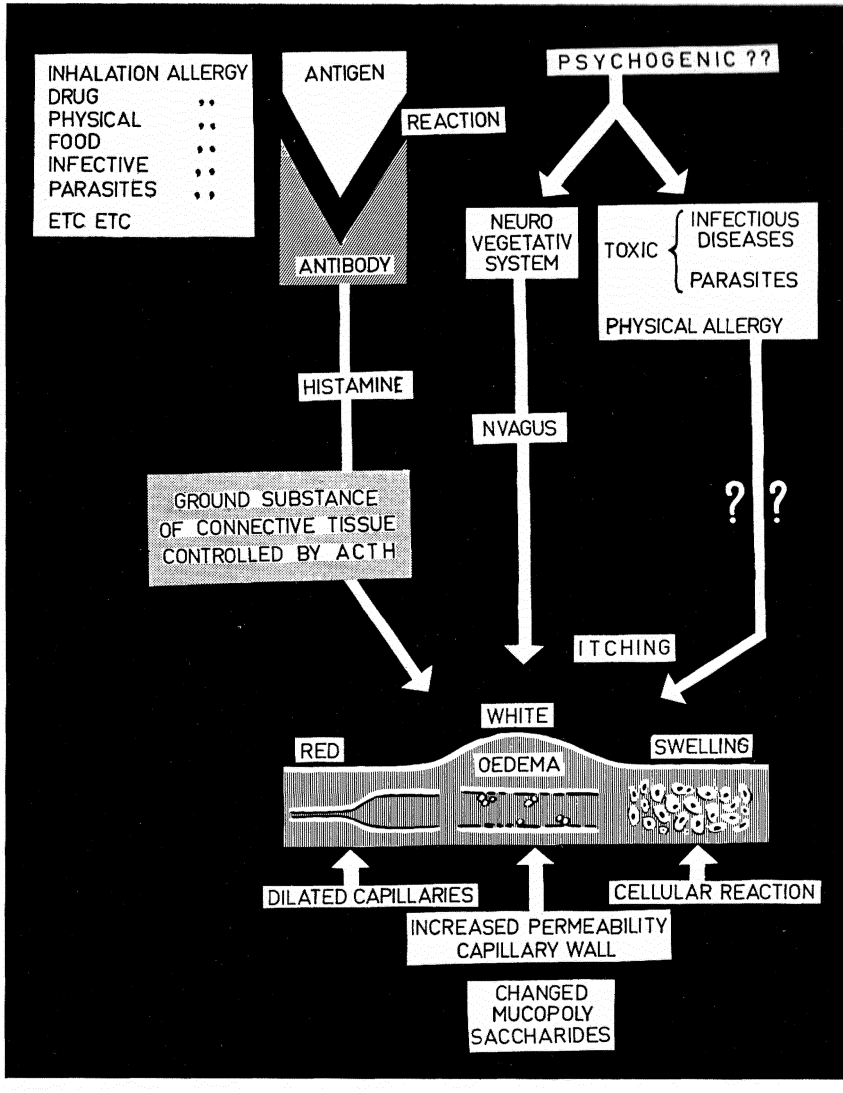

Fig. 4.
Causes and mechanisms leading to the urticarial wheal.

II. Pathophysiology and Pathologic Anatomy of the Urticarial Papula

The urticarial wheal is characterized by a swelling, redness with a white centre (the inflammatory oedema in the corium causes dispersion of the tissue cells over larger or smaller areas; the pressure

of the exudation prevents the blood from penetrating into the vessels in the papillary layer of the skin, so that hyperemia only appears in the marginal area).

Lewis' view on the pathogenesis of the papula is the one most commonly accepted, the action on the capillaries of histamine liberated in the tissues (dilation of the capillaries and increased permeability of the vascular walls) results in *oedema* and *redness*.

Lewis studied local vascular reactions in the human skin to various types of stimuli. With each stimulus, the reaction consisted of three components (triple response) : a primary capillary dilation, dilatation of the neighbouring arterioles and wheal formation from increased permeability of the vascular wall. He showed that an intracutaneous injection of histamine produced a similar reaction. He concluded that the response of the skin (urticarial wheal) or subcutaneous tissue (Quincke's oedema) to stimuli is concerned with the release of histamine or a histamine-like substance ("H" substance).

The extent to which other substances are also involved continues to be obscure. The papula induced by "exogenous" histamine differs slightly from the genuine urticarial wheal; it persists for a much shorter period and posseses no pseudopods. These features, however, are present in urticarial papulae resulting from the intravenous injection of "histamine liberators". Even more obscure is the question which factors give rise to the release of histamine. To begin with, it might be due to allergic reactions; in a number of cases, methods such as the Prausnitz-Küstner test may be used to reveal the presence of circulating antibodies (food or drug allergens, serum sensitivity). So far, it is difficult to understand why one attack of urticaria is associated with a few elevated patches and another with several small or a few very large elevations. Why do the elevations appear on particular areas of the skin in some cases and on other areas or all over the body in others? Nor has the problem of the site of the primary reaction resulting in wheal formation, capillary wall or intercellular substance, been solved.

The nature of other processes which may be involved, continues to remain vague. Rost stresses the fact that urticaria, very seldomly observed in patients with "eczematoid marked by late exudation" ("spätexsudatives eczematoid", in which he regards vagotonia as the most important feature in the history of the patient himself or his family), may be suppressed by vagotonia or promoted by sympathicotonia. He cites this view as a possible explanation of the chronic form of urticaria.

Histologically, the urticarial papula is characterized by oedema in the papillary layer and stratum reticulare, dilatation of the blood vessels (hyperemia), changes in the mucosaccharides of the base-

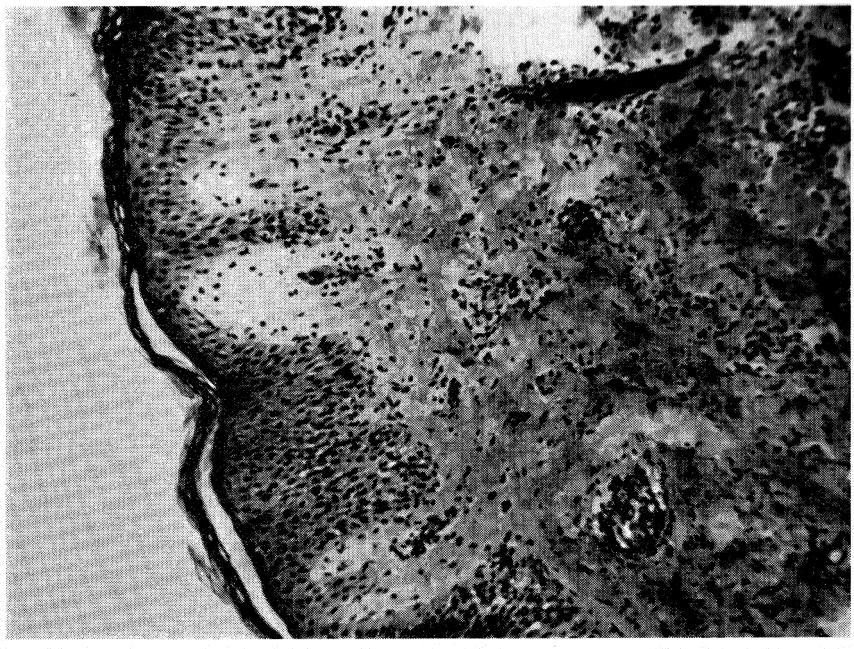

Fig. 5 a.

Papula of Strophulus Infantum.—The skin shows marked oedema. This is most pronounced in the stratum papillare. As a result, not all the boundaries of the basal layer of the epidermis are sharply defined. The epidermis shows locally some spongiosis. The capillaries in the skin are dilated and the endothelium is swollen. The skin—and especially the pericapillary portion of it—is marked by a fair degree of inflammatory infiltration which consists of neutrophils and a fairly large number of eosinophils. (Dr. Vossenaar) February 22, 1957.

ment membrane of the capillaries (increased permeabilitiy of the vascular walls) and changes in the mucosaccharides of the ground substance of the connective tissue and infiltrating cells (mast cells, eosinophils), (Kline, Cohen and Rudolph, Mali, Vossenaar and Quarles van Ufford).

In an investigation carried out in conjunction with Vossenaar on the histological study of the urticarial papulae, cold urticaria, dermographism, histamine papulae, and papulae in skin reactions of the immediate and delayed type, it was shown that the outstanding feature in every case is the reaction of the capillaries (dilatation, increased permeability of the vascular wall), while the cellular reaction is liable to show marked variations, both in regard to the number of cells and the type of cells involved. In histamine papulae, pressure urticaria and cold urticaria, little if any neutrophils were observed. The urticarial wheal, when specific allergens could be determined,

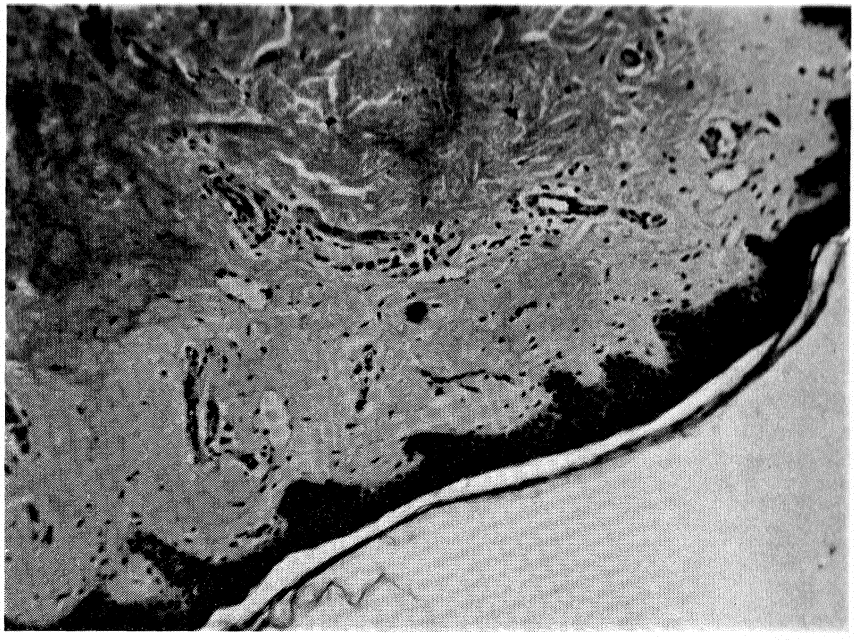

Fig. 5 b.

Urticarial Papula.—With the exception of a slight hyperkeratosis, the epidermis shows no particular changes. The skin, especially the upper layer, is oedematous. The capillaries are dilated and the endothelium is swollen. The walls of the capillaries do not stain homogeneously and show evidence of local oedema. Judging from the site where the extravasated cells have been mainly deposited, the impression is gained that the permeability of the capillary walls has increased locally. The number of cells discharged by exudation is relatively small. These cells consist of lobed and eosinophilic leukocytes. The neutrophils predominate. Roughly, the ratio is 3:1. (Dr. Vossenaar) February 2, 1957.

was characterized by high eosinophil and neutrophil counts; much fewer cells were observed in the urticarial papula when no allergic constitution was detected. Cell counts ranged from low to high in skin tests and large numbers of infiltrating cells were found in the 24-hour-old bacterial papula.

In the swollen capillary wall, using period acid-Schiff stain, red colored mucopolysaccharide substances are found; these have also been found in some cases in the upper layer of the epidermis.

III. Examination

In the study of the causes of urticarial papulae or Quincke's oedema, it should be determined whether the lesions are due to a single agent or to several. Are there any presdisposing factors involved?

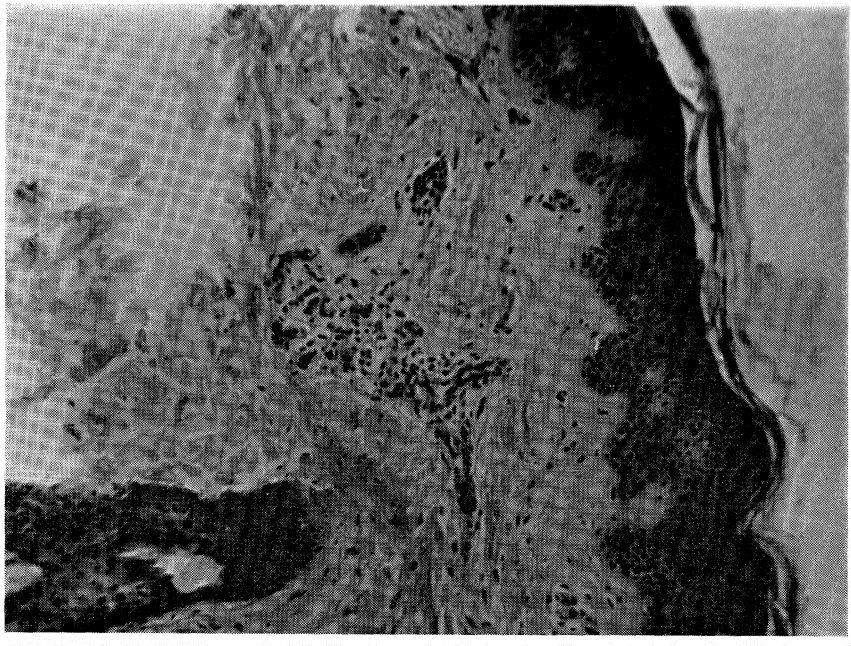

Fig. 5 c.
Urticaria Elevata. Dermographism.—The upper layer of the skin is marked by oedema. The collagenous bundles are readily separable. There are empty perivascular spaces. The endothelium of the capillaries is swollen and the walls themselves also appear to be slightly thickened in places. There are no inflammatory cells. (Dr. Vossenaar) March 5, 1957.

When an allergic origin is considered likely, the history of the patient will have to indicate the presence of one or several allergens, (cosmetics, dietary habits, false teeth, clothing, animals, occupation, etc.). The difficulties involved are apparent from the case reported by Pasteur Vallery-Radot and Blamoutier, in which the causative agent was found to be ordinary drinking-water. Ten Cate reported two cases in which he was able to identify a particular brand of cigarettes to be the cause. Van der Werff reported a case in which the urticarial symptoms in a businessman were attributable to nervous tension, as they always appeared on the occasion of important business talks. A more detailed examination showed that these were accompanied by elaborate lunches and finally the symptoms were found to be caused by a common food allergy. In cases of this type, the history of the patient will have to be examined for the presence of predisposing factors and symptoms suggesting an allergic constitution (family history, other allergic conditions of the patient himself). When attacks occur only at intervals, the patient should be

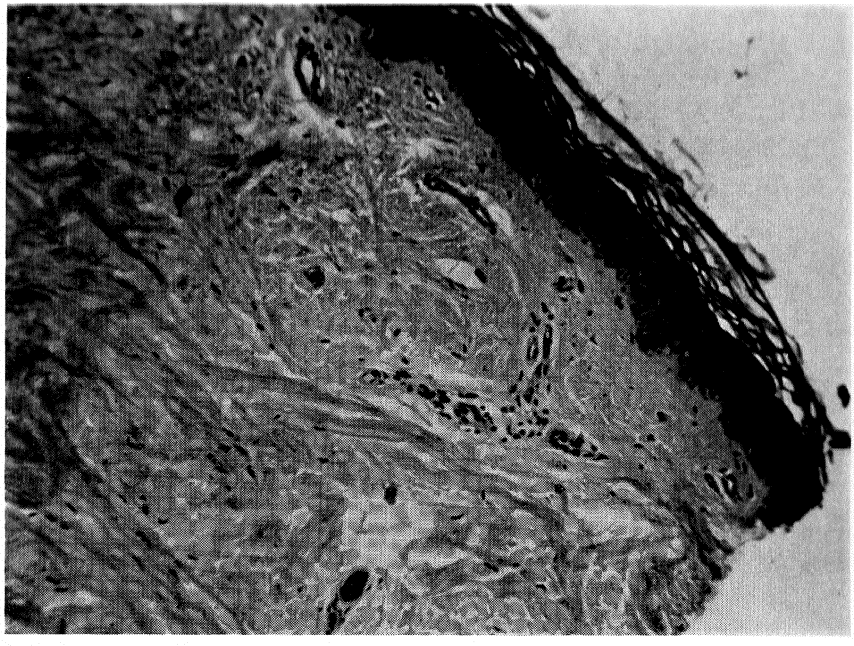

Fig. 5 d.

Histamine Papula.—These specimens show considerable oedema of the skin, which is rather more marked in one specimen than it is in the other, so that the collagenous fibres have been separated to some extent. The walls of the capillaries and the endothelium are swollen. The walls have stained a slightly deeper red locally and are non-homogenous in these areas. The tissues contain no inflammatory cells. (Dr. Vossenaar) February 21, 1957.

requested to note down accurately on each occasion what he did, ate and drank and what he came into contact with during the preceding 48 to 72 hour period. This is essential especially in those cases which are due to rare allergens or in which a particular combination of allergens gives rise to the outbreak of the symptoms.

Further examination is conducted according to the following general outline:

(1.) The patient is examined for allergic stigmata (eosinophilia, hypotension, low blood sugar levels, absence of free hydrochloric acid or low hydrochloric acid levels in the gastric juice revealed by the fractional test). In some cases, the histamine provocation test may indicate the part played by histamine in the appearance of the symptoms. Histamine administered by iontophoresis (Walker) occasionally does not only induce the normal local reaction, but also induces a systemic reaction: new urticarial papulae are seen to appear and previous papulae will completely recur.

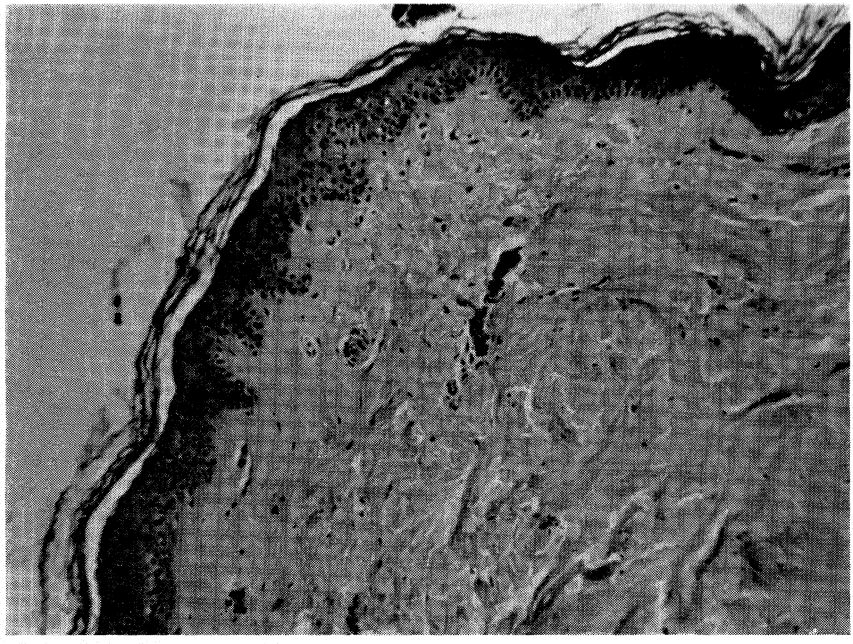

Fig. 5 e.

Reaction within 15 minutes after house dust test.—The epidermis shows marked hyperkeratosis. One half of the skin is characterized by severe oedema. The capillaries in this region show marked swelling of the walls and endothelial linings. A number of eosinophils are observed in places on the external surface of the wall. (Dr. Vossenaar) April 8, 1957.

(2.) The patient is examined for the presence of an internal disease, in which case the urticaria may be a complication of this condition (infectious disease, leukemia, etc.).

(3.) The social and environmental conditions are examined for a possible origin of emotional tension.

(4.) An examination is made to detect the causative agent which may be allergic or psychogenic in character. In examining the patient for possible allergens, the fact should be borne in mind that reading the results of skin tests is often difficult owing to the rapid response of the skin to stimuli, including non-specific ones, resulting frequently in false positive reactions. It is advisable to keep the dose of the extracts at the lowest possible level (the smaller the dose injected, the less likely the non-specific responses will be, although the concentration used is also an important factor in these tests).

In addition to intradermal, prick or scarification tests, a number of patch tests (cosmetics, wool, nylon, etc.) will undoubtedly have to be considered in patients with urticaria. The fact that no satis-

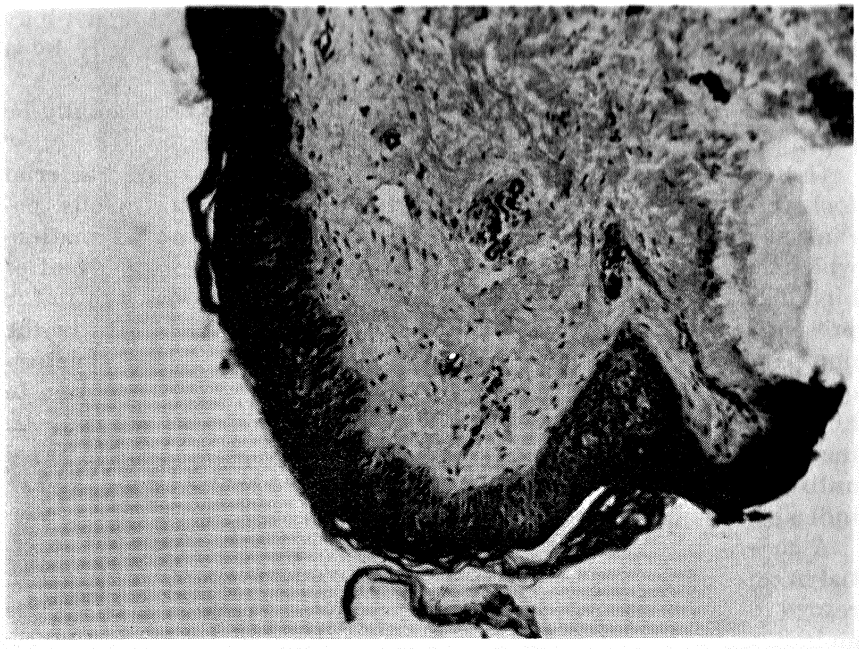

Fig. 5 f.

Papula obtained approximately 24 hours after a bacterial test.—The epidermis shows some hyperkeratosis. The skin is slightly oedematous. The number of capillaries affected is relatively small. These capillaries are characterized by marked swelling of the walls and endothelial linings. There is slight chronic inflammatory infiltration of the pericapillary regions. The collagen of the skin also shows some swelling in places. (Dr. Vossenaar) March 3, 1957.

factory results were obtained in skin tests in a number of cases, induced Jiménez–Díaz and Arjona to develop a serological method: the microprecipitation test in which the serum of the patient is examined for antibodies. Elimination diets and/or provocation tests are frequently helpful. Occasionally, the leukopenic test (Vaughan) and the thrombocytopenic test (Storck) may also be useful in hospitalized patients. The principle of nephelometry (Hoigné, Cormane) and the gel-diffusion test (Ouchterlony, Augustin) apparently offer great potentialities in drug allergy.

It should be pointed out that the examination may fail in some cases, as the onset of the symptoms is due solely to a combination of allergens. In addition, the incomplete digestion of foods, resulting in the assorption of larger molecules, may induce reactions to these larger breakdown products. In these cases, treatment with acidol-pepsin, liver extracts and pancreatic extracts may occasionally be successful.

In cases of urticaria due to photosensitivity, a roentgenologist may be requested to determine if the reactions are induced only by a certain length of the spectrum.

In cold urticaria, the Prausnitz-Küstner test may occasionally be positive (Bruun).

(5.) An investigation should be made for parasites and bacterial foci which might cause the sensitivity reactions: teeth, tonsils, paranasal sinuses, gall-bladder, intestines etc. In the stool examination, which should be performed several times (especially in the event of high blood eosinophilia), particular attention should be given to the presence of worms and worm eggs, as well as to variations in the non-pathogenic intestinal flora, which may be detected by bacteriological methods of culturing. Jiménez-Díaz has drawn attention to histamine-producing organisms among the intestinal bacteria. An increased erythrocyte sedimentation rate, leukocytosis, increased antistreptolysin and antistaphylolysin titres, etc., may provide an indication in these cases.

A general internal examination of the patient, undoubtedly essential in cases of chronic urticaria, may be of considerable importance in regard to treatment. The detection of a concommitant anemia will be an indication for iron therapy, the finding of diminished hydrochloric acid levels in the gastric juice for hydrochloric acid and pepsin administration, impaired liver function tests for corresponding treatment and the results of gall-bladder examinations may suggest surgical intervention.

IV. Treatment

The two main objects in the treatment are: (1) suppression of the present attack; (2) prevention of future ones. Treatment will vary according to the length and frequency of attacks.

In the event of an occasional acute attack of short duration, treatment will be confined to the administration of drugs such as 10 ml. of 10 per cent calcium gluconate or levulinate, injected at a very slow rate and possibly combined with an antihistaminic drug which may be given orally or subcutaneously. A subcutaneous injection of 3 ml. of adrenaline (repeated if necessary) may provide rapid relief, especially in oedema of the glottis.

These drugs will also be resorted to in the treatment of persistent severe attacks; their administration being continued for days in some cases. This treatment may have to be combined with injections of vitamin K (which also has an effect on the increased permeability of the capillary walls). When food allergy is believed to be the cause and it has not been possible to determine the offending

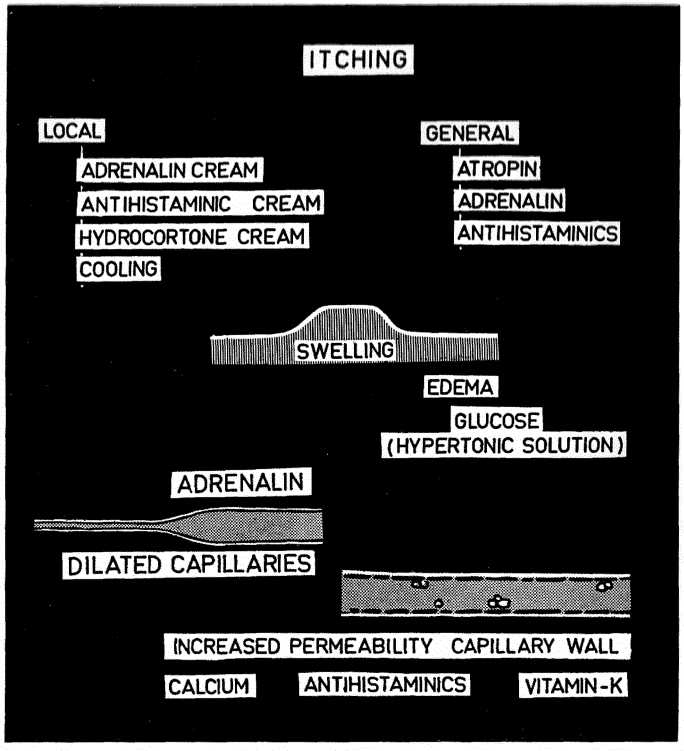

Fig. 6.
Therapeutic measures against the various manifestations of urticaria.

food, the patient may be put on a hunger diet for a few days, the diet being composed only of water and apples or rice, if tolerated. Aspecific treatments, intramuscular injection of 20 ml. of the patient's own blood, fever-producing injections of sulphur, or an injection of 10 mg. of lobeline may be very useful in some cases. ACTH or adrenal cortex preparations may be administered when other treatments have failed.

Prevention of subsequent attacks requires determination and elimination of the cause. With certain allergens i.e. pollen, dust, elimination is sometimes impossible, so that desensitization is indicated. When several essential foods are involved, their elimination could be a handicap to pleasure in life or rule out the possibility of composing a sufficiently adequate diet. In this event, the question arises as to whether any results may be obtained by desensitization treatment, administration of propeptans, peptone, histaminase or an antihistaminic drug given preventively.

Finally, there is the treatment of chronic recurrent urticaria. In

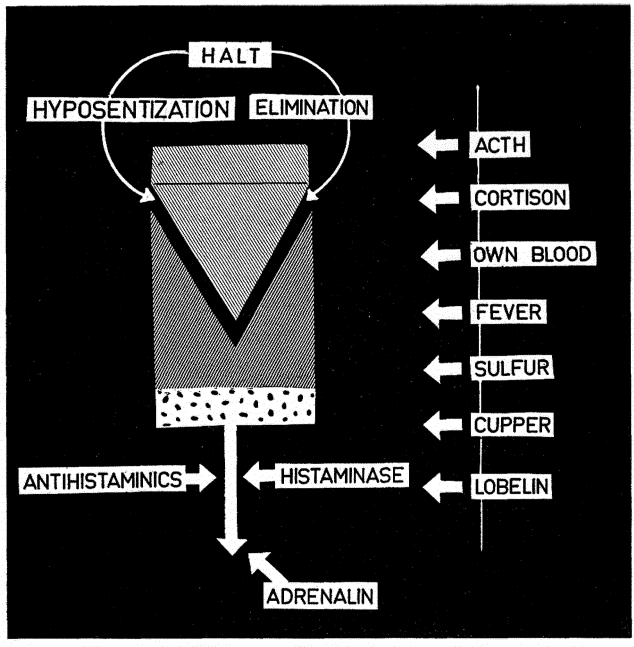

Fig. 7.
Principles of the general treatment of urticaria.

this case again, general measures to control the itching will be indicated; treatment with atropine, phenobarbital, preparations of strontium and cold ablutions being useful in some cases. Specific methods such as elimination and desensitization and non-specific therapies e.g. intravenous injections of calcium, administration of vitamin K, histaminase, antihistaminic substances or a few drops of ichthyol (ichthyol, 10; distilled water, 20;10 drops dissolved in a large quantity of water three times daily after meals) can also be employed in this condition. Treatment with histamine, daily by iontophoresis, the initial dosage being small and gradually increased to larger ones given at longer intervals, or by injections which may be successfully combined in some cases with staphylococcus toxoid, as well as non-specific stimulation therapy using peptone, sulphur, auto-hemotherapy, bacterial vaccines; an alternating acid alkali diet (Pasteur Vallery-Radot), a ketogenic diet and treatment with ACTH and corticosteroids may be prescribed.

Difficult cases are those in which the urticaria is of physical origin. In cases of cold urticaria, elimination is feasible when the symptoms occur only when swimming in cool water. Precautions may be taken against heavy exposure to sun's rays but not against

ordinary cold rain, the cold winter air or the intense light of spring. Histamine therapy may be successful in some cases. Results may occasionally be obtained in cold urticaria by gradually accustoming the patient to cold ablutions, the washings being initially confined to brief spongings of an arm or leg with cold water; subsequently, the ablutions are slightly prolonged and extended to other parts of the body until finally the whole body can be washed with a cold sponge.

When the rays producing the symptoms in urticaria solaris have been determined, careful desensitization may be attempted using artificial sunlight or another type of irradiation.

In urticaria due to exercise, strenuous physical efforts have to be avoided during the period when symptoms occur, henceforth, rejection of the patient from military service will be unavoidable and strenuous athletics will often have to be refrained from for the time being. As a rule, non-specific treatment will be indicated in these cases. Results may occasionally be obtained by gradually increasing the amount of physical exercise, strict attention also being paid to adequate ventilation. Closely supervised breathing exercises combined with kinesitherapy, progressively more vigorous, may sometimes keep the patient almost entirely free of symptoms.

Difficult cases are those with pressure urticaria and severe dermographism in which allergic factors usually do not play a part. In the rare cases, in which they are involved, considerable improvement may be obtained by eliminating these factors. Treatment with calcium or injections of vitamin D has been successful in certain cases, administration of a thyroid preparation being effective in cases marked by a decrease in basal metabolism.

The fact that this already extensive list of possible methods of treatment might undoubtedly be doubled by adding a number of drugs also regarded as useful by some investigators, clearly shows the difficulties (and disappointments) frequently encountered in the treatment of chronic urticaria. This will especially be the experience of those who make it a rule to constantly adopt the same methods of treatment, consisting always in the administration of the same antihistaminic drug in the same dosage, liquid calcium, cortisone and a routine diet. The more accurate the examination and the more carefully the precipitating causes have been determined, the greater the chances of success will be. In certain cases, one should also have the courage to state that an allergic origin seems unlikely, as neither the history of the patient nor the examination have revealed any allergic stigmata. This type of case will frequently respond to psychotherapy.

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ALIMENTARY AND GASTRO-INTESTINAL ALLERGY

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Alimentary Allergy is an expression used to signify that whole complex of allergic reactions which are the consequence of the action of allergenic foods on living organisms particularly susceptible to such foods. This term does not imply to a special organic localization; any vascularized tissue can be the site of an allergic reaction caused by foods.

Gastro-intestinal Allergy is a term used to indicate allergic reactions taking place in the stomach and intestines. This expression, however, very often includes allergic symptoms and syndromes localized in the upper part of the digestive tract, the oral cavity and esophagus, as well as in the associated glands, the liver and pancreas.

ALIMENTARY ALLERGY

A food allergen may be defined as an alimentary substance capable of producing, in a specific manner, an allergic manifestation. Any foodstuff practically may be considered as possessing allergic properties, nevertheless, some cause allergic reactions more frequently than others, either because they have a greater allergenic potentiality or because they are eaten more often.

The nature of the food is a more important factor in alimentary allergy than the consumed quantity. A food can be allergenic in its activity as soon as it is ingested in a sufficient quantity. If a particular food, however, has not produced a sensitization, no allergic reaction will ensue no matter how great the ingested quantity. On the other hand it is not enough that a certain food acts allergenically in order to produce an allergic reaction which is clinically perceptible, it is also necessary that the ingestion involves a quantity which exceeds a certain threshold of tolerance. That is to say that an allergic reaction always occurs in the tissues whatever the quantity of the allergenic food may be, however the reaction does not always reach an intensity whereby the internal equilibrium is upset in such a way that clinical symptoms and signs are revealed.

Every person has a certain margin of tolerance in respect to allergenic foods which is particular to his individual case. Furthermore, his threshold of tolerance is variable and influenced by various factors: climatic, endocrinological, metabolic, emotional and others, causing a more or less pronounced susceptibility to varying quantities of the allergenic food.

Every region in every country has types of foods which are characteristic of that particular region; consequently certain foods are of more statistical importance as allergens in certain regions than they are in others. For this reason, it is of little general value to draw up lists of allergenic foods as to their relative importance, as so much depends on the local eating habits. The hypothesis that the frequency of ingestion of certain foods determines their major statistical and etiological incidence has received much support and is based on a sound foundation. According to this concept, the fact that wheat, milk, and eggs produce ailment in such a large number of patients can be explained by the daily and repeated ingestion of these by the majority of the population. Bearing in mind, however, that these foods might possess a greater allergenic potentiality, it must be taken into account that they are eaten in larger quantities than any other food.

The preparation of the foods is also of importance, e.g. a prolonged cooking can diminish the allergenic property whereas frying might bring about the creation of new allergens. Powdered milk, however, does not seem to lose its allergenic property to any great extent in comparison to milk in its natural state.

A food-induced allergic manifestation may start immediately after the ingestion of the offending food, or occur only some hours later. In the former case, the allergen is the food as such, while in the latter it is possibly a product derived from the original food during the process of digestion. If, for instance, a few minutes after eating an egg, a patient develops gastritis, evidenced by pain and vomiting, the offending cause is the egg itself, whereas if the symptoms only develop several hours later, it is in all probability a substance derived from the egg through the action of the digestive juices, either a peptone or a polypeptide. This is the reason why skin tests with certain food extracts may show a negative reaction, although the ingestion of the same food produces allergic disorders. Results obtained with food extracts during the various phases of digestion have supported this hypothesis in many cases.

An unknown world of germs, fermentations, putrefactions and complex processes of a physico-chemical nature which take place in the intestines must be the source of an immense quantity of allergenic substances of which we know very little, originating from food-

stuffs but chemically and biologically different from the foods we eat. This is the reason why skin tests with food extracts permit only an evaluation of a small part of the vast problem of alimentary allergy.

Beverages may either contain allergenic substances from their original ingredients or acquire them through industrial treatment. This is e.g. the case with barley which may produce allergic symptoms when drinking beer or when patients allergic to rye drink whisky made from rye.

What has been said of foods applies to *condiments* as well.

Pathology.

The allergic reaction produced by food allergens is similar to that produced by other substances with allergenic properties (inhalants, drugs), the histologic differences being only of a quantitative rather than of a qualitative nature.

The human organism has a limited number of ways in which to react and possesses only a few physiological resources in the face of an immense range of physical, chemical and biological stimulants. In allergy, we are always faced with an *aseptic, specific and particular inflammation* presenting the general characteristics common to all inflammatory processes. In last analysis, perhaps, everything is reduced to merely quantitative differences and differences of combination within a sole reaction type, so far unknown. I hereby refer, of course, to the special case of food-induced allergy.

Against the action of the allergenic food or as a consequence of the produced inflammatory process, the mesenchyme will react by transforming a part of its fixed cellular reserve, endowing it with a migratory and phagocitic power. This is why, after the allergenic food has exerted its action for a certain length of time, and in proportion to the intensity of the inflammation, there appears in the infiltration, cells which are non-hematogenous, among others also plasmocytes, having various missions of which we still have only slight knowledge. The plasmocytes indicate a response from the mesenchyme which has been called into action through the allergen. They are not characteristic of allergy inasmuch as they appear in all types of aggression in the tissues.

In relation to the action of the allergenic substance, distinct types of antibodies are formed, probably in the mesenchyme and in the reticulo-endothelial system: *reagins* mainly found in atopic allergy and *precipitins* in the anaphylactic type. Other antibodies of the type that produce immunity are also formed in cases of allergy, such as the "blocking" or "neutralizing" antibodies which do not, like the reagins, have the property of sensitizing the skin, and which are

circulating. Jiménez Díaz and his collaborators have described circulating *microprecipitins* whose ability to produce flocculation *in vitro* serves as a basis for this special method of diagnosis.

Symptomatology.

Food induced allergic reactions do not always reach such an intensity that they cause a clinical disturbance felt by the individual and which can be observed objectively by the physician; the histologic reaction may indeed occur silently. In some cases there is "restitutio ad integrum', while in others, after a certain length of time, definitive organic lesions are produced. In these latter cases the result is a diminution of the adaptive function of the affected organ, in which the insufficiency only appears clinically when these organs are called upon to act at optimum under conditions of maximum stress. At other times, even during the process of adaptation to vital circumstances, considered as normal and habitual, the failure or deficiency of the organs may become evident, and that is when the "state of illness", which has started long before in a silent form, becomes apparent. It is in this manner, for instance, that some cases of periarteritis nodosa and endarteritis obliterans must be explained, although the hypothesis of allergic pathogenesis has, at present, much support. I have seen nasal polyps caused by alimentary allergy whose development started with a simple edema without any appreciable clinical symptomatology, and ended with a blocking of the nasal passages, which subsequently disappeared after the elimination of the offending food from the diet. I have also seen cases of multiple recurrent nasal polyps which required surgical removal of some of them, and which disappeared through a change of diet.

The phenomenon of alimentary allergy is a functional one, but when occurring repeatedly in the same place, definitive organic lesions may appear. The possibilities range from a clinically silent to a violent reaction involving various clinical signs and symptoms which can be expressed in syndromes and clinical pictures. It is to this aggregate of allergic reactions, that customarily the name of *clinical allergy* is given.

Certain clinical reactions in connection with alimentary allergy take place with such a speed and intensity that, when coupled with certain physio-pathological characteristics, they permit a diagnosis of human *anaphylaxis.*

Cases of asthma, rhinitis or neurodermatitis due to foods can, when a hereditary predisposition of similar syndromes is confirmed, allow a diagnosis of atopy. Even if the existence of *common, non-reactive allergy,* described by Coca, is the subject of much discussion, it is quite certain, however, that this extensive group of allergic re-

actions is brought about in a majority of cases by foods (urticaria, migraine, gastritis, colitis, subcutaneous edemas, etc.).

Nothing is more changeable in form as the symptomatology of food-induced allergy. It does not depend on the food itself, but on the sensitized organism and every allergic individual has one or more tissues which react with preference to an allergenic stimulus. Where there are various organs in a sensitized state (shock organs), it is possible that some of them are prepared earlier or more intensely than others and, when brought into contact with a sufficient amount of allergenic substance, they will react simultaneously or successively with varied intensity, according to their distinct degree of sensitivity. When a patient suffers from *allergic rhinitis,* it is because the mucous membranes of the nose have been allergized, while in those suffering from *asthma,* the tissues of the bronchioles are the site of sensitization. There are patients who, after eating an egg, react with eczema, whereas others may be afflicted with urticaria or migraine.

Many different hypotheses have been proposed to explain the localization in distinct organs. Perhaps the pre-existence of a non-allergic inflammation can bring about a condition whereby the allergic substance circulating in the blood will become localized and pass on to the perivascular tissue at the moment the capillaries become permeable. This is how it can be explained, for instance, that after an infectious bronchitis, an allergic asthma caused by foods can develop.

There are no clinical signs or symptoms which are pathognomonic for alimentary allergy. In principle, any vascularized organ can react in an allergic manner and on account of an allergenic food. The phenomenon of alimentary allergy can provoke a clinical response in any part of the body where medicine has established those artificial barriers which constitute the battle-field of distinct specialities. That is why every physician, whatever his speciality may be, needs a knowledge of the fundamental principles of alimentary allergy.

Diagnosis.

In order to diagnose an alimentary allergy it is necessary to prove that at least one food is responsible for the clinical symptoms and that this food, innocuous to the majority of people, has previously been in contact with the tissues of the organism.

The presumptive diagnosis of alimentary allergy is made on the basis of the patient's history. Many of them will easily connect the ingestion of certain foods with the appearance of cutaneous, gastro-intestinal, respiratory or other symptoms, whereas others are unaware of this correlation.

When during the interview with the patient, it is revealed that the

symptoms appeared within a few minutes after eating a particular food, the skin test with an extract of the suspected food will often result in a positive reaction whereas they generally remain negative when several hours have elapsed between the ingestion of the food and the appearance of the clinical symptoms. The reason for this, as previously mentioned, is that in the first case the allergen is the food as such, while in the second case, it is a by-product of digestion.

Skin tests. The tests which have given most satisfactory results are the intradermal tests, although they present a greater risk than the prick or scratch method. Patch tests are only exceptionally used in alimentary allergy.

Some allergologists advocate making a great number of skin tests, including all the foods which comprise the usual diet as well as those which are only occasionally eaten, while others prefer to reduce the number of tests to the habitual foods. Some use also extracts of predigested foods.

In order to avoid the risk of side reactions it is advisable that the extracts used for intracutaneous tests be standardized chemically so as to determine their allergic strength. It is recommended to use the Kjeldahl method of total nitrogen determination, a method used by many allergologists in the U.S.A. Even if it is correct that direct data on the allergenicity are not obtained, since it is not a biological evaluation, the results in medical practice are sufficiently good. With the exception of fish and dry fruits (almonds, peanuts, etc.) in which an evaluation of 0.001 mg. of T. N. (total nitrogen) per cc. is used, an amount of 0.05 mg. of T. N. per cc. is used for the other foods. In egg and milk extracts, a direct dilution is made, 1–100.000 or more for egg and 1–100 or 1–10 for milk. Taking into account that a test with egg extract can cause a violent reaction, it is preferable not to perform this test by the intracutaneous method in routine skin testing. In the list below are specified the foods which the author generally uses in his own patients in Buenos Aires. Every allergologist, however, should adapt this list according to the local eating habits.

milk	apple	cabbage	rice
egg	spinach	lamb	lemon
wheat	oat	squash	fish
potato	pea	peach	pear
sweet potato	tea	chicken	strawberry
beef	orange	coffee	cocoa
corn	pork	tomato	barley
carrot	bean	lettuce	
onion	lentil	banana	

The belief that a positive skin reaction with an allergenic extract is a certitude of the discovery of the causative agent of the clinical

picture which is studied, has lead to grave errors in judgement and therapeutic failures, which have disappointed many physicians and patients.

When faced with a positive skin reaction in general, and in this particular case with food extracts, it is first necessary to ascertain its specificity and therefore if it is of any clinical value. For this reason all other substances which are not allergenically related to the one which has created the state of sensitivity, should be incapable of producing an identical reaction.

A specific positive reaction with a food indicates that the patient has become allergic to it as a consequence of a previous contact. This, however, does not necessarily mean that this substance is the one causing the clinical symptoms.

When a specialist in allergy is asked for advice he is not only expected to give merely the results of skin tests but to give his opinion regarding the causes provoking the allergic illness and the way of treating them. The difficulty in regard to skin tests does not lie in the technique nor in the reading of the results, but in the choice of the test to be made, their interpretation, and the establishment of a relation between the results and the clinical symptoms.

Skin tests with foods can give *immediate, delayed* and *recurrent* reactions. The immediate reaction reveals an allergy to an integral (undigested) food; the delayed one can have a relation with an allergenic by-product through digestion, and the recurrent reaction can be interpreted in both ways.

The following remarks regarding the practical value of skin tests with foods should be pointed out:

1. They are of no value unless all precautions have been taken which guarantee their specificity (inadequate pH, dermographism, etc.).
2. A negative reaction does not permit one to state that the ingestion of the food will not produce the appearance of the clinical symptoms.
3. They constitute only a part of the diagnosis of alimentary allergy; they can direct one in the detection of the offending food.
4. They do not permit full information concerning all of the alimentary allergenic substances which have previously acted upon the patient.
5. They make it possible most of the time, even though by approximation, to estimate the intensity of the clinical reaction.
6. A positive cutaneous reaction is not a certainty, nor does a negative one invalidate the diagnosis of food-induced allergy.

The reactions of the micro-precipitants. This method has been devised by Jiménez Díaz and his collaborators and consists in the demonstration *in vitro* of specific micro-precipitants. Even if somewhat complex, this technique lies within the scope of experimental biochemists; the important matter is the interpretation. Considering that under normal conditions and even in cases of hepatic integrity, heterologous proteins pass through the blood stream, it is only logical to accept the existence of specific antibodies of the precipitating type as a process of immunologic adaptation. The existence of anti-food micro-precipitants could indicate a biological defence, but it is not necessarily evidence of clinical allergy. The ingestion of foods that have produced micro-precipitants does not always give rise to clinical manifestations. Notwithstanding, the knowledge of the existence of these antibodies can serve as a guide in the composition of test diets.

Test diets. These diets consist of a limited number of foods of little allergic potentiality and known as being well tolerated by the patient. In regard to the short length of time they are applied, it is not essential that they comply with the criteria of a correct dietetics, contrarily to the *elimination diets* which, after the offending food has been evidenced, must be followed for a prolonged period of time, and require an exact evaluation as to constitution, quantity, adequacy and balance.

Taking into account that the types of food vary from one country and region to another, these diets will differ accordingly. The physician must adapt his method by introducing such modifications as circumstances require: age, constitution, economic situation, dietary habits, financial possibilities, etc. Every case presents an individual problem requiring particular consideration.

Test diets have exclusively a diagnostic purpose, but can, under certain circumstances, turn out to be therapeutic from a symptomatic point of view. It is important to use them with care and not to prolong the dietary restrictions over a long period of time because of the risk of inadequate nourishment, which may result in serious consequences. Five days might be sufficient, or one or two weeks might be necessary, all according to the prevailing circumstances.

Rowe, in particular, has emphasized the method of alternating diets. This consists in prescribing a well outlined diet to the patient, which after a few days and according to the results is changed to another well defined one. When cure or evident improvement has been obtained, and in accordance with the observations made, the diet is enlarged with other foods which have proved to be tolerated. When a diet turns out to be harmful the allergenic substance among the components must be determined.

Rinkel prescribes a very restricted diet to be followed for four days consisting of only a few foods. Then, using special food tests, he proceeds with a careful study of the variations in the arterial pulse and of the clinical reactions with the object of identifying the offending foods. This technique is complicated and requires special training.

Coca's method relies on the pulse rate. According to this author, when there is an alimentary allergy of the *non-reactive type*, a slight or marked tachycardia is produced which permits identification of the causative agent. This technique is also complicated, time consuming, and requires special conditions for study.

The method of subtractions and additions consists of omitting from the diet the foods which most frequently cause allergy. After a variable number of days, the eliminated foods are added again and the results of elimination and reincorporation are noted. The addition of new foods can be done either individually or in groups, according to the circumstances. The time of observation for each new addition can be 24 hours or extended over two or more days. The allowed quantity of the food as well as the number of times it is to be eaten is variable and depends on many factors which are impossible to outline here.

Vaughan proposed the exclusion of groups of foods which are botanically related. This has proved useful in the case of cereals, but was not found to be practical with other groups. The pattern of the allergic vegetable substances is interrelated in a way which is not always in accord with the morphological classifications used by botanists.

Sanchez Cuenca advocates, in certain cases, a water diet for 48 hours. Less restricted diets permit in addition to water, glucose, amino acids, mineral salts and olive oil.

In establishing a minimum diet, the clinical picture, the age of the patient, his state of nutrition as well as the psychological aspects and eating habits, should be taken into consideration.

In cases of allergic syndromes of moderate intensity it is advisable to use not too restricted diets without limitations as to quantity. The choice of the foods should be made amongst those which are statistically known of producing the least number of allergic cases under the conditions in which the patient lives. Among many possible diets I have prepared the following for my own patients in Buenos Aires:

Breakfast and light lunch:

tea, sugar,
ham, olives, corn, walnuts, almonds,
honey, compote of pears or peaches.

Dinner and supper:

soup from permitted vegetables,
pork, lamb, chicken,
sweet potatoes, squash, carrots, turnips, celery, green peas,
lentils, lettuce, onions,
porridge, cornstarch,
peaches, pears, apples, bananas, grapes,
jam and compote of the permitted fruits,
compote of sweet potatoes and squash,
water, olive oil, salt, sugar.

During the investigation period, the choice of the foods is more important than the quantity. This does not mean that there is not a quantitative threshold, but this is more of a problem in the therapeutic type of elimination diets.

Some allergologists prefer to compose the test diet according to the results of the skin tests, permitting those which gave a negative reaction and omitting those which gave a positive one. Others rely on the case history and exclude those foods which, according to the patient's experience, have caused symptoms as well as those which are botanically or allergically related to them.

Urbach has devised the method of the propeptans. This method has proved useful to some authors, while it gave discouraging results to others. It is costly, requires sufficient competence and the possibility of being able to procure the specially prepared propeptans.

Prognosis.

The state of allergic sensitivity, once established, generally lasts throughout life although some patients occasionally experience a spontaneous disappearance of the allergic condition. It is, doubtful if this occurs in a definitive form; in the great majority of cases, as is met in certain forms of alimentary allergy, the repeated ingestion of the causative food will produce the allergic symptoms, even if it has been eaten without any inconvenience whatsoever for many months or years. These facts cannot be anticipated when making a prognosis, but they must be pointed out as a possibility.

Whatever may be the clinical manifestation of alimentary allergy, the prognosis will depend on various factors including: the competence of the physician, the mentality of the patient, the nature and ubiquity of the allergenic substance, the intensity and time of exposure to the food, the degree of allergic sensitivity, the interest of the patient in his own cure, as well as the possibility of undergoing an adequate treatment.

A patient who is not able to follow the dietary instructions and

who does not assist the physician with personal observations, diminishes the possibility of being cured.

A distinction should be made between a cure of the syndrome, in the sense of a suppression of the clinical picture, and an improvement in the allergic state. The prognosis of the former, which is of immediate interest, is excellent as long as the cause can be eliminated; the patient stops being ill even if he continues to be allergic.

More reserved is the prognosis in neurotic patients, as psychogenic reactions of the organism, through conversion or conditional reflexes can clinically be very similar to those of an allergic nature. They may complicate the latter or succeed them and thereby cause apparent failure in the treatment.

In case of pure alimentary allergy without complications nor the involvement of allergens of a different nature, the prognosis should be favourable provided the technique of anti-allergenic therapy is mastered and the patient is cooperative. When other etiologic factors intervene, such as inhalants or bacteria, the prognosis is conditioned to some extent by the possibility of treating those successfully.

Treatment.

The treatment of alimentary allergy consists primarily in the elimination of the offending food or foods from the diet. This abstinence must be carried on for a variable period of time, lasting at least several months, in order to allow a spontaneous improvement of the allergic sensitivity. In the immediate reacting type of food allergy the elimination may last for all time.

As a rule the results of hyposensitization, either parenteral or by the ingestion of increasing quantities of the allergenic food, have been disappointing.

The author is not in favour of the method of skeptophylaxis consisting in the ingestion of a small quantity of the offending food one hour before a meal comprising the same food, nor with the method of polypeptones specially prepared for producing skeptophylaxis. Without doubt these procedures have permitted the ingestion of the allergenic foods without major inconveniences, but as no opportunity is given for spontaneous hyposensitization, (which I prefer to call hypertolerance), it is necessary to continue throughout life the administration of peptones before eating the food. This method might prove temporarily practical, but it is not a safe procedure, nor is it totally satisfactory.

The symptomatic treatment of alimentary allergy does not differ from that of other allergic syndromes. Adrenaline and substitutes, ACTH, adrenocorticoids, derivatives of theophylline and the syn-

thetic antihistamines are the drugs of choice in emergency treatment.

In exceptional cases, where the avoidance of the offending food is not possible, one can try to raise the tolerance for it. Even if, for the moment, it will not be possible to obtain a true suppression of the acquired specific sensitivity, one can bring about a raise in the threshold of tolerance. This does not mean a higher resistance, so for this reason I prefer to use the term "hypertolerance" instead of "desensitization" when referring to this treatment.

The use of foods which have been industrially treated or modified have made it possible to tolerate greater quantities of the allergenic foods. This, for instance, is the case with powdered milk that has been predigested and condensed, and also with caseinates of calcium. There are, however, some patients who will not derive any benefit from this physical change in the food. The drying process will, to a certain extent, diminish the allergenic property, but does not suppress it entirely. It is, nevertheless, worthwhile trying. The method of boiling milk for half an hour and replacing the amount of water which has been evaporated, has given satisfactory results in many cases. With infants it is preferable, of course, that cow's milk be replaced by human, goat or donkey milk but it should be remembered that certain allergenic ingredients can pass through the mammary filter and that the infants may suffer from an allergic reaction due to a food eaten by the mother.

Rinkel recommends that after a long period of exclusion the offending food should be reintroduced once or twice a week in normal quantities for a period of a few months, according to the degree of tolerance, and never more than once in a single day. As a further prophylactic measure he recommends to vary the quantity of the foods.

If, in a diet, the elimination of a particular food is prescribed, this applies of course, at least in the beginning to all of the products derived from it, whether industrially treated or manufactured, as well as to all food preparations in which it is contained. In cases of milk sensitivity, for instance, cheese, cream, butter, milk bread, milk sauces, desserts made with milk, etc. must also be prohibited. Only after having made certain that some by-products can be eaten without risk, can the physician allow their reintroduction into the diet.

Gastro-Intestinal Allergy

Etiological Factors.

Foods and drugs are the most frequent causes of gastro-intestinal allergy. The intestinal system possesses a rich and varied pathogenic and saprophytic flora, together with fungi such as *Candida albicans*

and other fermentative agents which all possess allergenic properties and have to be taken into consideration when making an allergic investigation. Intestinal parasites, whether macroscopic e.g. tapeworms and nematodes, or microscopic such as amoebae, may act in the same manner.

Microorganisms found in other parts of the organism, for instance, tonsils, bronchi, teeth, paranasal sinuses and even in the skin, must also be considered as possible causes of allergy of the gastro-intestinal tract, until the contrary has been proved.

Injected substances, such as insulin, vaccines, antibiotics, sulphonamides, hepatic extracts, insect bites, etc., can cause local allergic reactions in the digestive system. The same applies to allergenic extracts injected subcutaneously during desensitization treatment.

Pathology.

At present there is no histological picture which is pathognomonic of allergy. This means that the pathologist, without knowledge of the circumstances which have caused the inflammation in the tissues he examined on a slide, is unable, in this way, to make a safe diagnosis of allergy. We must at present resign ourselves to the fact that even if the allergic inflammation is characterized by an increased amount of eosinophil cells, this only permits a presumptive diagnosis. In order to obtain a confirmation, we must therefore consider the circumstances which have caused the aseptic and specific inflammation characterized by a high content of eosinophils.

Every inflammation implies:

Vasomotor phenomena,
disturbance of the capillary permeability,
disturbance of the interstitial perivascular ground substance,
disturbance of the lymphatic circulation,
excitation of the nerve endings,
cellular activity of the mesenchyme,
spasm of the smooth musculature.

The stomach and intestines constitute a long membranous canal into which flow the secretions of the glandular organs, the liver and pancreas. The digestive tract, which is susceptible to inflammatory reactions and for that reason subject to intense *congestion* by capillary vasodilatation, and to edema due to disturbance of the permeability of the interstitial ground substance of the tissues, can be the site of clinical symptoms, characterized by a diminution of the intestinal diameter and a reduction of the sphincters (cardia, pylorus, Oddi), causing stasis, obstruction, colic, vomiting, etc.

When the allergic inflammation affects the digestive system it will create various symptoms, signs and syndromes, and as these can be clinically similar to those produced by other diseases, they require a careful differential diagnosis. In this respect the possibility of an allergic origin should be considered from the beginning and the diagnosis should not be made *per exclusionem*.

Diagnosis.

In order to make the diagnosis of allergy when faced with a gastrointestinal clinical picture it is necessary to identify the etiologic factor and to establish that this substance, innocuous to most people, has been in contact with the tissues of the digestive tract at a previous time. A substance which has acted allergenically, and tissues of the digestive tract which have been qualitatively altered in their manner of reacting, are two indispensable factors for producing the clinical picture of *digestive allergy*.

The fact that a patient is allergic does not imply that his gastrointestinal complaints will be of an allergic nature. He may be allergic to milk, for instance, causing an eczematous skin lesion, but his digestive tract might not be allergized, or he may develop pollen asthma and suffer from an enterocolitis or a gastritis of a nonallergic nature.

The diagnosis of digestive allergy can either be based on a presumption or be established with certainty.

Presumption of Allergy.

As the allergic reaction takes the form of an inflammation, any aseptic inflammation in the digestive tract permits a presumptive diagnosis of allergy. The presence of eosinophil cells in the tissues, secretions and/or excretions from the digestive system, as well as an increase in the blood eosinophilia are also presumptive but not pathognomonic signs. A personal or family history of allergy supports the presumption.

Another method of making a presumptive diagnosis of allergy is by exclusion of all other possible etiologies, infection, intoxication, neoplasms, etc. This should, however, be only an exceptional procedure. When faced with a characteristic clinical picture the possibility of an allergic origin should be considered from the beginning and investigations made accordingly.

When a digestive manifestation appears to be related by cause and effect to a substance which does not have any pathogenic action, whether a normally consumed food or a drug in a therapeutic dose, it is suggestive of allergy.

The same applies when the symptoms improve or disappear upon

administration of adrenaline, ephedrine, synthetic antihistamines, ACTH or prednisone.

Certainty of Allergy.

As there are no pathognomonic signs of allergy one cannot make a certain diagnosis of allergy unless the allergenic substance has been identified or tests have been made proving its specific pathogenic action.

These have been summarized by Sulzberger in the following manner:

1. A positive elimination test: an improvement or disappearance of the clinical manifestations, in the course of a reasonable period of time after the elimination of the suspected allergen.
2. A positive reappearance test: the exacerbation or reappearance of the manifestations in the course of a reasonable length of time after the reintroduction of the suspected allergen.
3. Complete cure or improvement as a result of specific treatment against the suspected allergen.
4. Favourable effect of a treatment, recognized as being effective against diseases produced by microorganisms, suspected of being the cause of the allergy.
5. The existence of immunity reactions or characteristically changed responses, before a clinical or experimental reinfection.

As an allergen is any substance which will specifically cause a state of allergy, then in a case of presumptive allergy, a substance which will fulfil all or some of these conditions, especially the first two requirements, can be considered as the cause of the allergy.

The differential diagnosis is difficult if one takes into account the number of factors capable of producing a similar clinical symptomatology. Moreover the digestibility of the allergenic foods will complicate the problem, as does the probable formation of new allergens from basic foods, and the existence in the intestine of bacteria, parasites and fungi of which little is known. Putrefactions, fermentations, infectious enteritis, neoplasms, digestive insufficiencies, psychogenic influences, etc, constitute some of the factors which must be taken into consideration.

Treatment.

The treatment of food allergy, regardless of its localization, has been delt with in the first part of this chapter, and the same applies to allergy of the digestive tract caused by foodstuffs, condiments and beverages.

Treatment of allergic manifestations of the digestive tract caused by germs and fungi consists essentially in the administration of antibiotics and antimycotics. In case the septic origin is located outside the digestive tract, it should be treated by medical or surgical means.

If a drug is the cause of the allergic manifestation, it should be completely avoided by ingestion, injection or any contact, whether vaginal, conjunctival or cutaneous.

Adrenocorticoids and ACTH should be used with caution in cases of digestive allergy. In patients with a previous history of gastritis, ulcers and hemorrhages, there is a relative contra-indication which will develop into an absolute one if these symptoms are active at the time of treatment.

Symptomatic non-specific medical treatment is indicated in allergic syndromes provided the patient is not allergic to the drugs he is prescribed.

An effective psychotherapy is important particularly in those patients who, after having been afflicted with allergic digestive syndromes for a certain period of time, have trouble with their conditioned reflexes and mental difficulties of adaptation or even neuroses which will make the symptomatology, diagnosis and treatment more complicated.

Allergic Gastritis.

The following signs and symptoms may be produced by an allergic process taking place in the stomach or outside the gastro-intestinal tract and exerting its action by a neurogenic way.

Clinical symptoms: nausea, vomiting, gastralgia, postprandial drowsiness, acidity, gastrorrhea, cardiospasm, colic, hematemesis, pyrosis, regurgitation, belching.

Radiologic signs: defective filling, spasms, hyperkinesia, pseudo "niches", signs of inflammation of the mucous membranes, disappearance of the folds of the mucous membranes, atony.

Gastroscopic signs: congestion, edema and swelling of the mucous membranes, submucous hemorrhages.

Laboratory findings: hyper-, hypo- or anacidity.

The symptoms may vary in intensity and appear either immediately or some minutes or hours after the ingestion of the offending substance. When the allergen is eliminated, the symptoms will disappear after a variable length of time.

General symptoms, such as fatigue, asthenia, irritability, nervosity, a feeling of intellectual inferiority, mental unbalance, etc. can indirectly be the result of an allergic gastropathy.

Edema of the mucous membrane and spasms of the gastric musculature are the characteristic signs of an allergic process which can be

evidenced by the gastroscopist or by the radiologist by mixing the allergen with the contrast medium. The presence of eosinophil cells in the gastric juices is also a characteristic finding.

Hemorrhages and necrosis may at times be produced by a severe allergic reaction and an intense, prolonged allergic inflammation may also cause atrophy of the glands of the mucous membrane, resulting in anacidity.

The following facts will permit the physician to make a *presumptive* diagnosis of allergic gastritis.

Improvement or cure obtained by a change in diet or the elimination of a drug the patient was using.

Positive skin tests of the immediate or delayed type with food extracts, bacterial substances, fungi, organic extracts, antibiotics, etc. with which the patient had come into contact at the time.

Aggravation produced by a particular diet.

The failure of all therapies used to cure a gastric syndrome which erroneously was not considered as allergic.

Ulcerative gastritis which is not improved with a milk diet (a possible sensitization to milk and its derivatives).

A personal or family history of other allergic manifestations such as asthma, eczema, urticaria, hay fever, Quincke's edema etc.

The finding of a blood eosinophilia.

When previously certain foods have not been well tolerated.

When the symptoms are improved by synthetic antihistamines, adrenaline, ephedrine, or adrenocorticoids.

When the erythrocyte sedimentation rate is normal.

The following facts permit a *reliable* diagnosis of allergic gastritis:

Cure or evident improvement of the symptoms after a sufficiently long period of adequate administration (ingestion or injection, etc.) of the suspected allergenic substance.

Cure or improvement in the clinical picture obtained through a specific treatment directed against the suspected allergenic substance.

The evaluation of the signs and symptoms by the case history and the clinical radiologic and laboratory findings make it possible to establish a presumptive diagnosis, while in order to make it a certitude, it is absolutely necessary to identify the causative factor.

In the case of allergic gastritis caused by drugs, their elimination is the final solution to the problem. The same applies to condiments. When it is a question of germs from foci of infection, the elimination of these if possible, is the best procedure.

When the causative food belongs to the category of those which are not indispensable or at least rarely eaten, one can use the treatment of hypertolerance, which is prolonged and requires the cooperation of

the patient; a favourable result can, however, not be predicted or guaranteed. Treatment in this case should start with a small quantity of the causative food, either in aqueous solution, in powder form or prepared in the same way in which it is ordinarily eaten. The quantity should be gradually increased every day according to the amount which the patient has been able to tolerate.

It is not possible to establish if the administration per os is better than by injections (intra- or hypodermic), but the first method is without doubt less dangerous. Fatal accidents have occurred with the injection method and this has never happened with the administration per os correctly carried out. Quite frequently, after months of treatment, whatever the chosen method might be, the result is a complete failure.

Gastric and Duodenal Ulcer.

Gastric and duodenal ulcers have been considered by some authors as having an allergic etiology. It is the author's opinion that they may be the consequence of a Shwartzman phenomenon located in the submucous membrane, or of an intense allergic inflammation of the mucous membranes with necrotic centers which later, by the action of the digestive juices on a certain area of the tissues without defence, will finally become ulcerated. In such cases, from this point of view, the ulcer would be a complication, the allergic phenomenon constituting the first phase of a process in two stages. As far as this problem is concerned we are, however, dealing with hypotheses.

Gastro-Enteritis.

In dealing with the subject of allergic gastritis the clinical consequences of the allergic reaction located in the stomach have been described. Rarely, however, is a gastric reaction found without participation of the intestine; in practice most frequently a combined gastric and intestinal symptomatology is observed.

Entero-Colitis.

The allergic inflammation located in the intestines may cause constipation, diarrhea, colic, anal pruritus, acute abdominal pain, appendicitis, intestinal obstruction, ulcerous colitis, etc.

The chronic but not very intensive allergic inflammation may be the cause of *constipation;* in such patients a diet in which the offending food has been eliminated will result in a normalization of the intestinal function. It is for instance not exceptional to hear from patients with other allergic manifestations due to alimentary causes that their digestion has been improved at the same time as they were

relieved of their asthma or eczema because they were put on a diet by the physician. It might be that the constipation has been cured by the indirect action of an improvement in the general gastro-intestinal condition or for other reasons, but it is, after all, certain that even if it is not prudent to make the diagnosis of allergic constipation, it may be included among the symptoms of a more general picture of gastro-intestinal allergy.

Diarrhea is a symptom which is more often connected with an allergic phenomenon. It may start a few minutes after the ingestion of a particular food or not until some hours later. Positive skin reactions with food extracts may or may not be found. By means of X-rays, using contrast media to which the allergenic food has been added, it is possible to evidence the processes of hyperperistalsis and even of spasms and edema which explain the diarrhea, the constipation and the partial obstruction, in rare cases even developing into occlusion. It is difficult to find eosinophil cells in the feces in cases of severe and very liquid diarrhea; it is however recommendable to make the examination and when found, they are an excellent basis for a presumptive diagnosis of allergy.

Intestinal colic may be the result of the attempt of the intestine to overcome an allergic edema which partially or totally obstructs the lumen of the intestine, or it may be the consequence of the action of chemical transmitters on the smooth muscle fibres of the intestines. It is sufficient to remember the discharge of histamine and acetylcholine in the area of an allergic reaction, which also explains the gastric hyperacidity. In some cases of intestinal occlusion with an "acute abdomen", the laparotomy has shown an extensive edema and serosity in the affected zone. The opportune administration of adrenaline has made it possible in some cases to avoid unnecessary surgical intervention.

The existence of acute and chronic *appendicitis* of an allergic nature must also be admitted. The differential diagnosis with an infection is difficult and is a great responsibility. When in doubt, it will be wise to incline in favour of a diagnosis of infection. Sooner or later a pure allergic appendicitis will favour anyhow the development of a secondary infection. Even the most experienced physician cannot make a safe diagnosis of an allergic appendicitis at the bedside of the patient and on the basis of the case history only. Nevertheless the existence of certain facts and a previous knowledge of the patient will permit a competent diagnostician to arrive at the conclusion of a presumptive diagnosis of allergy.

Even if it is not possible to ascertain that all cases of chronic ulcerous *colitis* or the totality of their symptoms are of an allergic nature, it is, however, certain that many patients are cured or ex-

perience a marked improvement when an offending food has been found and then eliminated from the diet. In these cases the infection will act as a concurrent cause together with the allergy and complicate the clinical picture. The possibility also exists that the colitis may be the consequence of a bacterial allergy complicating a primary infectious colitis; in this case the allergic inflammation prevents the cure and will favour the ulceration as a consequence of the action of the digestive juices and other irritating and proteolytic products of the intestinal contents. Treatment with adrenocorticoids combined with antibiotics has given excellent results, and this is, perhaps, due to the fact that the adrenocorticoids eliminate the edematous and infiltrative allergic barrier and thus permits the action of the antibiotics. In the present state of our knowledge we ought not to send patients to the operating table for ulcerative colitis without first having made a thorough study of the allergic component of this disease.

A rectoscopic examination will provide important information in regard to the condition of the mucous membranes.

Addendum

Stomatitis and *glossitis* can be of an allergic nature, they are characterized by redness, prurigo and edema. Their differential diagnosis from other forms may be difficult.

The majority of cases of *pharyngitis* are due to bacterial allergy. In addition to pruritus, a slight mucous secretion, an edematous aspect and congestion of the adenoids will be found.

Some of the symptoms which trouble certain patients with gastric allergy correspond, in part, to *esophageal* allergy, e.g. the feeling of a lump in the thorax and dysphagia.

It is very probable that certain cases of *hepatocellular jaundice* have an allergic origin. The interlobular tissue may constitute an excellent shock organ, and the edema located there may cause compression of the biliary intrahepatic ducts and also changes in the metabolism and nutrition of the hepatic cells causing jaundice through biliary intrahepatic compression.

Painful epigastric syndromes and vesicular colic have been observed in the absence of biliary lithiasis as a result of alimentary allergy. Furthermore, after cholecystectomy, some patients continue to complain of the painful syndrome of the right hypochondrium which had motivated the surgical intervention and which in certain cases could be cured by the elimination of an offending food. We now have sufficient experience to justify the necessity of making an allergic examination in all patients suffering from colic or a

painful vesicular syndrome before submitting them to surgery, even if there are signs of lithiasis or of infection of the gall bladder. The allergic factor may be the only cause or be a partial one, and both hypothesis should be clarified before running the risk of an operation.

The existence of allergic *pancreatitis* has been considered and may be possible. The difficulty lies in the diagnosis and in the ascertainment that the whole process has exclusively an allergic origin. It is, however, important to take allergy into account either completely or in part.

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ALLERGIC CONDITIONS OF THE EYE

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Intensive studies on the nature of allergy and anaphylaxis during the last ten years have convinced most of us that while any or all of the tissues of the human body may be involved in the trauma of an allergic attack, it is not only not usual, but indeed rare for the whole body to be involved at any one time. Rather does one organ, as the lungs or the nose, takes the "shock" of the attack, or indeed just one type of tissue or group of cells of one organ, as possibly the mucous membrane of the turbinate area of the nose or the glomeruli of the kidneys. The eye is no exception to this, since an allergic response may appear as unilateral or bilateral conjunctivitis, keratitis, iritis, choroiditis, etc., or two or three of its tissues may be involved simultaneously. Why a given tissue should become the central or shock tissue at any one time is not clearly understood, but perhaps the most generally accepted explanation is that of some previous trauma, either prenatal or postnatal, involving the affected part. Such trauma might be due to infection, to biochemical upset, or to psychological catastrophe. There seems no doubt that nerve tissue, either central or peripheral, may be the apex or allergic abuse on many occasions not always easily distinguished from other types of disease of the nervous system.

Investigation.

As in other branches of medicine, so in ophthalmology some conditions are now accepted as often, if not always, due to allergy; some as occasionally due to allergy, while in some the allergy may be suspected but very seldom able to be proved. The investigation of allergic conditions of the eye differs very little from those involving other organs, though greater caution is recommended in any positive local diagnostic tests, such as attempts to prove a suspected allergic cause by giving a provocative dose of an allergen, e.g., applying pol-

len grains to the conjunctiva when investigating a case of conjunctivitis during the hay fever season. The provocative inhalation of allergens such as feathers or animal danders may precipitate a dangerous increase in pressure in a case of acute closed-angle glaucoma. It is perhaps not sufficiently well-known that patients allergic to grass pollen may have their most severe recurrences of glaucoma during the late spring or early summer, usually, but not necessarily, accompanied by rhinitis and conjunctivitis.

As in all branches of specialized medicine accurate history taking is of paramount importance. There are thousands of possible allergens for any one patient, and one cannot do thousands of skin tests or even hundreds of trial diets on each patient, so a lead must be obtained from the history. In all cases of recurrent disease where allergy is suspected, details of the first attack, such as the season of the year, the time of day or night, foods eaten during the previous eight hours, contact with unusual drugs, atmospheric dusts or moulds, wood preservatives or paints, artificial fertilizers or weed killers should be recorded. Social stress, more often mental than physical, may be the trigger factor which turns a minor subclinical allergy into a major one and so precipitates an attack of keratitis or iritis. If an ophthalmologist wishes to be his own allergist, then he must be his own psychologist too. Financial burdens, family jealousies, or difficult relationships with one's superiors at work may be the immediate cause of a given attack at a given time and place, but would not be the real underlying pathology of the disease. Alternating manifestations of allergy must be noted; e.g., although ankylosing spondylitis and iritis are often associated in the same patient, the acute exacerbations of the two do not occur simultaneously, but rather as alternating pathologies. This has its parallel in the alternation of eczema and asthma, of asthma and rheumatoid arthritis, or of migraine and psoriasis.

Skin tests are of great importance when carried out by a fully trained allergist using carefully prepared test solutions. It needs a highly skilled technician to prepare testing solutions of the common foods which do not contain some small quantity of free histamine. The presence of histamine has caused many extracts to be so far diluted that no true selective results could be obtained. As the conjunctival and corneal epithelium form a sufficiently dense cloak to protect the other ocular tissues from atmospheric dusts and pollens, one can readily appreciate that most allergic diseases of the eye (other than conjunctivitis and superficial keratitis) are due to some endogenous process. It has been fashionable during the last twenty years to look for, and often find, some positive allergic response to bacterial proteins as a cause of non-granulomatous uveitis; and to

look for, and not find, such a response as a cause of keratitis, either interstitial or of the rosacea type. That foods are even more often the cause of iritis than bacterial proteins are, has been demonstrated recently, especially in those cases of recurrent iridocyclitis associated with chronic indigestion or with chronic rheumatoid arthritis.

A trial dose of histamine as a diagnostic test, when given by electrophoresis with a standard direct current for a varying time, so very helpful in an asthma clinic, has its uses in eye conditions as well. It is extremely useful in helping to decide whether a given patient with headaches or dizziness is really suffering from a true allergic migraine or from an allergic Ménière's disease, but is to be used with caution on patients with potential iritis, retinitis, glaucoma or other possibly irreversible processes. It is unwise to increase the dose beyond the point where a generalized histamine flush develops. The delayed, intracellular type is not exhibited by this test. Recently, it has been established that a patient who gives a clear positive selective allergic response to his skin tests of some inhalant or of some food, may exhibit either the immediate or the delayed type of iritis, as his own particular clinical manifestation of that allergy, that is, if the iris is his "shock" tissue. So far, there has been no demonstration that these two types exist simultaneously in the same patient, though there is no proof that they do not.

Treatment.

As in investigation of ocular allergy, so in treatment should there be little difference from the methods employed by clinicians responsible for the management of asthma, eczema, etc. It is very important for ophthalmologists to realize that a patient with allergic asthma or allergic migraine may present with recurrent corneal ulcers which may, or may not, be due to the underlying allergic state of the patient. As in all recurrent diseases, the clearing up of the present attack and the prevention of any future attacks are two different problems. Skin tests for allergy should be included in the routine investigation of any patient where no definite infection or systemic disease has been proved as the cause of his ocular condition: but even when a positive allergen has been found, a period of at least four weeks avoidance of that substance or substances is necessary before one can say that it may be playing a part in the etiology of the recurrent ocular symptoms. During that month, a short period of a few days treatment with either antihistamines or steroids is permissible. This should help to distiguish the type of lesion as either the extracellular, immediate type which responds to systemic antihistamine treatment, or the intracellular, delayed type which

responds well to hydrocortisone or other steroids. It is important to remember that while antihistamines locally or by mouth will occasionally relieve a conjunctivitis, keratitis, etc. due to atmospheric dust, mould or pollen, they often will not do so when a food is the offending allergen. In food allergy the mucous membranes of the gastro-intestinal tract are often oedematous and may not absorb medicaments given by mouth. A more rational method is to give one millilitre of Anthisan or Phenergan by intramuscular injection every twelve hours until relief is obtained, to a maximum of six millilitres.

In the more external of the ocular lesions, eye drops or ointments of Antistin, adrenalin, ephedrine, hydrocortisone, etc., may remove the symptoms temporarily, but will not prevent the recurrence of trouble. For the more deep-seated lesions antihistamines or steroids by injection are quicker and more effective in their action. As soon as the lesions have been healed by a short course of local or systemic treatment, and have not recurred during the weeks of "avoidance" of the suspected allergens, it is necessary to consider preventive measures. These may be:

(1) by continued "avoidance".
(2) by one or more courses of desensitizing injections.
or (3) by frequent treatments with histamine by electrophoresis, to reduce the allergic state of the patient.

Preferably, especially in the case of those potentially blinding diseases as rosacea keratitis, or recurrent iridocyclitis. A combination of all three methods cannot be too strongly recommended. Of (1), all that need be said is that much general knowledge and common sense is required to know how to avoid, strictly, any given allergen. Much better results will be obtained with (2) if the substances being injected are avoided while the desensitizing course is in progress. The same applies to (3), especially since the offending allergen acts as an uncontrolled liberator of histamine into the "shock" tissues. Histamine as a therapeutic agent has been used on and off for many years, but only recently has a satisfactory and easily controlled method of application been used on many ocular patients. Details of this method were published by Walker in 1953 for the treatment of eczema, and in 1957 for the treatment of asthma.

Results.

The percentage of good results obtained by using the methods of investigation and treatment enumerated above has increased year by year as knowledge and understanding of the subject has improved. The common denominator of all these cases where allergy has been

proved, and of many where it has been missed, is that elusive "allergic state". The ideal of every allergist must be to find some non-specific way of changing this more and more towards the "normal state" for the human individual. In this sense, all allergic eye conditions must be regarded as systemic rather than local abnormalities. While remembering that any ocular tissue may be the "shock" tissue, one becomes aware that the cornea and the iris seem to be more prone to allergic response.

Special mention must be made of *Rosacea Keratitis*. Though only 10 per cent of all cases of keratitis seem to come into the allergic group, a much greater figure (80 per cent) is obtained in a subgroup of those where the corneal lesion is associated with rosacea. Rosacea is the presenting symptom of an abnormality of the superficial epithelium of the face in adults between the ages of twenty and forty years. An attack may last a few weeks or months, but tends to clear up only to recur again at increasingly frequent intervals, eventually being accompanied by ocular manifestations, varying in degree from a mild conjunctivitis, through all the stages of blepharitis, tarsitis, and tarsal and bulbar conjunctivitis to keratitis and eventual visual incapacity. It cannot be emphasized too often or too strongly that every case of true rosacea is a potential candidate for the "blind" list. This condition should be arrested before marginal vascular infiltration shows that the cornea is involved. Recurrences can be prevented if the underlying allergic cause can be found and avoided while systemic anti-allergic treatment is given. By annual retesting and repetition of treatment if necessary, further deterioration of vision can be avoided, but so far no way has been found of removing corneal deposits once they have been formed.

Recurrent Iritis is becoming an important problem in our increasingly allergic world. The iris is a "diaphragm of blood vessels and unstriped muscle fibres held together by a very loose spongy stroma" (Parsons and Duke Elder) and is therefore an ideal setting for an acute anaphylactoid reaction. Allergic iritis may be primary, in that it is the first tissue to manifest an allergic attack due to some endogenous product of metabolism or infection, or secondary, due to some drug used during the treatment of other ocular disease or operation. Whatever the cause or type, routine dilation and other local treatment is urgent and will be greatly assisted by systemic treatment, by injection rather than by mouth, with antihistamine or steroid, according to the type of allergy (immediate or delayed), for two or three days but not longer. As soon as the acute attack is over, every effort must be made to identify the offending allergen to that it can be avoided in the future, or until some desensitizing treatment has been given.

TABLE 1
Frequency of Ocular Allergies.

Tissue	More than 75 % of cases proved allergic.	Occasionally allergic
Eyelids	Contact Dermatitis. Angioneurotic oedema. Constitutional eczema.	Blepharitis. Neurodermatitis.
Conjunctiva	Conjunctivitis associated with hay fever. Conjunctivitis associated with contact dermatitis. Phlyctenular conjunctivitis.	Recurrent non-infective conjunctivitis. Vernal catarrh.
Cornea	Phlyctenula keratitis. Rosacea keratitis.	Recurrent corneal ulcers. Interstitial keratitis.
Sclera and Episclera	Episcleritis.	Tenovitis.
Lens	Infantile cataract associated with eczema.	
Uvea	Recurrent non-granulomatous iritis. Phaco-anaphylactic endophthalmitis.	Sympathetic ophthalmia. Choroiditis. Secondary iridocyclitis.
Retina		Recurrent macular oedema. Perivasculitis. Serous detachment.
Optic nerve		Transient papilloedema. Retrobulbar neuritis. Tobacco amblyopia (very occasional).

In treating iritis, atropine has been the constant friend of both surgeon and patient, except in the odd one in a hundred cases who shows a specific allergy to this drug. Many more than one in a hundred are hypersensitive (not allergic) to atropine, being able to tolerate, and be well-dilated by, 1/1000 or ever 1/10,000 atropine solution, though the usual 1/100 causes local stinging and burning. Those who are allergic to the atropine molecule, or the tropine ring, also develop reactions in the surrounding tissue. If these are not very intense and atropine is really necessary, one tablet of an antihistamine given by mouth twenty minutes before each drop of atropine is applied to the eye usually keeps the condition under control during a short attack of iritis; but in severe cases some other mydriatic is necessary.

From the experience of testing hundreds of eye patients each year

for twenty years, the author would classify the common allergic manifestations of ocular allergy as shown in Table 1. This table agrees fairly closely with that of Boyd published in the most recent edition of Sorsby's "Systemic Ophthalmology". One must remember Osler's diction that "nothing in medicine is ever 100 per cent" and that there is always a ± 20 per cent variation in human reactions.

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ALLERGY IN VASCULAR AND COLLAGEN DISEASES

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There is evidence at present that the allergic mechanism is involved in the pathogenesis of vascular and the so-called collagen diseases. However, the extent to which this influence is exerted is as yet somewhat obscure. There is doubt as to whether it simply assists in the production of these conditions, together with other mechanisms, or plays a radical role. The viewpoint held will largely depend on the limits set as to what "allergy" actually is and on whether it should be narrowly defined as an unusually marked reaction due to antigen-antibody action. The diseases discussed here possess a series of features which differentiate them from those usually termed "allergic diseases", such as asthma, urticaria or hay fever. In the latter group the symptoms are paroxysmal, with more or less prolonged free intervals in which all symptoms or signs may be absent and in which there is only a latent dysreactive tendency which will become manifest in the presence of suitable conditions (allergens and other modifying factors). In the group of diseases which will be discussed here, the symptoms are more constant and the pathologic conditions persist even in the phases of partial remission; they usually run a progressive, severe course. It might be stated that in the former group there is a prevalence of symptoms and in the latter of lesions, in order to indicate a deeper, less reversible pathology.

Nevertheless, there are numerous reasons of decisive value to support the relationship between both groups of diseases:

1. *In their course.*—In asthma and chronic urticaria it is possible to follow the development from a paroxysmal, mainly functional stage to subsequent stages with deeper widespread visceral symptomatology. In asthma the writer (57) has distinguished a paroxysmal stage, a "pathic" stage and a subsequent angio-mesenchymal stage which is seen only in a limited number of cases of chronic

asthma. It is in this severe course that pulmonary infiltrations, arterial lesions and signs similar to those of collagen disease (periarteritis nodosa, rheumatoid arthritis, exanthema (56—b)) occur. Such severe aspects of the course have also been emphasized by several other writers (Harkavy (48—a, b), Rackemann & Green (92), Turiaf and associates (113), etc.). This course leads to the acceptance of a radical etiopathogenetic relationship. In practice it is often impossible to say when this malignant transformation begins to take place.

2. *In their association.*—In many cases, angio- mesenchymal disease is, indeed, initiated as such, but subsequently the symptoms of arterial and collagen disease are accompanied by urticaria, Quincke's oedema, attacks of asthma, etc., more marked and malignant than usual. It is then difficult to decide whether it is an *addition* or a transformation; in any case however, it indicates a deep-seated genetic relationship. A case of rheumatic fever may run the course of lupus erythematosus (L. E.) or give way to periarteritis nodosa (P. N.). Allergic granulomatosis of the type described by Churg & Strauss (15) is associated from an early stage with an asthmatic symptomatology. Loeffler's eosinophilic infiltration (73—a) may occur in an asthmatic patient and develop into verrucous endocarditis. Angioneurotic oedema may produce pulmonary and vascular symptoms which will subsequently predominate in the clinical picture and thus impart to it their malignant nature.

3. *In the presence of sensitizing factors* and the positive demonstration of specific antibodies. As in the case of primary asthma, sensitization may be proved in vascular and collagen diseases on the basis of reliable evidence. The role of different allergens, foods, inhalants and, primarily, drugs, tobacco, parasitic and bacterial allergens, is undoubtedly fundamental in a large number of cases.

Differences similar to those described in human diseases may be found in the study of the histo-pathology of experimental allergic reactions, according to the method used. The findings may vary from violent phenomena which, when not causing death, are reversible and result in tachyphylaxis, like the anaphylactic shock of the guinea pig, to the necrotic inflammation characterizing the Arthus phenomenon. The reaction may be proliferative, inflammatory (delayed reaction, drug reaction, tuberculin type) or granulomatous. However, oedema of the collagen substance and capillary involvement which may range from hyperpermeability to necrosis, thrombosis and perivascular infiltration according to the severity (Dienes & Mallory (24), Bergstrand (9), Roessle (97)) may be demonstrated even in shock. The Arthus phenomenon is associated with the features of serous inflammation (Roessle), with a more or less severe

cellular reaction, stasis, permeabilization of the capillaries, transudation of plasma in the vessel walls and formation of cellular, mainly perivascular infiltrates of eosinophils, plasma cells and histiocytes. In the initial studies of Guerlach (47), Vaubel (115), Klinge (63) and Roessle (97) with injections of heterologous sera, oedema of collagen and fibrinoid necrosis ("fibrinoiden Verquellung") predominate. One of the facts which had already been suggested by Roessle and subsequently demonstrated by means of direct determination with fluorescent antibodies, is the fixation of antigen in the reaction zone; it is therefore possible to consider granuloma formation as a manifestation of the repeated, local antigen-antibody reaction instead of as a nonspecific secondary reaction. Hyperergic inflammation is probably not only quantitatively but also qualitatively abnormal, as is pointed out by Goddard (42); the granulomatous reaction is marked by endo- and perithelial proliferation, histiocyte accumulations and, in addition, lymphocytes and plasma cells in the peripheral zones. The most essential part of these joint reactions remains to be the vascular and collagen involvement with fibrinoid necrosis, oedema of the ground substance, dissociation of fibrils and formation of infiltrates or granulomata. The variations in the picture obtained depend on the reactive situation and the degree of allergy and immunity present as a result of the technique employed, the dosage and the time of observation. Thus, in recent years it has been possible to produce conditions similar to some of the collagen diseases with heterologous sera or their protein fractions (Rich & Gregory (95), More and associates (83—a, b), McLean and associates (76), Ehrich and associates (27—b), Jiménez-Díaz and associates (58—a), Hawn & Janeway (50), etc.).

The demonstration of these angio-connective tissue lesions with fibrinoid degeneration in certain human diseases prompted Klemperer and associates (61) to propose the term "collagen disease" to this group. By this term it was intended to draw attention to the importance of the reaction of collagen, of vessels and of the connective tissue in pathology. The term, however, has no specific meaning defining a disease, even in the etiopathogenetic sense. Fibrinoid degeneration may indeed occur in numerous diseases of different nature; it has been reported, for instance, in gastric ulcer (Askanazy), in placental vessels in involution (Yarmudian & Kleinerman), in Addison's disease (Holman), in myodystrophy (Ogryzlo), etc. From an experimental point of view, this group of lesions can be produced not only by an allergic mechanism but also by histamine (Heinlein (51)), DOCA and methylandrostenediol (Skelton (103)), methyl-fluor-cortisol (Selye & Dubois (105—b)), and by interference with the kidney, either by uni- or bilateral clamping (Holman (54),

Koletsky (66)), nephrectomy (Grollman and associates (85)), cellophane perinephritis (Zeek and associates (125)), etc.

This variety of experimental procedures, which are discussed in more detail below, indicates a possible etiologic diversity in different cases of the same disease. In a strict sense, allergy may be the cause of these syndromes or it may assist in their development; and in some cases the pathogenesis is independent of allergy. In the sense used by Berger (7), the same disease may originate inside or outside the circle of allergy. In each case and in each type of disease, it is necessary to ponder the role played by the allergic reaction.

Allergic Vascular Disease, Experimental Basis

In a discussion on allergic disease conditions of vessels, different clinical and histopathologic types may be included. In some, the lesions mainly involve muscular, medium-sized vessels, macroscopic form of P. N. (Kussmaul-Maier); in others, they rather involve small visceral vessels, as in hypersensitivity angiitis or the so-called microscopic form of P. N. At times, the lesion is more strictly limited to the wall with fibrinoid degeneration of the intima and media (rheumatic type); at others, there is thrombosis with obstruction of the lumen of the vessel; or there is a prevalence of adventitial reaction and granuloma formation (pathergic granuloma, Fienberg (30–b)).

Such extremely different degrees of intensity likewise correspond to varying degrees of severity and the involvement of a varied symptomatology. The symptoms may be limited, for instance, to the appendix, or to the skin (necrotic arteriolitis, Ruiter (99), Schönlein-Henoch's purpura); however, involvement of various organs and tissues is more frequently observed: single or multiple infiltrates in recurrent outbreaks in the lung, necrotic glomerulonephritis, interstitial nephritis, subacute, extracapillary nephritis or granulomatosis in the kidney. The liver, spleen and also the nervous system may play an important part in the clinical picture. Thus, varied conditions are produced which are similar to those of other diseases and in which the most common finding appears to be the association of multiple organic involvement with outbreaks of recrudescence, fever and extreme general malaise. With regard to the mode of onset, the picture may constitute a deterioration of a preexisting allergic condition: asthma, angioneurotic oedema, later becoming "malignant"; it may be the visceral spread of infection, or of rheumatism, or the disease may begin as such and be of a primary nature. In these cases, the allergic influences, the toxic

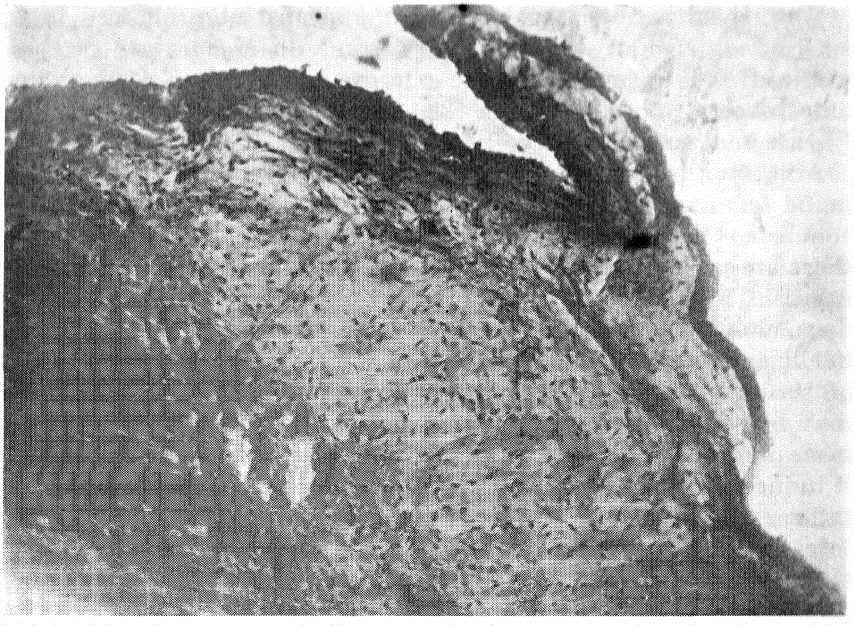

Fig. 1.
Fibrinoid degeneration in the base of the valve.

effect of a drug etc., may be found in the clinical history or on observation, or perhaps no apparent cause may be found at all.

A description of the methods that have been used in the experimental reproduction of these human diseases may throw some light on the problem.

The method of *injections of heterologous sera* was first used by Klinge (63), Vaubel (115), Guerlach (47) and Roessle (97) and subsequently followed by Rich and associates (95) who paved the way for the concept of collagen disease. The injection of serum into the carotid artery of the rabbit between two ligatures (Klinge & Fassbender (64)) gives rise to an adventitial reaction. In the case of an intravenous re-injection into a previously prepared animal, lesions appear in the arteries (renal, coronary, mesenteric) with involvement of the intima in the form of fibrinoid degeneration, frequently associated with formation of thrombi of P.A.S. positive material. The media, in the vicinity of the intima, may exhibit destruction of the muscle layer and fibrinoid deposit; in addition, there is a reaction of the adventitia and periadventitial connective tissue, with infiltrates of lymphocytes, monocytes and some polynuclear cells (Fox & Jones). Thus, the changes obtained bear a resemblance to rheumatic arteritis or to P. N.

With massive injections of serum, repeated at prolonged intervals, or with small, repeated doses, some differences are detected in the effect, respectively on the arteries, endocardium, kidneys and other viscera (More & McLean (83—b), McLean and associates (76), Ehrich and associates (27—b); Jiménez-Díaz (58—a) (fig. 1).

According to the technique used, lesions resemble those of rheumatic fever, or are more extensive in the arterial wall and in the connective tissue and, in addition to the involvement of the latter, there are periarterial infiltrates with true panarteritis and fibrinoid necrosis. By means of repeated injections we have been able to produce, along with necrotic lesions, regressive lesions showing fibrotic healing, and granulomata, particularly in the kidney. With fractions of serum proteins (Wissler and associates (122)) similar effects may be produced. The injection of ox gammaglobulin has largely been used (Hawn & Janeway (50), More and associates (83)), but it induces glomerular and endocardial lesions; the injection of crystallized ox albumin, however, gives rise to arterial lesions. The injection of gamma globulin, provided it is repeated, also gives rise to arterial lesions which in the kidney acquire a granulomatous nature (Heptinstall & Germuth (39) (53)). These variations in the severity and type of lesion probably depend on the time the antigen is present in the blood stream and on the degree of the antibody reaction. The lesions induced by these techniques may thus acquire varying appearances resembling periarteritis nodosa, vascular involvement in rheumatic disease or any other of the so-called collagen diseases.

With the injection of endotoxins the Minneapolis group have also produced arterial lesions with fibrinoid deposit. In rabbits infected with group A hemolytic streptococci, or with pneumococci, the injection of meningococcus endotoxin gives rise to bilateral cortical necrosis of the adrenal glands and fibrinoid deposit in the intima of coronary arteries and in heart valves, as well as to occlusion of glomerular capillaries with fibrinoid material (Thomas, Denny & Floyd (111)). The intravenous injection of endotoxin, repeated after 48–72 hours, gives rise to these phenomena with occlusion of renal capillaries and splenic and hepatic sinusoids with fibrinoid masses (Brunson, Thomas & Gamble (12)). With the injection of sodium polyanethol sulphonate (Liquoid Roche) into rabbits similar lesions are brought about; in the kidney they may acquire the "wire loop" appearance, as in lupus erythematosus (Hausman & Dreyfus (49)). The injection of endotoxin, simple or associated with Liquoid Roche, induces diffuse vascular damage which in many respects recalls human diseases (angiitis, panarteritis, L. E., malignant nephropathy, etc.). (Brunson & Davis (12—b)), included in the group of collagen

diseases and termed "systemic fibrinoid diseases" by these writers; nevertheless, the necrotic-hemorrhagic component is greater and the acute perivascular cellular reaction is, on the whole absent. In rats in cross circulation with others into which endotoxin was injected twice at suitable intervals, the widespread deposit of fibrinoid may also be induced 2–4 hours after the injection, suggesting that it takes its origin in some organ from which it would pass to the blood stream (Gamble & Brunson (35)). Recently, Thomas (111) was of the opinion that the toxic part of the endotoxin may well be the lipidic fraction (Westphal (119)) and the antigenic part the polysaccharide framework; fibrinoid would be precipitable fibrinogen. Simultaneously, endotoxin produces vasoconstriction and raises the sensitivity of vessels to adrenalin and noradrenalin. The resulting increase in blood pressure may help to bring about arterial lesions, since it has also been possible to obtain them by means of vasoconstriction and induced hypertension.

Byrom & Dodson have produced arterial fibrinoid necrosis with the intra-arterial injection of serum under pressure. Zeek and associates (104) (125) produced arterial lesions in rats with the aid of silk perinephritis of one kidney and removal of the other. It begins with fragmentation of collagen in the vascular bifurcation near the entry of vessels into the viscera; the oedema and degeneration of adventitial collagen are followed by an accumulation of fibroblasts in a radiate pattern which may encroach upon the media; subsequently, necrosis and exudative inflammation may be detected together with fibrinoid degeneration and pleomorphic cellular reaction with some eosinophils, histiocytes and fibroblasts. In the subsequent stage of regression granulation lesions are formed and large, fibrotic, vascularized masses are constituted which completely replace a sector of the arterial wall. These lesions would be assimilable to periarteritis nodosa and different from hypersensitivity angiitis in which there is no such predilection for the sites of bifurcation and in which the pulmonary arteries and veins are also involved. Various other methods of inducing arterial lesions with fibrinoid degeneration and features similar to those of human diseases (DOCA and Na; renin; methyl-fluor-cortisol (Selye and associates, Page and associates)), have a similar mechanism. The most severe lesions seen by the writer were those in Grollman dogs where the involvement ranged from initial oedema and fibrinoid degeneration to fragmentation of collagen fibrils and destruction of the muscularis. Muirhead and associates (85) have also described these lesions.

These experimental studies prove some facts which should be analysed before dealing with the conditions seen in clinical medi-

cine. In the first place, it may be concluded that similar lesions may be induced by different mechanisms, allergic and non-allergic (foreign proteins, Shwartzman's phenomenon, hypertension, renal failure, sodium retention) and likewise that certain mechanisms induce mainly a given type of arterial lesion, the greatest diversity in the production of lesions being found in those which bear the closest resemblance to the lesions of periarteritis nodosa. Some writers draw a distinction between periarteritis nodosa and hypersensitivity angiitis, the former being experimentally obtained by hypertension with renal failure and the latter by an allergic mechanism (Zeek (125—b)). However, the injection of proteins also induces lesions similar to those of periarteritis nodosa, which may also appear in serum sickness in man (Clark & Kaplan (16)). The different types of arterial lesion may indeed be produced by the injection of foreign proteins; the technique of injections, the interval between them and the doses vary (Heptinstall & Germuth (53), Jiménez-Díaz (58)). In our experiments with small, repeated doses of serum, the lesions ranged from arteriolo-capillary thrombosis with inflammatory, exudative reaction in the splenic follicles to perivascular granulomata and severe connective-tissue reaction with overdevelopment of reticulin. According to Letterer (69), the result depends on the relation between allergy and immunity. Periarteritis nodosa would correspond to the reaction of the type of Arthus phenomenon with marked hyperergy, with no immunity; the reactions similar to those found in Loeffler's syndrome or in Buerger's thrombo-angiitis obliterans would correspond to chronic, proliferative inflammation of the tuberculin type (delayed bacterial and drug allergy), and granulomata would occur when the degree of immunity is increased. It is however beyond doubt that the lesions obtained in Grollman dogs are different, in so far as the severity of necrosis and type of vessels mainly involved are concerned, from those seen after serum injections. Zeek and associates, who have carried out remarkable studies (104) (125) include all these lesions under the common term of "necrotic panarteritis" but they suggest that within this group hypersensitivity angiitis should be distinguished from periarteritis nodosa.

In the different types of experimental lesions referred to above as well as in human diseases, the lesions of the vessels and of the connective tissue are closely associated. Klemperer's term "collagen disease", which was effective in attaching due importance to this group of diseases, does not seem appropriate since collagen disturbances form a relatively non-specific group of lesions. The term "systemic fibrinoid diseases" coined by Brunson and Davis (12—b) also has the drawback that it merely describes a single aspect which

is not very specific. Even if the transformation of rheumatic disease into periarteritis nodosa is possible, it is obvious that these two morbid conditions are initially extremely different. As has been already pointed out, the fibrinoid deposit occasionally occurs in extremely disparate conditions; according to the findings of Ceballos at our laboratory, even being virtually physiologic in splenic vessels.

The outstanding fact, both in experimental and in spontaneous clinical lesions, is the association of connective tissue and vascular reaction. In respect to the connective tissue, there is a series of stages, some of which may remain undetected owing to their early occurrence or to the violence of the agent, marked by oedema, basophilism, loose transformation of the ground substance with dissociation of collagen fibrils, and fibrinoid deposit; these are followed by cell infiltration, mainly perivascular, and the development of fibrotic cicatrisation and granuloma formation in the neighbourhood of the glomeruli in the kidney. Regarding the vessels, the result is an arteriolocapillary stasis with diapedesis, formation of fibrinoid or hyaline thrombi; a mural reaction which, according to the stage and to the agent, may mainly involve the intima or the adventitia and the media, with fibrinoid deposit, myolysis, segmental infiltration within the wall of the round cells, fibroblasts and histiocytes, with formation of capillarized fibrotic thickenings and scars.

The writer believes that the term "angio-mesenchymoses" may prove more comprehensive.

Symptoms and Signs of Allergic Vasculitis ("Angio-Mesenchymoses") in Clinical Medicine

In clinical medicine these diseases may take on extremely diverse forms with some common clinical and pathologic features which have made their grouping possible, at least to a partial extent. On occasion, the symptoms are restricted to a certain organ, as in the cutaneous forms or in pulmonary infiltration, while at other times the symptoms occur in combination, such as in the nephropulmonary forms, polyserositis or pulmonary infiltration with myocardial symptoms. Finally, the involvement is sometimes extremely widespread or systemic, the symptoms occurring simultaneously or in succession in the skin, mucous membranes, lungs, kidneys, heart, liver, spleen, vessels, nervous system, etc.

Likewise, they may be of benign nature, like many of the cutaneous forms or the transient pulmonary infiltration, though recurrent outbreaks are frequently found. The course may be malignant, which is the commonest finding, in the acute, subacute or subchronic form.

The condition sometimes begins in the form of a severe febrile picture with asthenia, anemia, pallor, dyspnea, oliguria, skin and visceral hemorrhages which may acquire a necrotic nature in mucous membranes; abdominal colics, neuralgia, paralyses, mental confusion, delusions, etc. and death may occur within a few days or weeks. On other occasions, the condition starts as a febrile outbreak with skin manifestations (exanthema, purpura, exfoliative dermatitis, papulo-necrotic eruption) or pulmonary symptoms, with remissions and subsequent relapses marked by increasingly severe fresh outbreaks. Subsequently, increasingly extensive visceral complications (arthritis, nephritis, hemorrhages, status asthmaticus, oedema, polyneuritis, phlebitis, etc.) occur and death ensues in a few months.

In summary, these conditions may be mono-, oligo- or polysymptomatic, malignant or benign, acute, recurrent or subchronic; they may occur as idiopathic forms, in the course of previous allergic syndromes, or as a malignant transformation of a chronic infectious disease. Owing to their pleomorphism, it is convenient, in the writer's opinion, to describe the manifestations in the various organs and then attempt to synthesize the clinical pictures which will be more frequently found in practice.

1. *Cutaneous Manifestations.*

In addition to poorly specific types of skin disease such as erythema, purpura, urticaria, Quincke's oedema, there are more specific types. Ruiter (99) has isolated "allergic cutaneous arteriolitis" which would correspond to a localized form of periarteritis nodosa, as in the case e.g. of the forms described in the appendix. It is characterized by a generally symmetrical eruption in the limbs of urticarioid elements at the apex of which there may be pin-point vesicles or hemorrhagic crusts. It may also assume an appearance similar to that of papulo-necrotic tuberculides (Szymanski (109)). It is associated with peripheral eosinophilia and biopsy reveals involvement of arterioles, capillaries and venules in the chorion with fibrinoid deposit and some infiltration of leukocytes and eosinophils (fig. 2). The eruption may recur without general symptoms or the fresh outbreak may be associated with febricula. In a clinically similar case, the writer found the capillaries filled with histiocytes which obliterated the lumen, in a form that recalled the early appearances of Kaposi's disease. In the type of purpura described by Moschowitz (1925) (84) with fever, pleiochromic anemia and arteriolo-capillary thrombosis, at present called "thrombotic-thrombocytopenic", there is a history of allergy in many of these cases

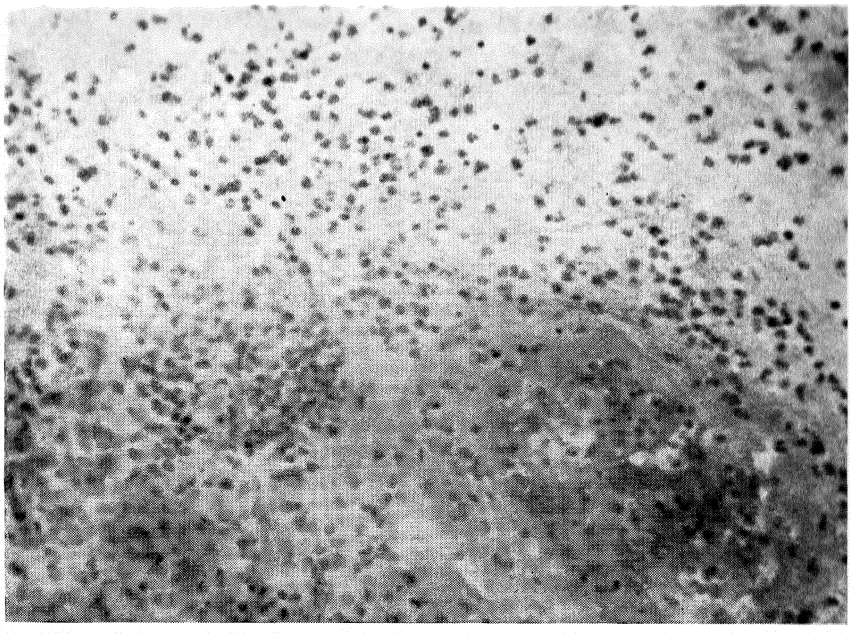

Fig. 2.
Necrosis of an arteriole in the derm.

(Adelson and associates (1)) and there are reasons at present to include it with fibrinoid diseases. The thrombi were initially regarded as being composed of platelets (Baehr and associates (5)); it appears, however, that the arteriolo-capillary lesions occur first. Recently, Craig & Gitlin (21) believe that the lesion is made up of fibrinoid, as in the case of Shwartzman's widespread phenomenon, the material being an insoluble derivative of fibrinogen. In a case seen by the writer, purpura was associated with rheumatoid polyarticular disease, neuromuscular pain, gingivo-nasal hemorrhages, jaundice, hepato-splenomegaly, high fever and hemolytic anemia requiring frequent transfusions.

Purpura of the Schönlein-Henoch type may also be found to be associated with these conditions. The etiology of this type of purpura is extremely obscure. While it is sometimes associated with rheumatism, in the majority of cases the articular condition is not typical of rheumatic disease. On the other hand, cultural examination for group A streptococci, and the investigations of specific antibodies, as in rheumatic fever, are for the most part negative (Bywaters and associates (13); Jiménez-Díaz). Its allergic (anaphylactoid, Glanzmann) nature is, however, obvious in many cases; it may

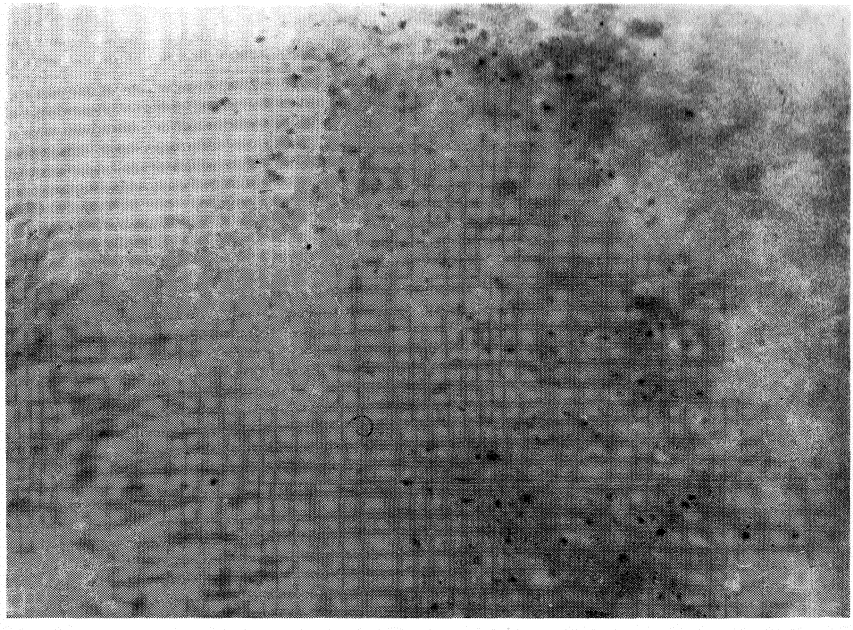

Fig. 3.
Subcutaneous rheumatoid nodule.

then be due to drugs or may be in relation to infective foci (tonsillitis, sinusitis, etc.) or even to foods (Alexander & Eyerman). The frequent relationship to bacterial allergy has been repeatedly detected (Gairdner (34), Storck (107), Miescher and associates (79)). The features of what G. Miescher terms "leukoclastic microbid" may appear on examination of biopsy material.

Schönlein-Henoch's purpura is sometimes accompanied by articular, neuritic conditions, nodules, nephritis—of particular characteristics—etc., and may accompany any collagenosis of severe evolution. The association of purpura with nephritis and other phenomena of vascular disease is similar to what has already been described by Osler in connexion with erythema. Gangrenous lesions of the skin associated with panarteritis (Gilman & Kaess (41)), phenomena of sclerodactylia with Raynaud's syndrome, or even distal gangrenes may occur in these diseases and, in addition, erythema of the marginatum or even multiforme type. Subcutaneous nodules, small as in Darrier's tuberculide, large as in rheumatic disease or juxta-vascular, may also appear in periarteritis. Biopsy study may then be of decisive diagnostic value (fig. 3).

The disturbances in the tongue and buccal mucosa should also be considered. The most frequent change is gingivitis with swollen,

bleeding gums, which sometimes follows a necrotic course, as in cases of Wegener's granulomatosis. On occasions, recurrent ulcers occur in the mouth (Sandler (100)). In an extremely severe case seen by the writer the whole bucco-pharyngeal mucosa was filled with large, necrotic ulcers having a very disagreeable odor.

Urticaria, particularly persistent, and outbreaks of angioneurotic oedema also accompany these conditions. The initial phenomenon sometimes recurs repeatedly before the symptomatology deteriorates.

2. *Respiratory Tract.*

The frequent involvement of the *accessory sinuses* should be underlined. On occasions, the sinus disease is clinically an outstanding feature. In the condition termed "rhinogenous granuloma" by Wegener (118) the complete severe picture developed after an involvement of the nose and sinuses, as in the previous case reported by Klinger (65) in which there was a necrotizing inflammation of accessory sinuses which spread to the mouth, larynx, trachea, esophagus and bowels. The syndrome is completed in the different cases subsequently reported in the literature and is at present known as "Wegener's granulomatosis" with arteritis, sometimes of the rheumatic or necrotizing type.

The sinus disease in this condition is of a necrotic, invading nature and according to Roessle (97—b), may spread to the cranium. However, in other forms of angio-mesenchymosis, sinopathy is also present; in the writer's experience, it is almost always present. Harkavy's cases (48) had sinusitis, some with positive cultures, and a positive intradermal reaction could be demonstrated by injection of an extract of the cultivated germ. In hay fever and allergic asthma, hyperplasia and oedema of the mucosa are produced with cellular, mainly eosinophilic infiltration which are reversible when there is no longer contact with the allergen. This "hyperplastic sinopathy" forms part of the general reaction of the respiratory mucous membranes, mainly in the so-called "intrinsic" or "infectious" forms of asthma (Jiménez-Díaz and associates (56—b) (57)), with which it almost always coexists. It persists in the periods of remission, though becomes frequently infected with the recrudescences of asthma or respiratory infections. The writer regards this sinopathy as one of the symptoms of the "pathic" stage of asthma, i.e. of the development of lesions into the angio-mesenchymal phase in which the recurrent infiltrations occur.

The *manifestations on the part of the lungs* associated with vasculo-connective allergy may be of varying severity. Harkavy (48)

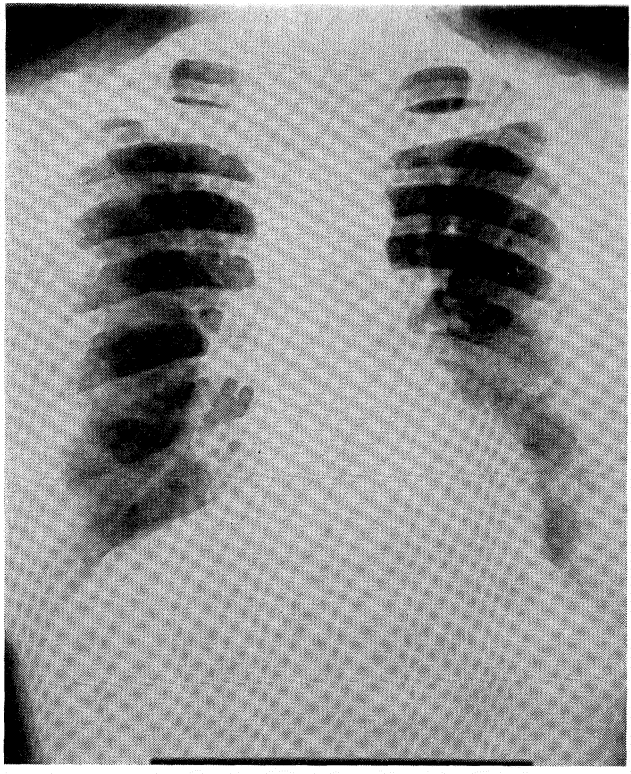

Fig. 4.
Relapsing lung infiltration in an asthmatic patient.

has described vascular infiltrations in the lungs which on occasion resembles pneumonia, from which they differ on x-ray by their less distinct outlines. Other workers, including the present writer (fig. 4), have in addition described the "relapsing asthmatic infiltration" which is accompanied by fever (Rackemann & Green (92), Turiaf and associates (113), Jiménez-Díaz (56—b), etc.). Sometimes the infiltration occurs spontaneously; at other times it is due to the renewed contact with allergens, to the action of drugs (mainly sulphonamides and penicillin), or is the result of an infectious accident. However, in some cases in our experience and in that of other writers, it succeeded an injection of a bacterial extract. The infiltration frequently follows an acute course, after which the general condition disappears though the radiological opacity does not clear up for some time. The infiltrations may also be multiple, of miliary appearance, in the form of small foci with intumescence of the hilia or in an irregular form like streaks or bands. In some cases seen by the writer, it was possible to observe, on successive films, the disappearance of some infiltrates with outbreaks of others in different

zones for several weeks. When the infiltrations are more persistent or recur at more frequent intervals, there is a simultaneous symptomatology which may be extremely varied. Pleural effusion, with eosinophilic features at first, may appear locally and change later on. Harkavy (48) has pointed out the frequent association with electrocardiographic changes corresponding to coronary arteritis or to infiltrative myocarditis, which may be found at autopsy; likewise, pericarditis with effusion may be found in some cases. In addition to asthma, infiltration and polyserositis, hemorrhagic phenomena of the mucous membranes, abdominal colic, digestive hemorrhages due to necrotic ulcerations and, above all, albuminuria, oliguria and development of uremia as an evidence of simultaneous renal disease, may appear as part of a general syndrome in many of the cases of vascular allergy. Attacks of asthma, urticarial eruptions and angioneurotic edema complete these violent pictures. The infiltrate may also develop into a cavity (Sandler and associates (100), Fienberg (30—b), etc.). Pulmonary thrombosing arteritis (Steuder) of eosinophilic nature (Danziger, quoted by Harkavy) may also be demonstrated at autopsy; according to some, this arteritis may be the cause of the subsequent development of hypertension in the pulmonary circulation. Wiessel & Eppinger had already mentioned the pulmonary arteritis which accompanied respiratory virus disease in the 1918–19 influenza epidemic. At present there are some observations, including one published by the present writer, of thrombosing disease of the pulmonary circulation, with pulmonary arteritis and a clinical picture of polyserositis whose etiology, which might be connected with vascular allergy, has not been cleared. Radiologic appearances may be variable; Garland & Sisson (36) have carried out a survey of these in collagen disease.

The relationship between these vascular infiltrations and Loeffler's eosinophilic infiltration (73) poses a difficult question. In characteristic cases Loeffler's infiltration is rather transient and not associated with other severe manifestations; v. Meyemburg (78) proved in a histologic study of 4 cases that there was mainly intra-alveolar exudation with giant cells and some occasional Charcot-Leyden crystals. In one case however, Baggenstoss and associates (6) found interstitial granulomatous lesions and necrotizing inflammation of arteries and veins in addition to the pneumonitic exudate with eosinophils in advanced organization, with fibroblasts and giant cells. Ehrlich & Romanoff (28) described the association of asthma with eosinophilic infiltration and granuloma. Recently, Marsden & Morgan (75) have described a case of Loeffler's infiltration with verrucous endocarditis and granuloma formation in the kidney; in addition to granulomata, there was fibrotic invasion and

hyalinization of the glomeruli. These various features render the case similar to allergic granulomatosis. Other cases such as those of Zuelzer & Apt (127), Schwartz (101), etc. likewise lend support to the transition from the simple, reversible infiltration of Loeffler's type to more or less widespread allergo-mesenchymosis. Even the eosinophilic granuloma of the lung may in some cases be related in the light of histo-pathologic data and clinical history to Loefflers' infiltration, on the one hand, and to allergic arteriopathy (Auld (4)) and periarteritis nodosa, on the other; it may be due to an attenuated antigen of prolonged action. It would appear that in the course of asthma the vascular system acts as shock tissue in a significant manner; in experimental asthma of the guinea-pig sensitized to egg (Jiménez-Díaz (56–b)) and of the rabbit (Cannon and associates (14)) vascular lesions are detected. In bacterial asthma this angio-mesenchymal development takes place more easily though it is probable that other dysreactive conditions are required to explain why this happens only in a limited number of cases.

3. *Heart.*

Mention has previously been made as to the occurrence of pericarditis in the forms with an acute evolution. In the majority of cases, the effusion is reabsorbed in the long run and the clinical and radiologic signs may become normal. Nevertheless, a syndrome of backward heart failure with engorgement of the jugular veins and congestive hepatomegaly may remain in some cases. This picture may indicate the presence of concretio cordi, but it may also be due to rigidity of the right ventricles through a process of fibroelastosis. Loeffler (73—b) described endocardial fibroelastosis with eosinophilia. Subsequently a large number of cases have been reported in the literature; the cases seen by our group (Ceballos & Ramírez Guedes) include some with a previous respiratory history (fig. 5).

Coronary arteritis and periarteritis associated with myocardial alterations (fibrosis, with cellular, predominantly eosinophilic infiltrations) appear in human serum disease (Clark & Kaplan (16)) as well as in the experiments on animals with injection of heterologous sera or foreign proteins (Gruber, Klinge, Vaubel, Rich & Gregory, etc.). Frequently repeated injections of small doses of heterologous serum induce, together with endocarditis, coronary involvement and sometimes large fibrinoid deposits in the aortic wall. Simultaneously, there is myocardial involvement of an ischemic nature, exhibiting in addition interfibrillary infiltrates of cells among which eosinophil clusters may be seen. In humans, similar

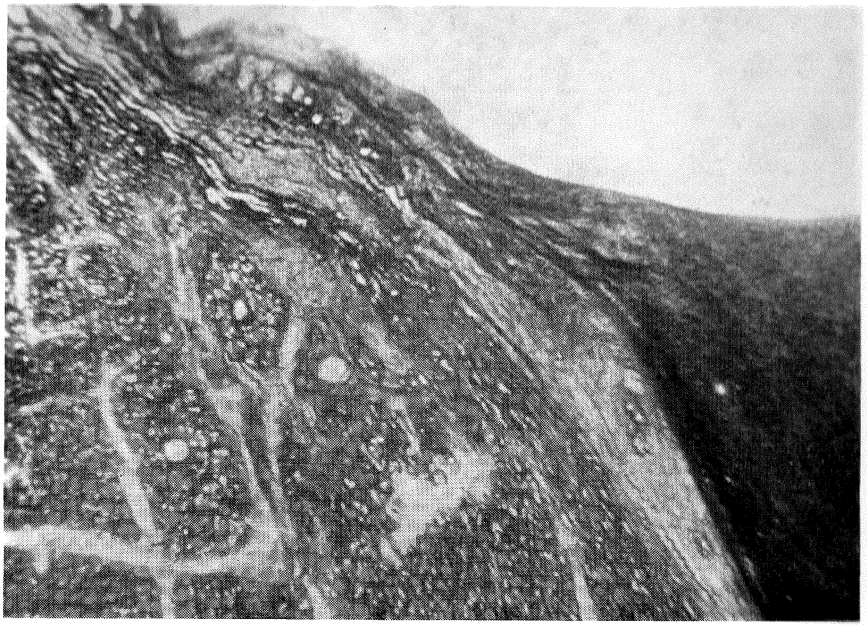

Fig. 5.
Fibroelastosis of the endocard in an adult.

appearances have also been described (Harkavy (48)) (fig. 6). This accounts for the electrocardiographic changes in these patients, more marked in acute outbreaks, which may be the cause of death.

Verrucous endocarditis is frequently associated in complex conditions. Its clinical manifestations are more or less conspicuous. In some cases it may be a rheumatic endocarditis which has undergone malignant transformation owing to the secondary development of angio-mesenchymal lesions. In D.L.E. one of the major symptoms is Libman-Sacks endocarditis. In periarteritis nodosa, dilatation of the left ventricle which may be the consequence of hypertension, and, occasionally, endocarditis of the rheumatic type, are found at autopsy. Friedberg & Gros (33) have described the picture of thrombotic endocarditis with prolonged fever, arthritis, serositis and widespread vascular lesions. This condition bears a close resemblance to "non-bacterial malignant endocarditis" described by the writer (58—d) and also to the bacterium-free stage of bacterial endocarditis described by Libman & Friedberg (71).

The changes in heart dynamics may, therefore, play an important role in the clinical picture of these diseases. A picture of angor may be seen, particularly in the forms of hypersensitivity angiitis, less frequently in periarteritis nodosa, though it is pointed out that it

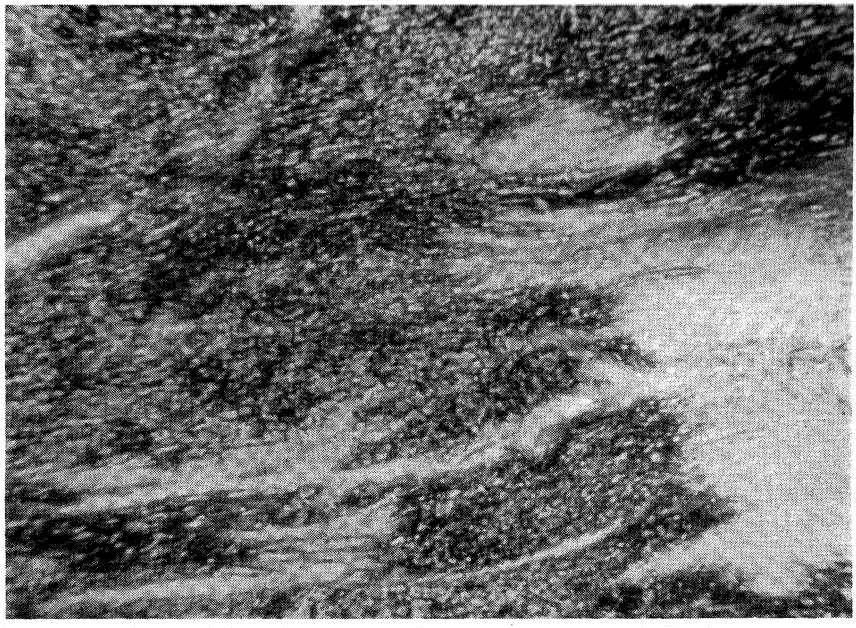

Fig. 6.
Myocardial lesions in fibroelastosis.

is more frequent in children. Heart failure may be derived from myocarditis with EKG signs or from backward stasis due to fibroelastosis or to constrictive pericarditis. Likewise, endocarditis may accompany the picture of Loeffler's syndrome or of pneumonitic infiltration.

4. *Kidney.*

From a clinical point of view, the renal involvement is one of the most marked. It frequently manifests itself in the form of hematuria which occurs suddenly, without any other symptom, but it may be preceded or accompanied by uni- or bilateral pain in the renal areas, similar to that of renal colic. Such is the case, particularly in periarteritis nodosa, in which renal symptomatology has been taken into account from the first descriptions. Ralston & Kvale (91) have reviewed renal involvement in a series of cases. However, renal symptoms do not necessarily persist when hematuria disappears; nor is urea retention necessarily produced. On examination of some kidneys, the writer has seen multiple infarctions, pale or hemorrhagic, but the intermediate renal parenchyma was fairly healthy. In long-standing cases renal sclerosis may be found with markedly irregular, knobby surface. In other clinical pictures of allergic angio-

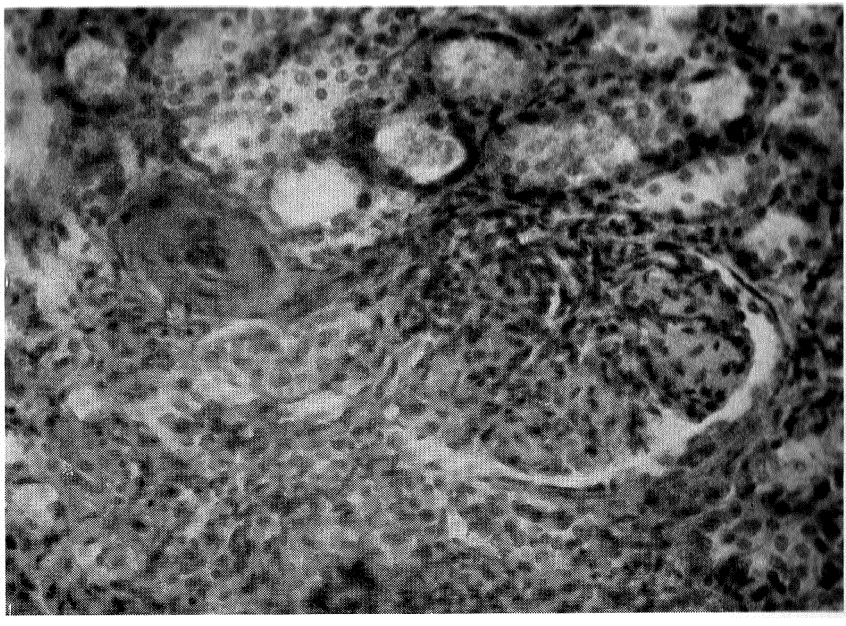

Fig. 7.
Necrotizing glomerulonephritis in generalized visceral angiitis.

mesenchymosis renal involvement may be revealed by oedema and albuminuria, sometimes extremely marked, of 10 grams or more per 100 ml. In asthma developing into a vascular malignant form the writer has seen the appearance of a true nephrotic syndrome. The course of hypersensitivity angiitis is almost always associated with renal symptoms, sometimes violent, leading to hypertension and to progressive uremia; this corresponds to "necrotizing glomerulonephritis" described as peculiar to this condition by Zeek and associates (125) (104) (fig. 7). Renal failure is also found in granulomatous angiitis (Churg & Strauss (15), Wegener (118)), which can be accounted for by the lesions found at autopsy: granulomata in the connective tissue, usually located near the vessels or in the wall of small-sized arteries, with an eosinophilic centre and accumulations of macrophages and giant cells similar to those of granuloma due to a foreign body.

In each case the interpretation of facts may prove difficult, since once conditions similar to periarteritis nodosa have been experimentally produced by removal, ligation or lesion of the kidneys (experiments of Grollman and associates, Holman, Koletsky, Zeek and associates, etc.) there is naturally room for doubt as to whether it is a previous renal disease with secondary vascular involvement,

or a widespread arterial disease with manifestations in the kidney as well as in other organs. In malignant hypertension, arterial lesions with fibrinoid degeneration and necrosis of the wall may indeed pose such doubts. Davson and associates (23) contend that the so-called subacute nephritides of extracapillary course with crescents (Volhard-Fahr) could actually be, for the most part, microscopic forms of periarteritis nodosa; the writer (56—c) has seen cases which illustrate this assertion or at least suggest both possibilities (fig. 7).

On the basis of the comparative study of experimental renal lesions with nephrotoxic globulin (Masugi's nephritis) and of those obtained by repeated injections of heterologous sera, the writer believes that two types should be distinguished within this group of kidney diseases, which may be regarded as allergic. The interstitial lesion is, in our opinion, always important, although the majority of writers have attached little importance to it, or regard it as secondary (McLean and associates (76)). This reaction manifests itself not only in the interstitial, intertubular tissue of the kidney, but also in the mesangium which is the glomerular mesenchyme. In Masugi's nephritis the lesion affects primarily (Jiménez-Díaz and associates (56—c)) the interstitium (oedema, infiltration) and the glomerular mesangium, giving rise to intraglomerular transudation which sometimes compresses the capillary loops. Masugi himself also pointed out the simultaneous involvement of other organs, particularly the liver, in mesenchymo-capillary reactions. These mesangio-nephritides may be reversible; the oedema and the transudated plasma are then reabsorbed and the glomerular circulation is reestablished. Lesions similar to these are also obtained in serum-induced nephritides (Jiménez-Díaz; Forman and associates); but the lesions induced in animals treated with repeated injections mainly involve the glomerular capillaries which become hyperpermeable and thrombose, giving rise to glomerulolysis, having an aspect which the writer has described as "burnt glomeruli". This type of lesion, capillary desmonephritis, is accompanied by more severe lesions of the small-sized arteries and arterioles with fibrinoid necrosis and perivascular infiltrates, and corresponds to the necrotizing nephritis described by Zeek and associates (104) (125) in hypersensitivity angiitis.

5. *Liver and spleen.*

The manifestations of allergic shock in the liver are well known. In a case of a fatal asthmatic attack, the writer has seen a pronounced engorgement of the sinusoids with stasis alternating with

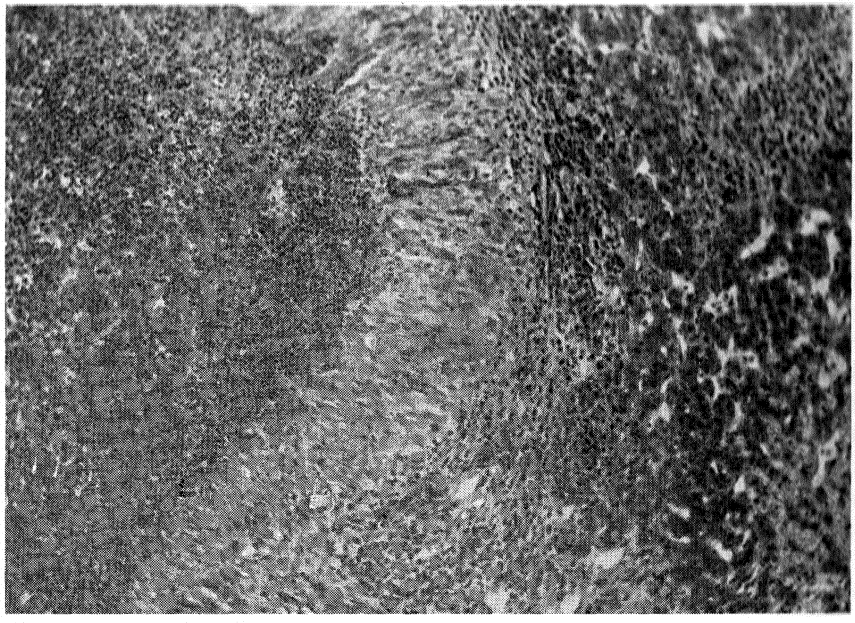

Fig. 8.
Eosinophilic infiltration of the liver.

zones of ischemia, and violent hypersecretion of mucus into the small ducts. The liver may also participate in Loeffler's syndrome, and occasionally the eosinophilic infiltration is located there. The writer had the opportunity of carrying out a biopsy in an eosinophilic infiltration of the liver (fig. 8). In periarteritis nodosa in man, arteritis and necrotic foci, which may even develop into abscesses, are oftentimes demonstrated at autopsy. Clinically, the symptoms are less frequent (Talbot & Ferrandis (110)) though pictures resembling hepatitis, biliary occlusion or cholecystitis may appear. In hypersensitivity angiitis, Zeek and associates (125) describe phlebitis of the portal vein with normal neighbouring arteries. Harkavy (48) and also More, McMillan & Duff describe foci of necrosis and arteritis (83—c).

Splenomegaly occurring in thrombotic-thrombocytopenic purpura and in D.L.E. is not very frequent in periarteritis nodosa; it is more frequent in allergic vasculitis. On histological examination necrosis in the arteries and veins with inflammation of the trabeculae are common findings. Amyloid deposit may be found as well. In allergic granulomatosis, nodules may also appear in the spleen.

6. *Gastrointestinal Tract.*

The gastrointestinal tract may participate in these complex syndromes in different ways. Abdominal tenderness on examination or spontaneous pain and colic are frequently observed. This is associated with diarrhea which may be hemorrhagic. Harkavy (48) has seen the occurrence of mesenteric thrombosis, infarction of loops and peritonitis. In periarteritis nodosa the gastrointestinal picture may initiate the clinical symptomatology; it may then imitate the picture of acute abdomen, which on occasion has led to surgical intervention. Appendicitis due to periarteritis has been described as the only visceral location of the condition. The arterial lesions of the intestine involve mainly the small intestine (jejunum-ileum) and the terminal colon; in addition to arteritis, necrotic-hemorrhagic foci with oedema may be found. In the general syndromes of hypersensitivity, the gastrointestinal participation is much less frequent than in periarteritis; nevertheless, it may also occur, as well as in allergic granulomatosis.

The writer has seen two cases associated with an extremely severe diarrhea with early peritonism and melena which led to death in a state of shock. They were very similar to those described by Grégoire (45), which recall Shwartzman's widespread phenomenon.

7. *Nervous System, Muscles and Joints.*

Varied conditions of nervous system involvement may be associated with the other symptoms of these diseases. The involvement of peripheral nerves is the most frequent. It gives rise to isolated, extremely painful neuritis in the cranial (facial neuralgia, etc.) or peripheral nerves. In a case of hypersensitivity due to penicillin seen by the writer, pain was widespread and extremely violent and there was marked skin hyperpathy. In periarteritis nodosa, polyneuritis is one of the main symptoms. It may involve mainly a sensory or a motor distribution. Occasionally, it may assume the features of "neuronitis", even associated with facial paralysis like Osler's polyneuritis. The Guillain-Barré syndrome has been described as an initial phenomenon. In some cases it is extremely difficult to elucidate the respective roles of neuritis and myositis in pain and in the antialgic posture of the limbs. Pressure on certain specific regions may give rise to a violent painful reaction. The mechanism of this form of polyneuritis is mainly the involvement of the vasa nervorum and the compression exerted by nodules on fibrillae (fig. 9). In addition, they are due to hemorrhagic phenomena throughout the length of the nerve. In other clinical types,

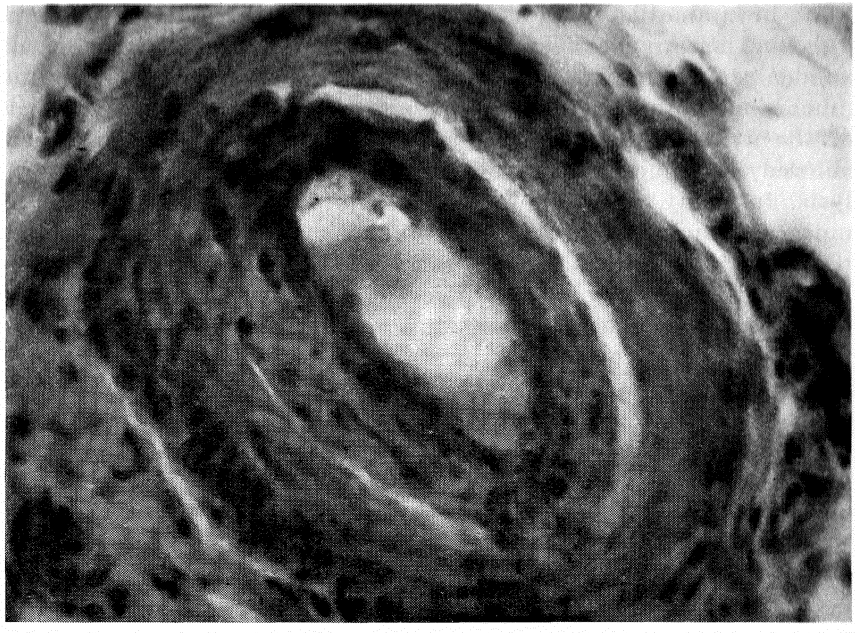

Fig. 9.
Arterial lesion in the perineurum (perineuritis in a case of P.A.N.).

angiitis, granulomatosis, the neuritic picture may also appear. Facial paralysis, vertigo, deafness due to the involvement of the VIII nerve and ocular paralysis may likewise be found.

In some cases symptoms appear in the central nervous system. A thrombotic or hemorrhagic ictus may occur through involvement of brain vessels, or a picture of encephalitis may develop, as is seen in bacterial endocarditis or in the severe forms of rheumatic fever and in salvarsan encephalopathy. In a case of sensitivity to pyramidon, the writer found diffuse erythroderma with high temperature and an encephalopathic picture. In these cases the condition may be due to multiple brain ecchymoses, to subarachnoid hemorrhage and, too, as has been described in Wegener's granulomatosis, to an infection communicated from the necrotic, secondarily infected naso-sinusal mucosa. In addition, the granulomatous tissue has occasionally been found to extend along the nerves as far as the central nervous system. The neurological picture, despite its variety, together with the remaining visceral manifestations, is in itself an effective diagnostic clue.

Apart from polyneuritis, there is pain of myo-articular origin which may immobilize these patients. Sometimes there is visible

joint inflammation with effusion, mainly in hypersensitivity angitis and serum sickness. In severe syndromes death may occur suddenly with a picture of fever, hemorrhages in the skin and mucous membranes and marked, widespread polyarthritis. A patient of the writer who died in severe shock induced by sulphothiazol showed a similar picture which included, in addition, ocular paralysis. In many cases, however, articular pain on mobilization is not accompanied by articular inflammation or by effusion, though it is associated with pain in muscle insertions, a true periarthritis. Localized pain may occur in different zones of muscles in which a nodule can be palpated; biopsy may reveal local interstitial oedema and fibrinoid necrosis at the level of the myotendinous junction or in the perimysium internum. The biopsy of the deltoid or gastrocnemius muscles may be of decisive diagnostic value in periarteritis nodosa. On two occasions the writer has seen extremely painful hemorrhages inside the gemelli muscles, which occurred spontaneously.

8. *Peripheral Vessels.*

Vascular lesions find their main clinical expression in the previously mentioned visceral symptoms which are essentially derived from the involvement of vessels. Vascular involvement occurs mainly in small-sized arteries, arterioles and capillaries, but the veins in certain organs, particularly the liver, are also affected. Peripheral phlebitis of the limbs may occur, though infrequently, in periarteritis nodosa; it is, however, more frequent in severe cases of allergic vascular disease. Harkavy (48) has described endo-thrombophlebitis in some of his cases, as well as endophlebitis migrans in allergic patients with clear sensitizations. The pathogenesis of phlebothrombosis is on the whole extremely obscure, and biochemical changes, instability of fibrinogen (fibrinogen C), which probably underlies systemic fibrinoid diseases (Thomas and associates (111)), may participate in its production. It may therefore be assumed that an allergic sensitization or a reaction of the type of Shwartzman's phenomenon may be capable of inducing widespread vascular disease and at the same time of facilitating venous thrombosis.

Concerning the manifestations of arterial diseases in the limbs, pain along the course of the vessels and the occurrence of nodules in periarteritis, or even spontaneous aneurysms, should be mentioned. In Buerger's thromboangiitis obliterans, whose allergic genesis is probable, the participation of muscle vessels gives rise to phenomena of claudication and gangrene; diffuse or segmental phlebitis, sometimes of the migrans type, and neuritis are frequently

associated. The association in allergic angiitis of muscular pain, fever, exanthema, eosinophilia and arteritis may give rise to a picture indistinguishable from trichinosis. In a case diagnosed by the writer as periarteritis, the vessels of the lower limb, which had to be amputated, owing to gangrene, were teeming with thrombi of trichinae, while in the vessel wall, the adventitia and the perivascular connective tissue, lesions similar to those of periarteritis were found.

With regard to the histologic aspects of these vascular lesions, of which brief mention has already been previously made, their degrees and types as well as situation vary. The findings range from the rheumatic arteritis type to the most severe necrotic forms with nodose or granulomatous periarterial reaction. This is the main basis for the classification of the clinical manifestation included in this group (see figs. 10, 11, 12 and 13).

9. *Laboratory Data.*

The cytologic examination of the blood may be of great value in the diagnosis. It is usual to find an anemia, particularly in severe febrile forms, though generally it is not as marked as would be expected from the intense, ischemic pallor of these patients. The leukocyte count may be low at the onset of drug induced shock, but it is generally high both in hypersensitivity angiitis and in periarteritis nodosa, in which it may reach outstanding values. In many cases the main diagnostic difficulty arises from sepsis, because of the high temperature, the general manifestations and the marked leukocytosis, which may even exceed 40,000. While an eosinophilia is characteristically found in the differential count, it is mild in some cases and there is a shift to the left. The differential count may be similar to that found in lymphogranuloma. Nevertheless, eosinophilia is the prevalent finding in many cases; in one of the writer's it was as high as 90 %; the usual figures range from 20 to 50 %. Those diseases which may give rise to diagnostic confusion when associated with similar data are, in addition to vascular disease, tropical eosinophilia, trichinosis, eosinophilic leukemia, Hodgkin's disease and other types of parasitosis. Tropical eosinophilia is a condition *sui generis* of obscure etiology whose course resembles an asthmatoid condition; it also exhibits pulmonary infiltrations; occasionally it may give rise to a persistent, violent asthmatic picture. De Zoysa (126) believes that it bears a close relationship to Loeffler's syndrome and to periarteritis nodosa, as different degrees of the same condition. There are no safe diagnostic data; only the reversibility with organic arsenicals and a less severe overall picture. Trichinosis may be diagnosed on biopsy and in the light of the

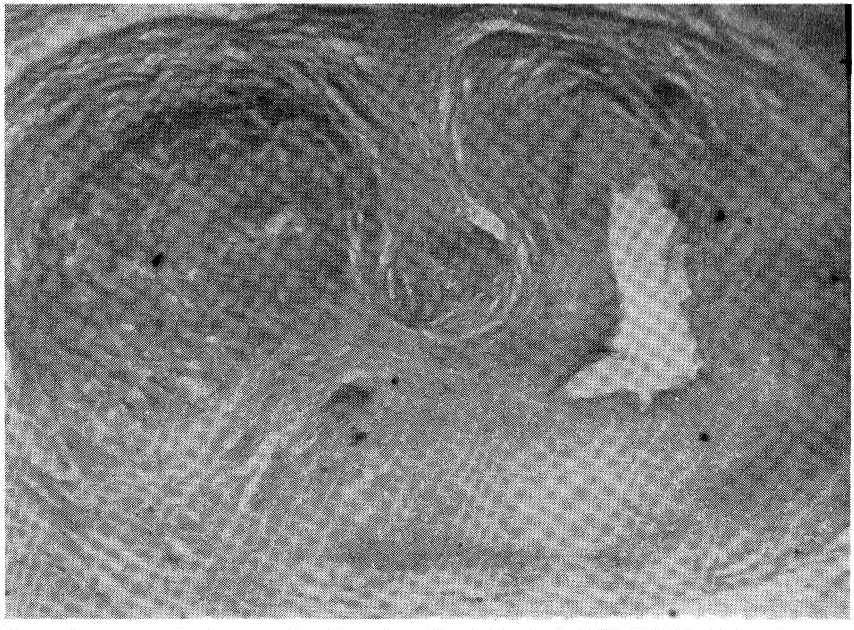

Fig. 10.
Coronary artery in P.A.N.

clinical syndrome and the history, apart from specific tests. Nevertheless, in Gelfand & Aronoff's series (38) of 5 cases of periarteritis nodosa, 3 gave a positive precipitin reaction for trichinosis. The concept of eosinophilic leukemia is a very flimsy one, but whatever the case, immature forms are found and sternal puncture may prove decisive. In allergic vascular disease sternal puncture reveals only eosinophilia and activation of the reticulum, sometimes with plasmacytosis. Other types of parasitosis producing eosinophilia, particularly ankylostomiasis, have a very different picture. The writer has seen two cases of myiasis which, owing to the presence of eosinophilia, fever and muscular pain presented a diagnostic problem for some time.

The sedimentation rate is usually elevated, which is associated with a disturbance in the electrophoretic spectrum of plasma; hypoproteinemia and reversal of the albumin/globulin ratio are usually found. In the writer's experience, the increase in gamma globulin is prevalent. In patients with asthma of the intrinsic or bacterial type, the writer has seen hypergammaglobulinemia in the inveterate cases in the pathic or angio-mesenchymal stage, in the course of which these diseases usually occur. A positive cryoglobulin re-

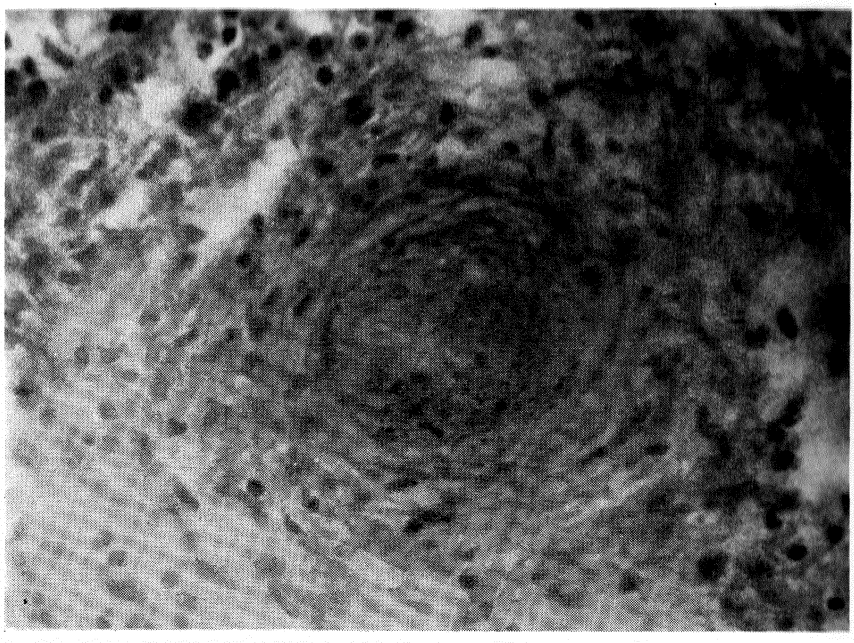

Fig. 11.
Granulomatous arteritis.

action and increase in the hexosamine levels of the plasma may also be found. Serum lability tests (Hanger, McLagan, etc.) may be positive, even in the absence of an hepatic syndrome. Coombs' tests may be positive, and antiplatelet antibodies may appear. The Rumpel-Leede phenomenon is frequently positive, especially in types accompanied by purpura (of Schönlein's type and thrombotic-thrombocytopenic purpura), and the platelet count, which on the whole undergoes fluctuations in correlation with the overall clinical picture, may be low.

The Wassermann reaction may be falsely positive. This fact had already been pointed out by Gruber in relation to periarteritis nodosa. Recently Moore (81) has seen D. L. E. develop in subjects who had previously given false positive Wassermann tests. Rheumatic activity tests behave in a variable manner. The C-reactive protein tests are usually negative in asthmatic patients (Kaplan and associates (60), Tuft & Sherr (112)), but may become positive not only during intercurrent respiratory infections but also, according to our experience, in asthma that undergoes malignant transformation. Rose's reaction and the investigation of antistreptococcal antibodies are usually negative except in rheumatic patients in whom angio-

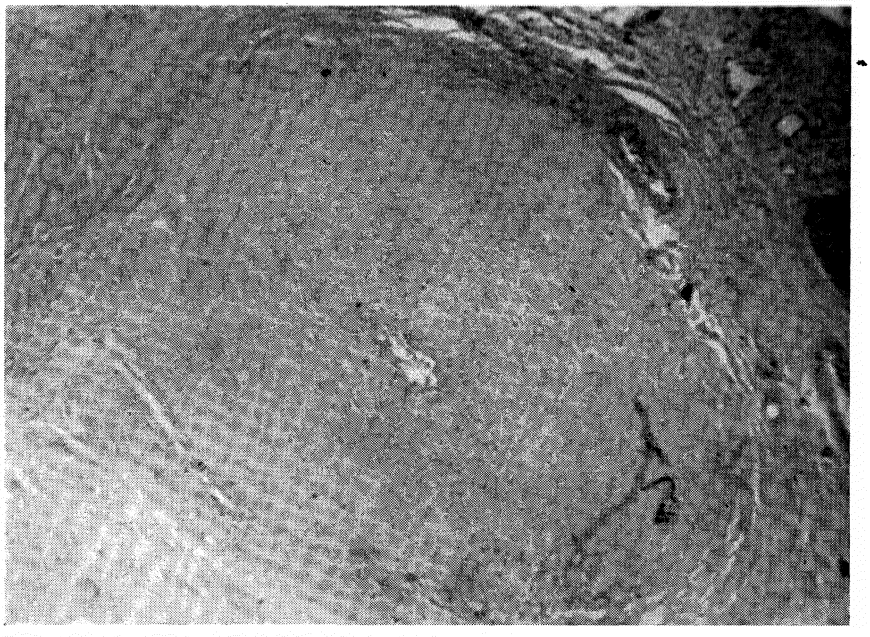

Fig. 12.
Obstruction of an arteria arcuata of the kidney in P.A.N.

connective malignant transformation is secondarily produced. The L. E. phenomenon may be positive, but usually this is not the case; even with negative L. E. hematoxylin bodies may be seen, as in Worken & Pearson's patient (124) with severe asthma and allergic angiitis.

On urine examination albuminuria is frequently found, as has been pointed out above. An interesting datum in the diagnosis of visceral angiitis is Krupp's phenomenon (67) in the urinary sediment. It consists in the association of a sediment like that of recent nephritides (red and white blood cells) with that occurring in the terminal stages (wide, waxy casts). Krupp's phenomenon has been termed "telescopic sediment" by Cole (17).

The examination of exudates with their eosinophilic nature, the cerebrospinal fluid in cases associated with neurological symptoms (it may be hemorrhagic or exhibit pleocytosis and, occasionally, albumino-cytologic dissociation) and liver and kidney function tests constitute further accessory methods of assistance in diagnosis and prognosis.

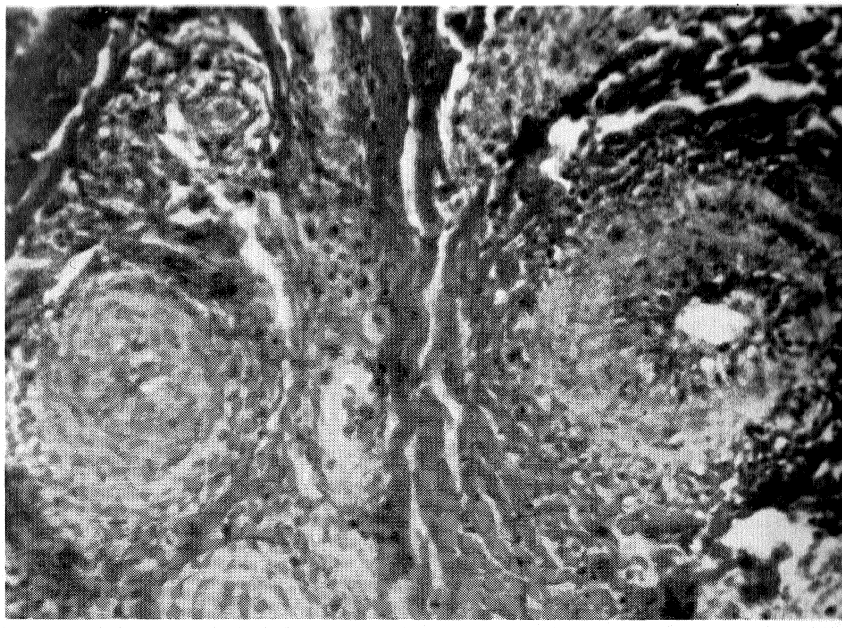

Fig. 13.
Arteritis in Wegener's granulomatosis.

Main Clinical Syndromes of Allergic Angio-Mesenchymoses

The symptoms and signs described and analyzed above combine with one another in a variable form in clinical medicine. This results in diverse clinical pictures whose differential diagnosis from other diseases is sometimes extremely difficult and should receive due consideration. The extent to which they are essentially different diseases, even if vascular lesions are different, poses a further problem. Though similar etiologic factors may come into play and some aspects of their histopathology (fibrinoid degeneration, destruction reaction of the collagen) are common, some writers segregate some of these conditions as different diseases. This is largely due to the moment at which the condition is recognized and to the degree of severity in relation to constitutional, nutritional, endocrinological and other factors in the etiologic constellation, and also to the therapy employed, particularly at the present moment of "use and abuse" of sulphonamides, antibiotics, steroids and new drugs. Nevertheless, they may be regarded at present as clinically and, in part, pathologically different rather than radically different diseases, and some clinical syndromes may be synthezised.

1. *Widespread Vascular Allergy (Harkavy-Zeek) or Hypersensitivity Angiitis.*

In a large number of cases this condition occurs in patients who have already had allergic manifestations, most frequently asthma, angioneurotic oedema and recurrent urticaria. Data evidencing sensitizations may be obtained from the history; and even reagins may be found which make transfer of the sensitization possible. Cases have been described caused by sensitivity to foodstuffs, pollen and other allergens. Allergy to drugs is, however, the most frequent. In some cases, as usually occurs in allergic diseases, the patient is in a "dysreactive" state and no exogenous influences can be demonstrated; it may then be accepted that it is an "intrinsic" condition. Bacterial allergy, which on occasion may be demonstrated beyond doubt in a direct manner, or a dysreaction on a constitutional basis can be incriminated, the mechanism of antibody-antigen allergic reaction being of no decisive importance. The acuteness of the onset is variable. In cases due to sensitivity to drugs it may be violent and is usually preceded by fever, asthenia, tachycardia, erythema or exanthema, and even exfoliative dermatitis, purpura and visceral hemorrhages. Subsequently the condition may be accompanied by albuminuria, renal failure, pulmonary infiltration, colic with melena, jaundice, splenomegaly, arthritis, neuromyositis, etc. Uremia, marasmus or a central encephalic condition may preceed death which may occur within a few days or weeks.

On other occasions, particularly when it is a case of asthma developing into a malignant form, the picture may be primarily thoracic with regressions, infiltrations, status asthmaticus, effusions, albuminuria, myocarditis, remissions and recrudescences may alternate till the end.

In the more violent types, the following diseases may be considered in the differential diagnosis: malignant sepsis, nonbacterial endocarditis, severe types of rheumatic disease, metastasizing tumours or severe hemopathies (plasmocytemia, aleukemic leukemia), malignant forms of syphilis and tuberculosis. The pleomorphic picture by itself, the previous history and the demonstration of sensitizations or a recent administration of drugs or sera may be of aid in the diagnosis which may be confirmed by the elimination, on successive examinations, of the other conditions whose possibility had previously been borne in mind.

Vascular lesions are extremely diffuse with the feature of fibrinoid necrosis of the wall spreading to all the layers (necrotic panarteritis) (fig. 11). Zeek (104) (125) attaches special importance to the diffusion, the location in pulmonary and splenic vessels, the

lack of affinity for bifurcation zones and, above all, to the possibility of demonstrating at autopsy that the lesions were simultaneously induced in the absence of pre-exudative lesions.

2. *Allergic Granulomatosis (Churg-Strauss).*

These writers (15) initially described 13 cases with a severe, complex syndrome of violent, persistent, febrile asthma, pulmonary opacities, eosinophilia and malignant course (of these 13, 11 had a fatal outcome). Autopsy revealed granulomata, fibrinoid degeneration, perivascular infiltrations with local eosinophilia and arteritis resembling the aspect of allergic angiitis and periarteritis nodosa (see fig. 13).

3. *Klinger-Wegener Granulomatosis.*

The first case published was that of Klinger (1931) in a subject 71 years of age who suffered from maxillary sinusitis associated with a septic picture, polyarthritis, nephritis, pulmonary gangrene, destructive suppuration of the nose and, at autopsy, diffuse periarteritis, mainly in the respiratory tract. Wegener's description (1936) refers to a "peculiar rhinogenous granulomatosis with special involvement of the arterial system and of the kidneys". Apparently, the most characteristic feature (29) (70) from a clinical standpoint is the onset, which is in the form of a torpid infection, almost always of naso-sinusal origin (Fanger & Hoffman (30) have recently described a case which began with prostatitis), the course being attended by marked general malaise, septic manifestations, visceral involvement (mainly in the lungs, kidneys and myocardium) and necrotic lesions of the nasal, pharyngeal and even laryngotracheal mucosa. In contrast to the usual eosinophilia of the Churg-Strauss syndrome, Fahey and associates (29) and Godman & Churg (43), who have emphasized Wegener's description in excellent papers, point out the absence of eosinophilia and the usual lack of allergic stigmata, as well as the prevalence of lesions in the respiratory tract where necrosis may spread all over the mucosa from below upwards and there may be infiltrations which may develop through necrosis into gangrene. At autopsy, in addition to necrotic, destructive ulcerations, there may be inflammatory and necrotic foci in the lungs and bronchial system, and granulomata with fibrotic proliferation and giant cells. The arteries may exhibit lesions bearing some resemblance to panarteritis nodosa, and the damage to the kidneys may vary from focal glomerulitis with granulomata to glomerulonecrosis, and fibrinoid arteritis with obstruction of the lumen.

4. *Periarteritis Nodosa (Kussmaul-Maier).*

New knowledge has been gained in recent years concerning periarteritis nodosa, with its broad symptomatology, and of the extremely variable clinical pictures it may produce. The improved knowledge as well as frequently performed biopsies are responsible for an apparent higher prevalence, in comparison with previous years, and it may well be possible that the condition is merely diagnosed more frequently. However, there are in addition some factors —the use of certain drugs like sulphonamides, antibiotics, etc.— which in isolated instances, have been shown to play a fundamental etiologic role and which might account for the present frequency of diagnosis. The picture is extremely variable and a detailed description falls outside the scope of this chapter. There are extremely violent forms running a malignant course and characterized by fever, leukocytosis, very high sedimentation rate, renal failure or hypertension, circulatory failure and neurological symptoms, in which death may occur in a few days or weeks. In contrast, there are cases with a long evolution as that followed up for 21 years by Kampmeier & Shapiro (59). The writer has seen a case whose course was characterized by febrile outbreaks accompanied by polyarthritis, polyneuritis and anemia, with periods of regression, which exhibited tendinous retraction and articular anchylosis. It was diagnosed with the aid of biopsy.

A clinical diagnosis can now be made much more frequently, since the clinical pictures are better known. In febrile types it may be necessary to consider in the differential diagnosis brucellosis, tuberculosis and, especially the malignant syndrome of neoplasms. The last mentioned syndrome occurs primarily in neoplasms of the lung producing few focal symptoms, and pulmonary involvement with cough and hemoptysis is frequently encountered in periarteritis nodosa. In the so-called "microscopic" forms with mainly renal involvement, differentiation of the subacute, hypertensive type of nephritis is likewise extremely difficult. In persistent conditions marked by polyneuritis, the possibility of periarteritis nodosa should be borne in mind as emphasized by Scheiffarth.

The nature of periarteritis nodosa has been the object of much discussion. Gruber had already suspected the possibility of an allergic origin. Subsequently, the trend was in the opposite direction and the role of allergy in its etiology was doubted (Griffith & Vural (46), etc.). This standpoint was influenced by the report of cases who had never had allergic symptoms and in whom no sensitizing factor could be discovered, and also by the fact that it has been possible to recreate the condition by mechanisms other than

allergy, such as malignant hypertension and renal failure induced in different manners. Nevertheless, positive cases should not be consigned to oblivion. Wilson & Alexander (121) in a survey found a history of asthma in 18 % of cases; Rackemann & Green (92) have seen the same association; Bergstrand (9) has reported 4 cases; and also cases were published by Cohen, Kline & Young (18) (62), Trassoff & Scarf (114), Berger & Weitz (8), Nuzum & Nuzum (87). On the other hand, there are cases in which the relationship to a drug is obvious (sulphonamides, iodine, aspirin, penicillin, sera, organic arsenicals, etc.), as will be discussed below in the general section on eiology. In some cases skin tests have given unequivocal results (Randerath (93)).

However, there is no evidence of its constant allergic origin. An infectious etiology could be accepted in cases consecutive to infection or parasitosis. The writer has seen a case in which the condition developed after 18 months of Malta fever with two recurrences. Mention has also been made of a case of trichinosis in which both clinical picture and arterial lesions were extremely similar to this condition. The relationship to rheumatic fever might be supported by the finding in some cases of high titres of antistreptolysin O and by the cases with a previous history of rheumatism in which Aschoff's nodules were found at autopsy. The writer believes that both the allergic factor and infection act on the complex etiology as factors giving rise to a special reactive state capable of originating the lesions. The specific factor is this mode of reaction rather than the cause that precipitates it. It may, therefore, be assumed that the disease may have a multiple etiologic induction. On occasion, periarteritis nodosa results in a general condition or in the involvement of organs; this may well be the primary process on which the development of periarteritis is based rather than its expression. As has been pointed out already, it is extremely difficult to ascertain whether the disease gives rise to a rheumatic syndrome or is a subsequent malignant development of rheumatic fever; similarly, hypertension and kidney disease may either be its consequence or the conditions on which periarteritis may have developed. Periarteritis nodosa is no exception to the fact that all the different conditions may occur both in and outside the circle of allergy. This is, if anything, more frequent in this disease.

Etiology and Pathodynamics

A hereditary factor, not in the sense of the disease itself but of allergy, or dysreaction, is extremely frequent. Harkavy (48) estimates it at approximately 50 %, but the writer believes that it is

somewhat higher. The problem of heredity in this case, as in any allergic disease, lies in ascertaining what the inherited factor is. In our opinion, it is a "dysreactive nodule" which may be the expression of a dysenzymic constitution. This would facilitate a subsequent sensitization to one or several allergens, simultaneously or in succession, and violent reactions to drugs, infections, etc. which need not be of a genuine allergic nature in a strict sense but dysreactive in a wider sense. The writer had the opportunity of seeing a case of unusual severity after the injection of serum in a subject who had never received an injection. Psychic, physical and climatic influences are obvious in these diseases, particularly on their recrudescences.

Among the allergens reported, all those which are known for asthma might be listed, but in these severe types of allergic vascularitis those which give rise to sensitizations of the delayed type, bacteria and drugs, are of major importance. Concerning the drugs regarded as responsible, mention should first be made of the sulphonamides whose role was evidenced by Rich (96) and subsequently by Black-Schaffer (10), Lichtenstein & Fox (72), More and associates (83—c), French (32), Godman (44), Gelfand & Aronoff (38). At present, similar observations are being repeated by several writers. Iodine, in addition, has been incriminated by Rich (96—b); Muller (86) published a case of iododerma associated with asthma and periarteritis nodosa. Rasmussen (94) subsequently reported 2 cases; in one he was able to demonstrate antibodies. Serum shock, also reported by Rich & Gregory (95) may indeed be found in the history of these patients with a certain frequency. Clark & Kaplan (16) have described the vascular lesions of serum shock in man. Numerous writers have reported the role of antibiotics, particularly penicillin (Waugh (117), Surdakowsky (108), Edge and associates (26), Jiménez-Díaz (56—d)) and others (streptomycin, chloramphenicol). The manifestations caused by sensitivity to penicillin may acquire unusual severity and pursue a violent course. Other drugs may be mentioned e.g. aspirin and pyrazolone derivatives (in allergic patients these drugs show a special tendency to produce urticaria, erythema, occasionally, severe erythroderma, Quincke's oedema, etc.). For reasons which are not understood, a large number of patients sensitive to aspirin are also sensitive to pyramidon and even to quinine, while they can tolerate phenacetin. Phenyl-butazone (O'Brien & Storey (88)), dilantine sodium (v. Wyck & Hoffman (120)), hydantoine (Rottermuch (98)), organic arsenicals (Miller & Nelson (80)), thiourea and thiouracil (methyl- and propyl-) (Gibson & Quinlar (40), Dalgleish (22), McCormick (77)), etc. have been the sensitizing drug in other cases.

Sensitivity to tobacco, to which Harkavy (48) has attached great importance in the production of these conditions of vascular allergy, deserves special notice. He produced vascular lesions and necrosis in rats by the injection of tobacco extracts. In the zone of positive skin reaction, biopsy evidenced connective tissue oedema and eosinophil perivascular reaction, which has also been observed by Sulzberger. The passive transfer of this sensitization has also been attained.

The problem posed by the participation of bacterial allergy is just as important as sensitivity to drugs. This interesting problem, which received due attention elsewhere (56) (57) cannot be discussed here. The reality of bacterial allergy appears to be beyond doubt at present, though it is a peculiar type markedly different from that induced by other allergens. Nor is it clear in these cases as to what extent the manifestations in relation to infection belong to bacterial allergy in a strict sense, that is, are due to sensitization to bacterial products (toxins and endotoxins). In some infections, allergy plays a very important role in the shaping of clinical facts, as is known mainly in the case of tuberculosis, in which necrotico-exudative, proliferating reactions and granuloma formation may be seen. Also the anatomicopathologic and clinical course of typhoid fever, as Roessle has emphasized, exhibits a reaction similar to induced allergic phenomena. In rheumatic fever, the role of group A streptococcus appears obvious, and the angio-connective tissue reaction is the paradigm of the reactions that have been described above (fibrinoid degeneration, granulomata). Nevertheless, here we come across a series of facts which cannot be accounted for merely by the simple diagram of infection-sensitization such as the progression and persistence of the disease even after the disappearance of the infection, the ever-increasing rise in the titre of antistreptolysin O, on occasion after the disappearance of the agent, etc.

The conditions described as vascular and connective tissue allergy may on occasion be associated with a focal infection, and the therapeutic effect of its elimination may be beneficial, though this is not always the case. Sinus infection has mostly been blamed; germs, mainly staphylococci, may be cultivated from the fluid obtained by puncture. An extract may be made from this culture with which violent, and even necrotic, local reactions and severe general reactions may be obtained (Jiménez-Díaz (56—c), Harkavy (48), Danzigers' fatal case quoted by himself). However, the observation of the disease in the sinuses reveals that there is a hyperplastic, noninfected sinopathy in many cases and that the infection of the cavity is intermittent. In the writer's experience, sterilization with antibiotics may prove beneficial, but does not essentially influence

the course of clinical phenomena. The fact that these become more marked when cryptic or widespread, intercurrent infections develop is far more evident than their disappearance when the infection is combatted. In other words, everything seems to indicate that active infection plays an important role, but is not in itself the cause responsible for the condition. The role played by infection is probably based on a previous change in the reaction of the body; or it may be of assistance in bringing it about.

In recent years it has been possible to learn factors capable of inhibiting and stimulating this reactive change or dysreaction. A series of coincidental clinical states (hypothyroidism, pregnancy, jaundice, nephrotic syndrome) may cause the disappearance of all the allergic symptoms, as we had pointed out a few years ago (58). These are the same circumstances that Hench (52) subsequently described in the case of rheumatoid arthritis and the same circumstances hold good for experimental disease as well. Holman & Jones (55), for instance, have reported the fact that the disease induced according to their method of renal failure and fatty diet does not occur in the pregnant bitch.

These facts have led to the knowledge of inhibitors and facilitators in the pathogenesis of these conditions. Their remission, particularly in rheumatoid arthritis and rheumatic fever, by cortisone and ACTH, found by Hench, has been the fundamental step in the possible explanation of the genesis of the disease in man and of the mechanisms of spontaneous regression of remission under certain circumstances. The writer (58—c) subsequently described the effect, similar in many aspects, of N-mustard which may take place partly by stimulation of the adrenal cortex (Arjona and associates (3)) and partly by direct action on tissue-cell reactions. In contrast to this, other hormonal conditions may favour dysreaction. In this respect, mention should be made of the effect of thyroxine and of the mineralo-corticoids (Selye (105)). Perry (89) has induced arteritis by injections of pituitary hormone, FSH, in animals whose testicles had been previously damaged by estrogens. The most salient fact is that the actions of these hormones or N-mustard may be seen both in the paroxysmal types of allergy, asthma or urticaria, and in vasculo-connective tissue diseases; and both in hypersensitivity angiitis, which appears to be evidently allergic, and in periarteritis or in L. E. This indicates that, apart from a common etiologic background (which is not always present), the common factor is something deeper and more essential lying in the pathodynamics. This explains, independently of the diversity of clinical pictures, and even of lesions, the frequent occurrence of remissions and relapses, the progressive tendency, and likewise the occurrence of mixed clinical

pictures and the transformation of one form into another within this group of diseases.

The association of dermatomyositis and scleroderma is very frequent, to such an extent that the writer described some years ago scleroderma-dermatomyositis as a distinct disease entity in which poikiloderma, scleroderma, myositis, Raynaud's phenomenon, arthritis, etc. may each predominate. Occasionally we have seen a positive L. E. phenomenon in this disease. Endocarditis may occur not only in L. E. but also in the course of transformed asthma, in Loeffler's infiltration and in rheumatoid arthritis. On occasion, a differentiation between S. L. E. and P. N. is nearly impossible or problematic (Shaffer and associates (102), Baggenstoss (6)). Bock (11) mention several cases of these associations and transformations. We have described nonbacterial malignant endocarditis in which rheumatic endocarditis develops, at a given moment, into a malignant condition with polyvisceral manifestations due to angio-mesenchymal lesions, while it is impossible to demonstrate the presence of bacteria responsible for the change in reaction either in the lesions or in the blood stream. The disturbances in the electrophoretic spectrum and the biochemical changes bear a close resemblance to those of allergic angio-mesenchymoses. Other workers have described similar conditions in bacterial endocarditis or in the so-called bacterium free stage of bacterial endocarditis.

From a morphological point of view, one of the most important common facts is fibrinoid necrosis. Nevertheless, there is a diversity of opinion on what the fibrinoid substance is and, in addition, it is questionable that it is always the same substance. The view held by Altschuler & Angevine (2) is that it is a precipitation of collagen mucopolysaccharides by an alkaline protein resulting from cell destruction. In a series of important histochemical investigations, Montgomery & Muirhead (82) have reached the conclusion that fibrinoid is mainly derived from altered smooth muscle of the media of vessels. Craig & Gitlin (21) believe that fibrin is at the end an integral component of such fibrinoid material; interstitial fibrinogen would be transformed into fibrin in situ as a result of the inflammatory reaction of the tissue. It may easily be assumed, in the light of the results of studies with fluorescent anti-fibrin, that the histochemical methods for the recognition of fibrin are not specific enough. Klemperer (61) suggested that there may be more than one fibrinoid, even if they have a common appearance with certain staining techniques, and recently Wolman & Laufer (123) draw a similar conclusion. In the case of L. E. it might be a by-product of nucleoprotein breakdown; in other cases it might be fibrin or other plasma protein transudated, in the arterial wall. Skelton (103)

subscribes to a mixed point of view; he thinks that it may be derived from transudated protein or from muscular breakdown products. The writer has seen fibrinoid in vessels with fairly intact media and is of the opinion that a more likely explanation would be provided by the local precipitation of preexisting fibrinogen into a form insoluble in the body fluids (Brunson and associates (12)) or of fibrin itself (Gitlin & Craig (21)) brought about by something in the blood stream. The point is to ascertain what it is that is present in the circulating plasma, that is capable of bringing about such transformation, and may be transferred, as was pointed out above, by cross circulation.

It is interesting in this respect that it has been possible for the Minneapolis group of research workers (Thomas, Brunson, Gamble, Davis) to produce fibrinoid and impart plasma with the property of transferring it, with the injection of endotoxin. Endotoxin includes a lipid component which, according to Westphal and associates (119), would be the toxic fraction, and a protein-bound polysaccharide acting as a haptene. The toxic lipid may be dissociated from it and transferred to another protein, casein for instance, whereby the same action of the endotoxin is preserved. Apart from the antigenic effect of the polysaccharide, the toxin gives rise to fibrinoid, on the one hand, and to sensitization to the vasomotor effect of adrenalin and noradrenalin, on the other. Torpid, or local, infection might act in this way like Shwartzman's widespread phenomenon. Diverse factors such as antigen-antibody reaction, endotoxin, macromolecules, hormones may lead to the same final results. Lastly, the disease derived from the use of hydralazine (Dustan and associates (25), Perry & Schroeder (90), etc.), so similar to S. L. E., has been reported. Experimentally it has been possible to produce the same condition in the dog (Comens (19)). It would appear that such different agents may bring about a change in body fluids responsible for the lesions. Changes in the electrophoretic pattern of the plasma proteins are a common phenomenon. A tentative explanation was advanced by the writer in which the increase in gamma globulins was regarded as the disturbance in body fluids responsible for the effect through the possible presence of some self-nocuous factor in that fraction (auto-nocivity). A similar viewpoint has subsequently been suggested by Ehrich (27). Gear (37), too, accepts the secondary production of antibodies. Later, Vazquez & Dixon (116), by using fluorescent antigamma globulin antibodies, have been able to demonstrate their deposit in the lesions of patients with rheumatic fever, L. E. and rheumatoid arthritis. The L. E. phenomenon due to a substance present in the plasma is in fact a good example of the presence of self-nocive factors in the plasma. At present it would

appear that this factor is a globulin included in the gamma fraction, and its effect might consist in the displacement of the factor inhibiting desoxyribonuclease (Kurnick and associates (68)). It occurs not only in L. E. but in other collagen diseases as well and its presence has likewise been reported in myeloma, leukemia, recurrences of pernicious anemia and in reactions to penicillin.

Nevertheless, the alteration of the protein pattern may well go beyond what we now assume. Plasminogen may be activated into plasmine or fibrinolysin by bacterial toxins, by anaphylactic shock, traumatic shock or by burns, etc. and a correlation with the fibrinoid deposit is likely. A common result of such diverse actions, the alteration in the delicate system of enzyme chains maintaining the solubitity of fibrinogen (which is just as important in immunity reactions as in coagulation), might be a new pathogenetic approach to the mode of production of these diseases. Finally, it seems possible that substances regarded as auto-antibodies may be fibrinogen derivatives. It is possible that allergy, persistent torpid infection and certain toxic factors may in the end give rise to similar alterations.

In the case of sensitization to drugs, it is probably necessary for them to be linked with appropriate proteins which are thus changed into auto-antigens; the chemical radical would endow them with its specificity as in the works of Landsteiner and associates. It is possible that bacteria present in the body also originate neo-auto-antigens which produce antibodies; but there is no positive evidence in this respect, though there are some data which lend support to this view. Our results with extracts of organs by the collodion precipitation technique have been negative. It is interesting that Stetson (106), on the basis of the similarity between delayed-type allergy and the action of endotoxins, believes that the change in reaction in the latter may be congenital, constitutional, a sort of hyperreactivity similar to allergic hypersensitivity.

However this may be, it is necessary to attempt the elucidation of the respective roles played by allergy, infection, toxic actions and factors facilitating dysreaction (hormones, foods, etc.) in the etiologic analysis of each patient.

Basis of Therapy

The fundamentals in treatment of these conditions are:

1. Verification of the allergic mechanism; search and prevention of the nocive action of allergens.
2. Investigation and removal or treatment of infectious or toxic factors.

3. Response modification by inhibitors of dysreaction.
4. Accessory treatment.

1.—*The investigation of allergic influences* does not differ from the general procedure in all possible allergic conditions. The history is of first-rate value; so are skin tests, particularly in the case of sensitizations to pollen, animal products, dust, molds. The demonstration of reagins by the P.-K. method is important in every case. Alimentary sensitizations are not faithfully disclosed by skin reactions and it is necessary to use elimination diets such as those of Rowe, pulse count according to Coca, Rinkel's method, or microprecipitin reactions according to our technique. The participation of drugs is mainly suspected from the history, but on occasion, owing to the fact that they are drugs whose use is extremely common and indiscriminate, attack precipitation tests may be required. The sensitivity to tobacco may be tested by skin reactions, using extracts of different types of tobacco.

Specific desensitization is of secondary importance in comparison with the elimination, provided the latter is possible, and is not without danger in these cases. In a case seen by the writer, 1 unit of penicillin gave rise in a sensitive patient to an almost fatal reaction from which she recovered only with difficulty, after suitable treatment. But the main danger lies in stimulating the specific reaction instead of depressing it, in view of the hyperreactivity, sometimes incommensurate, of these patients. In the treatment of rheumatic patients by vaccines, amylosis is occasionally induced in certain organs. Recently, the writer has carried out desensitizations with the simultaneous administration on the injection days of prednisolone.

2.—*The search for and eradication of septic foci* are of certain importance though their effect is not radical or definitive, as has been pointed out already. While a factor of activation of the condition is removed by this means, the cause of that condition is not suppressed, and may progress in spite of this therapy. In the case of sinus infection, the writer is not in favour of radical operations but of general antibacterial treatment, aspirations and local lavages. Antibiotic therapy is of fundamental importance and should, in the writer's opinion, be carried out by using large doses (1–10 million units of penicillin for several weeks, provided it has been proved that there is no sensitization to it. In this way we have obtained excellent results in some patients who had not improved at all with the usual doses. When infection persists and germs are cultivated, their susceptibility to the various antibiotics should be tested.

3.—*Treatment with ACTH and cortisone, hydrocortisone, pred-*

nisone and prednisolone, almost always in association with antibiotics, is doubtless the most important step in the treatment of these cases. Some respond unfavourably, especially with ACTH. We have recorded cases of deterioration, and the literature reveals patients with severe asthma and phenomena of angio-mesenchymosis in which this therapy had a lethal result. Fortunately, this occurs rarely and, in the writer's experience, less frequently with cortisone than with ACTH. Nevertheless, Edge and associates report (26) a case of sensitivity to penicillin, who died of renal failure when treated with cortisone and they believe that ACTH should be preferred. When the patient's state is not severe for the time being, the writer prefers to start treatment with prednisone in doses of 40–60 mgm. daily; these may be increased under observation. Subsequently it may be possible, according to the effect, to use ACTH instead (initially 30 mgm. in injections at eight-hour intervals, or in gel form); the dose may be increased, in the light of the effects, up to 50 mgm. or more; or cortisone may be used in progressive doses up to 200 mgm. The dosage is decreased once its ineffectiveness has been verified or its effect attained. No rigid scheme of dosage or successive use can be outlined for any allergic disease, even more so in these cases.

4.—*The following are co-operative factors in treatment.*—Low sodium diet; potassium administration when steroids are used; a suitable diet when there is hypertension, renal failure or liver insufficiency as well as coagulants, vitamin C, etc. Transfusions are of decisive importance in cases with purpura, hemorrhages, thrombocytopenia and anemia. Evidence of the utility of the antihistamine drugs in these cases is lacking at present.

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ALLERGY AND HEMATOLOGY

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The subject of allergy is of special interest to the hematologist. In the first place there are certain classical changes in the formed elements of the blood which accompany generalized allergic processes though these are by no means constant. Secondly, hematology is deeply concerned with the whole concept of immuno-allergic disease in relation to specific hematologic disorders and is perhaps the branch of medicine in which the greatest amount of precise scientific data can be cited to support this concept.

The hematological aspects of allergic diseases can be divided into:

1. Hematologic manifestations of generalized allergic diseases.
2. Hematologic aspects of immuno-allergic disorders,
   A) Iso-immune mechanisms.
      *hemagglutinins—incompatible blood transfusions.
        – erythroblastosis fetalis.
      *granulocytopenias.
      *secondary thrombocytopenias.
      *circulating anticoagulants.
   B) Autoimmune mechanisms.
      *acquired hemolytic anemias.
        – idiopathic acquired hemolytic anemias.
        – secondary hemolytic anemias and dysproteinemias.
        – hemolytic anemias associated with chemical substances.
      *agranulocytosis or leukopenia by auto-antibodies.
        – idiopathic leukopenia and leukocyte auto-antibodies.
        – symptomatic agranulocytosis by auto-antibodies.
      *idiopathic thrombocytopenic purpura.
3. Allergic purpuras.
   Henoch-Schönlein syndrome.
4. Hematologic manifestations of diseases with a questionable immuno-allergic etiology.

1. Hematologic Manifestations of Generalized Allergic Diseases

Any of the blood cells may be affected in a particular allergic state, the most common finding being leukopenia with eosinophilia.

Leukopenia. Though a decrease in the total leucocyte count is a very common accompaniment of allergic conditions, it is questionable whether its measurement is of value in diagnosis. Numerous diseases induce a leukopenia so that the field of differential diagnosis is wide. In the past, the total leucocyte count has been used as the basis of the "leukopenic index" of Vaughan. Serial leucocyte counts are made before and after exposure to an allergenic stimulus, usually a food to which the patient is supposed to be sensitive. Depression in the leucocyte count is taken to indicate that an allergic mechanism is operative. Though diagnosis may frequently be confirmed by this means, further statistical enquiry into the method has shown that an induced leukopenia of this type may so often be absent in a known allergic state as to render the test almost valueless diagnostically, and conversely that leukopenia may be observed following the injection of innocuous foods.

Eosinophilia. The rise in eosinophil count seen in so many allergic conditions is probably an indicator of the part this little understood cell plays in the host's reaction to foreign protein. It is particularly prominent in vasomotor rhinitis and is said to be commoner in those types of allergy where there is an infective element.

In practice, this eosinophilia coinstitutes little more than an interesting curiosity. It is of doubtful value to the clinician since its failure to occur does not in any way invalidate the diagnosis of allergy but, when it does occur, there is still the necessity to eliminate other possible causes of eosinophilia such as infestation by parasites.

Great interest has centered around the Thorn test and its modifications which compare the eosinophil count before and after an injection of ACTH. Such a test is of some value in assessing adrenal function but is difficult to interpret in cases where there is any strong allergic element. The eosinophil is as baffling scientifically as it is disappointing clinically.

2. Hematologic Aspects of Immuno-Allergic Disorders

Agglutination experiments with erythrocytes provide one of the most useful tools available for immunologic studies in human pathology. The ease with which the phenomenon of agglutination may be

observed and the reproducibility of results give unassailable advantages to immuno-hematologic over other methods of investigation. The leucocytes are far less predictable in their behavior in vitro so that the whole subject of leucocyte agglutination is lacking in precision. The platelets lend themselves even less readily to agglutination studies, one important reason being their inherent propensity to adhere to adjacent objects. There is wide disagreement regarding the behavior of platelets as antigens and their proper place in immuno-allergic mechanisms.

A. *Iso-Immune Mechanisms.*

Hemagglutinins.

The incompatibility of blood from different persons is a superb example of biochemical individuality and the organism's intolerance of foreign protein. The impracticability of skin grafting between individuals demonstrates that no two people, apart from monovular twins, are antigenically identical and recent studies indicate that the red cell antigen patterns are almost equally complicated. However, many of the antigens are so unimportant immunologically that it is possible to find a suitable donor who is sufficiently compatible for the red cells to survive after transfusion.

Since Landsteiner's demonstration of the four major groups of the ABO system, nine other blood group systems have been discovered, many of which (notably the Rh-Hr system) contain a very large number of antigens. Combining these various systems, it is now possible to demonstrate many thousand blood group combinations. The possibility of any two people having the identical red cell antigens is consequently very small indeed. Fortunately for the transfusionist, a great many of the red cell antigens never, or only rarely, give rise to antibodies and become clinically important.

The ways in which antibodies are formed to the red cell antigens differ markedly between the various blood group systems. Thus the hemagglutination tests provide excellent illustrative examples of a large number of immunologic principles.

In the case of the ABO system, the patient's serum always contains antibodies to the antigen which is lacking from the cells. For example, if the cells are group A the serum contains anti-B antibodies. This is known as Lansteiner's rule and the exceptions to it are extremely rare (agammaglobulinemia, chimerism). Some authors have expressed the opinion that the antibodies, like the blood groups, are spontaneously produced as the result of genetic factors but Wiener believes that the immunity is acquired, the antibodies being the result of exposure to A and B substances which are ubiquitous

in nature (bacteria, animal proteins, etc.) and, once encountered, provocative of an immune response in an individual who lacks them.

In sharp contrast to the situation with the ABO groups, the N and M antigens hardly ever give rise to antibodies in man. Although about half the population lack either M or N in their red cells, the patient is entirely receptive to repeated transfusions of blood containing the factor which he lacks without the development of any type of immuniologic reaction. Serum for use in distinguishing between these types is made in the rabbit since this animal can be differentially sensitized fairly easily. This illustrates an interesting species variation in immune response.

The Rh-Hr or CDE blood group system illustrates a third type of immunologic situation. Some 15 % of Europeans are Rh negative, that is they are lacking in the Rh_0 or D factor. These people do not normally have antibodies against the antigen that is lacking but will develop them on exposure to the factor in the course of blood transfusion or pregnancy. It is not known why some Rh negative persons will develop antibodies much more readily than others. If a pregnant woman has antibodies of this type against an antigen present on the red cells of the fetus, the child will develop the very serious hemolytic anemia, erythroblastosis fetalis. The great majority of cases of this disease are due to the factor Rh_0 or D being present in the fetus and not in the mother but the condition can also arise in association with the various other antigens of the Rh-Hr system. It is curious that transuterine incompatibilities in the ABO system much less commonly give rise to erythroblastosis fetalis and, when they do, the antibody involved appears to differ in certain ways from the usual anti-A and anti-B antibodies.

It should be remembered that no marriage can be pronounced entirely insusceptible to erythroblastosis fetalis since a large number of the less frequently studied antigens may occasionally sensitize the wife.

The Kell blood groups system illustrates how an antigen, which usually does not produce antibodies, may very rarely do so under exceptional and little understood circumstances. About 9 % of Europeans have the factor K which is absent from the rest of the population. There are numerous instances reported in the literature where a wife lacking the antigen K (genotype kk) has become sensitized to this antigen when the fetus has inherited it from the father. The reverse has also been true in one family, described by Levine, where the allele of the K gene, k, became antigenic, when a woman of the genotype KK became sensitized to the red cells of her fetus which contained the k antigen.

The use of the Coombs or anti-globulin reaction in the investiga-

tion of incomplete antibodies is dealt with in the section on hemolytic anemias.

Erythroblastosis Fetalis. Not only is there a marked difference between the behavior of the antigens of the various systems with respect to the formation of antibodies but there also appears to be a completely random incidence of erythroblastosis in marriages where known incompatibility is demonstrable. Many Rh negative women have a series of successful Rh positive pregnancies without mishap but, in general, the likelihood of erythroblastosis increases with successive pregnancies. Though the reasons for these differences between couples are unknown, there is some evidence to show that erythroblastosis due to Rh incompatibility is less common when ABO groups of the mother and fetus are different than when they are similar. It has been suggested that such ABO incompatibility is responsible for the rapid removal of fetal cells from the maternal circulation and consequent shortening of the time of maternal exposure to the Rh antigen.

In spite of increasing knowledge of the pathogenesis of erythroblastosis, there is as yet no specific therapy which may be directed against the underlying mechanism. Steroids are ineffective against the development of antibodies. Treatment consists in the careful management of the mother during pregnancy and preparation for immediate exchange transfusion of the newborn infant. It is often advisable to terminate pregnancy at the 30th week but opinion with regard to the expediency of this measure is by no means unanimous.

In giving the prognosis for any given marriage, an attempt is made to determine whether the father is homozygous for the appropriate antigen, in which case all children will be candidates for erythroblastosis, or heterozygous when there will be a 50 % chance that the infant will be safe from the disease. This question is best answered by typing the blood of the husband's parents and any other children whom he may have fathered.

Qualitative serological determinations are helpful in determining the titre of antibody which a woman has developed against the appropriate antigen and hence measuring the chances of her giving birth to a child with erythroblastosis. A rising titer during pregnancy is an indication of further sensitization. Nevertheless, in spite of strong serological evidence of sensitization, many cases are recorded where a woman has had a live incompatible child which has remained healthy either with or without exchange transfusion even though she had a previous history of stillbirths and neonatal deaths. This is believed to indicate physiological differences in the permeability of the placenta between different pregnancies.

Granulocytopenias.

In 1922, when W. Schultz published the first report of a new clinical entity, characterized by the sudden onset of necrotizing angina, prostration, high fever and extreme reduction of granulocytes from the peripheral blood, no causative agent could be found. Since then, a relationship has been demonstrated between this condition and the taking of certain drugs. Compounds containing a benzamine group are generally incriminated in the production of agranulocytosis.

It was originally thought that the offending compounds acted by a leukotoxic effect due to an oxidation product. Extensive work has shown that amidopyrine and related drugs fail to induce agranulocytosis in animals. Furthermore there appears to be no relationship between the amount of the drug absorbed and the decrease of granulocytes in the blood. It has been noted at the same time that drugs listed on p. 551 frequently provoke manifestations of hypersensitivity such as oedema, asthma, rash and urticaria. The presence of chills, headache and dizziness associated with the onset of the disease might also suggest an allergic nature. It was subsequently demonstrated that plasma from a patient with sensitivity to pyramidon induced a marked but transitory fall of granulocytes in normal, healthy individuals. A substance in the globulin fraction of patients' plasma and serum was also capable of causing agglutination of homologous and heterologous leukocytes in vitro. Moeschlin has postulated that the offending drug combines with a serum protein to form an antigen (drug plus haptene). The antibodies so formed coat the leukocytes which are subsequently agglutinated and destroyed by the interaction of the leukocyte-bound antibody and the antigen. This destruction of agglutinated granulocytes occurs mainly in the lung capillaries and perhaps also in the spleen and liver because of massive agglutination of leukocytes in peripheral blood. This results in an excessive demand on the bone marrow, with an increase of immature cells, and finally, in severe cases, in complete exhaustion of marrow cells. Agranulocytosis related to hypersensitivity to drugs seems to be based on a similar immune mechanism as in sedormid thrombocytopenic purpura.

The first symptoms are usually general malaise, sudden fever and chill followed by a period of extreme fatigue and prostration. In the final stage, infection occurs in regions normally harboring microorganisms. Gangrenous ulcerations are found on the gums, tonsils, soft palate, lips, pharynx or buccal mucous membranes. Skin lesions have been observed in about 10 % of cases. Splenomegaly, generalized lymphadenopathy and hepatomegaly are unusual. There is

always a slight degree of anemia. The reduction in the number of granulocytes is usually drastic and often there is a diminution of the absolute number of other types of leukocytes. First, hypertrophy of the bone marrow is observed with an increased production of cells; if the increased demand persists, marked immaturity of cells is noted and finally exhaustion of the marrow may develop.

According to the older literature the course of the disease is often fatal, death occurring within 3 to 9 days after the first symptoms. Less fulminating cases have been described however, and since the introduction of intensive antibiotic therapy the prognosis has become more promising.

Until now, drug-induced immune granulocytopenia has been demonstrated with the following compounds: amidopyrin (pyramidon), butazolidin, phenacetin, sulfonamides, barbiturates, aniline and probably hydantoin and gold. The list of drugs should not be confused with cytostatic drugs such as urethane, nitrogen mustard, TEM, demecolcine and benzene derivatives e.g. chloramphenicol etc.

Agents Occasionally Associated with Granulocytopenia.

Analgesics: Amidopyrine (pyramidon) and drugs containing it (amidophen, amytal compound, causalin, cibalgin, neonatral compound, neurodyne, peralga, pyraminal, yeast vite), antipyrine, novaldin (novalgin), phenylbutazone (butazolidin).

Antithyroid drugs: Thiouracil, propylthiouracil, methylthiouracil, methimazole, carbimazole.

Anti-convulsants: Trimethadione (tridione), phethenylate, phenacemide, diethazine.

Sulfonamides: Sulfanilamide, prontosil, sulfapyridine, sulfathiazole, sulfadiazine, succinylsulfathiazole, sulfisoxazole (Gantrisin).

Antihistamines: Pyribenzamine, methaphenilene (diatrin, phenalhiazine).

Antimicrobial agents: Organic arsenicals, chloramphenicol, thiosemicarbazone (tibione).

Miscellaneous: Dinitrophenol, chlorpromazine, gold salts, industrial chemicals.

Secondary Thrombocytopenias.

Bedson showed in 1922 that the administration of anti-platelet serum in guinea pigs caused thrombocytopenia and damaged the capillary endothelium with resulting purpura.

Thrombocytopenic purpura due to specific drug hypersensitivity rather than drug toxicity is infrequent, but may be caused by a wide

variety of drugs. In order of frequency, they are: sedormid (allylisopropyl-acetylurea), arsenobenzol compounds, combined bismuth and arsenic therapy, the sulfonamides, quinidine and gold salts. A few cases of thrombocytopenic purpura have been reported following the administration of digitoxin, iodine compounds, chrysarobin, phenobarbital, allylisopropyl-barbituric acid, nirvanol, sodium salicylate, insulin, tetraethyl ammonium chloride, ergot, colloidal silver, bismuth, streptomycin, thele, antabuse, isonicotinic acid hydrazide, paramethadione, p-aminosalicylic acid, propylthiouracil, ethylallylacetylurea, Marbadal, amidopyrine, antazoline. Isolated cases of thrombocytopenic purpura have also been reported by exposure to DDT insecticide or insect bites, by eating mistletoe berries or application of "leg make-up preparations". Food very seldom induces thrombocytopenic purpura.

The antibodies are highly specific. Quinine, the optical isomer of quinidine had no effect on cells coated with quinidine antigen.

Thrombocytopenic purpura due to sedormid has been extensively investigated by Ackroyd. The administration of this drug to sensitive subjects was followed by marked thrombocytopenia within thirty to sixty minutes. The application of sedormid (solvent: propylene glycol) to the skin of sensitized patients resulted in purpura of the skin in the area to which the drug was applied. As no hyperemia or wheal formation becomes apparent, release of histamine is not likely. The blood clot of sensitized patients does not retract adequately in the presence of sedormid. This drug causes agglutination of the platelets of normal and sensitized persons, if suspended in serum of sensitized persons, but the presence of complement is necessary to produce lysis.

Four factors are concerned in the process: platelets, sedormid, complement and a lytic factor present in the serum of sensitized individuals. The interpretation of these findings is that sedormid unites with platelets and, acting as a haptene, confers antigenic properties upon them whenever the drug is taken. The compound formed by the union of sedormid and platelets must be very labile and consequently only weakly antigenic since so few patients taking the drug develop purpura. Lysis of this platelet-sedormid antigen by antibody and complement occurs only if the immune reactions are highly stimulated by the antigen. The antibody is a panagglutinin since all human platelets and not only those of sensitized patients are agglutinated. The petechial hemorrhages are independent of thrombocytopenia, for capillary hemorrhages produced by patch-testing occur in the absence of any change in the platelet count. It is supposed that the capillary damage is due to the action of an antibody formed upon the antigenic sedormid-endothelial cell compound.

Antibodies remain for a long time in the blood of sensitized patients, even though the platelet count has returned to normal.

Thrombocytopenic purpura associated with the intake of quinine, quinidine, sulphamezathine, benadryl, dormison and antazoline has been investigated in detail and seems to have a similar pathogenesis. All these chemical agents may cause a thrombocytopenia and a hemorrhagic diathesis with associated platelet deficiency in sensitized patients without influencing the red or white cells of the bone marrow or peripheral blood. Other drugs will regularly produce thrombocytopenia, granulocytopenia and anemia provided the intake is large enough. These drugs damage the megakaryocytes directly by their toxic effect, no peripheral platelet agglutination or lysis being observed. Benzol, antimetabolic agents and most of the drugs used to treat leukemia and lymphomas fit in this category, which is clearly distinct from the previous one.

The clinical symptoms of the hemorrhagic diathesis are petechiae or ecchymoses in the skin and bleeding from mucous membranes. There is no local edema, erythema or infection of the affected skin. Red and white cells are normal. The platelet count may be as low as 20,000 cu.mm., the bleeding time is prolonged and the tourniquet test positive. The most important abnormal clotting test are poor retraction, slow consumption of prothrombin in serum, diminished heparin tolerance and a low generation of plasma thromboplastin. All these tests are normalized by the addition of a normal platelet suspension.

The proper treatment in all cases will be the avoidance of the offending chemical agents. The administration of prednisone or related compounds and transfusion of fresh blood, plasma or platelet suspension should be reserved for cases with clinically severe bleeding. The blood should be collected in plastic bags or carefully siliconized glassware. Heparin or disodium ethylene diamine tetracetate dihydrate (Na_2EDTA) are the best anticoagulants. Prednisone and Prednisolone act chiefly on the vascular walls with a temporary reduction or normalization of the tourniquet test and bleeding time.

Circulating Anticoagulants.

The mounting evidence for physiologic anticoagulant in normal blood has focused the attention of hematologists on the role of these blood clotting inhibitors in hemorrhagic diatheses. Various types of anticoagulants of high titer have been described in the blood of some bleeding patients. An increase in antithrombin activity is not necessarily associated with bleeding and is not likely to be the sole cause

of a hemorrhagic diathesis when bleeding is present. Other types of potent anticoagulants were found but are probably not involved in normal hemostasis. Most of them interfere with the first phase of blood clotting, namely the generation of thromboplastin, or inhibit the activity of formed endogenous plasma or tissue thromboplastin.

The group of patients with circulating anticoagulants, preventing the formation of plasma thromboplastin can be subdivided as follows: 1) idiopathic cases with no other known disease; 2) patients where the presence of an anticoagulant is associated with lupus erythematosus, tuberculosis, periarteritis nodosa, chronic glomerulonephritis, pemphigus, Duhring-Brock disease or with the appearance of paraproteins; 3) in females following pregnancy (not later than 12 months after parturition); 4) in females not related to pregnancy; 5) in patients suffering from hemophilia (type A or B).

In a second group of patients the circulating anticoagulant prevents the activity of formed endogenous plasma or tissue thromboplastin. Idiopathic cases are known with a species specific anticoagulant, inhibiting only human brain thromboplastin; others are species non-specific (acting against human and animal brain or lung extracts). This group also includes many cases where the formation of an anticoagulant occurs concomitantly with lupus erythematosus or other collagen diseases.

In many cases there is reasonable evidence that the anticoagulant is an immunologic response to antigenic stimulus. This stimulus is sometimes obvious as in the hemophilic who develops an anticoagulant after repeated transfusions of plasma or antihemophilic globulin. In other cases, incompatibility of transfused blood or fetal red cell antigens producing maternal antibodies may be incriminated. The simultaneous presence of a circulating anticoagulant and immunologic disturbances (leukoagglutinins, red cell agglutinins, positive Coombs test) as in the various conditions conventionally grouped under the term "collagen disease" also points to a similar pathogenesis. The fact that the anticoagulant is present in the gamma globulin fraction and that in several cases a positive precipitin test was found also supports the theory that circulating anticoagulants are antibodies.

The anticoagulants preventing the formation of plasma thromboplastin have a similar mode of action. They interfere only in the early stages of the first phase of the clotting mechanism. The formation of an intermediate product between antihemophilic globulin, calcium and factor IX (P.T.C. or Christmas factor) is prevented. The anticoagulant activity is without influence once these clotting factors are linked. Consequently coagulation is severely impaired; whole blood and plasma clotting time is prolonged. Mixtures of

patient's and normal plasma or blood also have a prolonged clotting time. The utilization of the prothrombin in serum is slow but the prothrombin time of plasma is normal.

If the anticoagulant inhibits formed thromboplastin, a prolonged plasma prothrombin time is also found. Human and animal thromboplastins should be used to determine species specificity.

The clinical picture is very similar to hemophilia, even hemarthroses may occur. Large subcutaneous ecchymoses, intramuscular hematomas, gastrointestinal bleeding and epistaxis are frequent complaints. Minimal trauma may be followed by prolonged and extensive bleeding. Purpura never occurs.

Little comment can be made with regard to therapy. Since the immunologic mechanism may be involved in the pathogenesis of circulating anticoagulants, steroid therapy has been tried by several authors. In cases of hemophilia and in conjunction with pregnancy the formation of an anticoagulant may be the result of therapy and is often a self-limiting condition. Since bank blood may further stimulate the process, only washed compatible red cells should be given. ACTH may be tried in the absence of other satisfactory therapy.

B. *Autoimmune Mechanisms.*

Acquired Hemolytic Anemias.

The hemolytic anemias, when not consequent upon some congenital structural weakness of the erythrocyte, are the result of pathological functioning of the immunologic mechanisms. This is the acquired form of the disease. The globulin of the patient's serum which normally forms antibodies against foreign cells and bacteria is prevented in its action to the extent of producing antibodies to the patient's own red cells.

The process may be cryptic as in idiopathic hemolytic anemia, it may be the result of obviously demonstrable lesions of the sites of gamma globulin formation as in hemolytic states secondary to myelomatosis or certain leukemias or, thirdly, it may involve the intervention of a drug or toxic chemical in the antigen-antibody reaction.

Of fundamental importance in the diagnosis and investigation of acquired hemolytic anemias is the anti-globulin or Coombs test. The essential reagent is the serum of a rabbit which has been immunized against human globulin. Its serological use is in the detection of globulin which has been attached to the surface of red cells. If washed red cells become agglutinated on suspension in anti-globulin serum, then it may be assumed that they are coated with globulin that has attached itself as an incomplete or blocking antibody. This

is the direct anti-globulin reaction which is positive in many acquired hemolytic anemias, indicating that incomplete antibody is present and that this is predisposing the red cells to early removal by the spleen and consequent shortened survival.

The anti-globulin reagent may also be used to demonstrate the presence of incomplete antibodies in the patient's serum. Normal red cells having the antigens appropriate to the test are suspended in the patient's serum and incubated. These cells are then washed free of all serum and suspended in the anti-globulin reagent. If agglutination occurs, it indicates that globulin is attached to the cells and that the patient's serum therefore contained incomplete antibodies against the antigens of the test red cells. This is the indirect antiglobulin reaction.

The indirect anti-globulin reaction is used in cross-matching blood for transfusion and in typing cells for those normal red cell antigens which give rise to incomplete antibodies. Thus, in using the test to investigate an Rh negative woman's serum for anti-Rh antibodies, the cells appropriate to the test would be normal Rh positive cells or, more specifically, the cells of the husband.

Idiopathic Acquired Hemolytic Anemia. In primary forms of the disease it is unclear by what mechanism the pathological antibody develops. There are probably several different paths by which the common end result may be reached. There is some evidence to suggest the action of viruses in certain cases. The patient may develop a hemolytic anemia following an upper respiratory infection and it is supposed that it is the virus in combination with the red cell that has become antigenic to the patient and hence provocation of antibodies in the serum which render those same red cells liable to early destruction.

It seems very likely that a mechanism of this type is operative in cases of infectious mononucleosis which are complicated by hemolytic anemia since it seems likely that this disease is caused by a virus, though none has been isolated. Another example of interference with the immunologic mechanism brought about by infectious mononucleosis is the curious observation that in a large number of cases the serum becomes inordinately capable of agglutinating sheep red cells. This forms the basis of the heterophil antibody or Paul-Bunnell test.

Secondary Hemolytic Anemias and Dysproteinemias. In certain hemolytic anemias secondary to other diseases, it is easy to point to the causation of the disorder in the sites of abnormal gamma globulin production. These are the bone marrow, the spleen and the other parts of the reticulo-endothelial system, the cells involved being the lymphocytes and the plasma cells.

Chronic lymphatic leukemia, for example, is characterized by lymphocytes which are abnormal in function and in number. The plasma cells also are pathological or, at times, absent. The derangement of gamma globulin production by these cells may manifest itself in a number of ways. Failure in antibody production may expose the patient to the dissemination of microorganisms against which the appropriate antibody is no longer produced. The red cell antibodies, instead of being active only against incompatible red cells, develop the capacity to agglutinate the patient's own red cells. Consequently, a secondary hemolytic anemia is common in chronic lymphatic leukemia. In occasional cases of this disease there is complete agammaglobulinemia. Since there is no gamma globulin, the serum may be found to be entirely devoid of iso-agglutinins so that the patient becomes an exception to Landsteiner's rule and is therefore receptive, at least theoretically, to transfusion with blood of any group.

In multiple myeloma, a variety of complex disorders of protein synthesis is to be seen. No two cases are quite the same. The myeloma cells, probably abnormal derivatives of the plasma cells, manufacture quantities of abnormal globulin which are easily demonstrated as heavy bands in the electrophoretic pattern of the serum. These physico-chemical pecularities are accompanied by immunological disturbances. Here again, these take the form of susceptibility to infection and auto-immunization. In many instances, gamma myeloma presents an interesting paradox; a heavy band of protein in the gamma globulin zone is seen on electrophoresis of the serum but this protein is so abnormal that functionally the case behaves like one of agammaglobulinemia—the capacity to form antibodies to bacteria is lacking and there is an extremely low titre of iso-antibodies to the ABO antigens which are lacking from the patient's red cells.

The group of disorders here discussed have been assembled under the generic term *dysproteinemias*. This name is perhaps not intended to be strictly definable but gives a certain unity to a diverse number of conditions whose clinical picture presents numerous immunoallergic manifestations which are traceable to faulty protein synthesis.

Many of the lymphomas and malignant neoplasms fall into the category of dysproteinemias. Another member of the group is Waldenström's macroglobulinemia. This is characterized by progressive anemia, enlarged lymph glands and a hemorrhagic diathesis. The serum contains an abnormal globulin which has a molecular weight of one million.

These examples are instructive in revealing the relationship be-

tween gross physico-chemical disturbances of protein synthesis and immuno-allergic phenomena of the type easily studied by the classical methods of immunology. Present knowledge leans heavily upon recently developed investigational techniques such as electrophoresis. It is reasonable to hope that future advances in the knowledge of physical and chemical structure of protein molecules will yield considerable further information which will contribute to the understanding of the basic nature of immuno-allergic disease in general.

Hemolytic Anemias associated with Chemical Substances. In hemolytic anemias associated with exposure to drugs and other chemical substances, it is of interest to note that the same compounds may be incriminated as in drug-produced leukopenia and thrombocytopenia. This is certainly true for benzene and for acetanilid, for example.

Furthermore there is the widest possible range of susceptibility when different individuals are studied, one patient being specifically prone to develop a hemolytic state from one compound and another patient, equally characteristically, from a second compound. The dosage of offending substance need not be large, often a severe hemolytic reaction may be induced from a very small exposure for a short period, notably in the case of paraphenylenediamine, a common constituent of hair dyes.

These facts encourage the belief that many substances cause hemolysis not by direct destructive action upon the cells (though this can happen, as in the case of phenylhydrazine) but by some participation in an immuno-allergic process. The elucidation of the mechanism whereby this occurs must await a better understanding of the true nature of antigens and antibodies. It may be postulated however that the red cell, in favorable circumstances, becomes antigenic by the incorporation of an exogenous chemical substance and thereby evokes antibodies which will cause destruction of the red cells when at any future time they become exposed to the same substance.

If leucocytes and platelets are capable of becoming auto-antigenic by being exposed to chemicals then it is not surprising that many substances responsible for the depletion of one of the formed elements are also toxic to the other cells of the hematopoietic system.

Agranulocytosis or Leukopenia by Auto-Antibodies.

In this group of neutropenic patients, no causative drug can be incriminated and the antileukocytic properties of the serum remain permanently. The antibody acts directly on the surface of the leucocyte without the intervention of any chemical substance as described in the chapter on agranulocytosis due to drugs. The me-

chanism is similar to that causing immune hemolytic anemias. Two main groups may be distinguished: the primary leukopenias with no other underlying disease and secondary leukopenias associated with lymphomas, splenic tuberculosis, acquired hemolytic anemia, lupus erythematosus, Marchiafava-Micheli syndrome etc. As it is still impossible to distinguish naturally occurring leucocyte antibodies from those produced by multiple blood transfusions, this last condition should also be included in the list.

Idiopathic Leukopenia and Leukocyte Auto-Antibodies. Francke demonstrated in 1940 that the serum of a patient with idiopathic agranulocytosis had an agglutinating and lytic effect on immature, but even more intensively on mature, normal leucocytes. His findings were subsequently confirmed by Oliva and Turbetta, Ninni and others. Dausset and his group have isolated at least 33 cases of leukopenia associated with leucocyte agglutinating properties in the serum.

The age incidence of the disease is highest in the fifth and sixth decades and the male to female ratio is 2:1. The disease begins insidiously with fatigue, asthenia and minimal dyspnea on effort. The symptoms usually continue for 1 or 2 months before the patient seeks medical help, by which time there is usually a moderate anemia with thrombocytopenia and severe leukopenia affecting particularly the granulocytes. The bone marrow at first shows a reactive picture, but is later hypoplastic. Leucocyte antibodies are present in the blood and have agglutinating and sometimes lytic properties. The antibodies are gamma-globulins. Complement is required to obtain a lytic effect. Leucocyte auto-antibodies do not always necessarily cause auto-agglutination but the leucocytes become coated with antibodies and phagocytosed by normal cells.

Some cases have a chronic course for months and even years while others make a complete clinical recovery though maintaining some of the biological abnormalities. There are two complications which may even be fatal: a bleeding tendency due to thrombocytopenia and a greatly increased susceptibility to infection.

Treatment is disappointing. ACTH has been tried extensively but seldom improves the clinical condition. Splenectomy causes a clinical improvement with a transient amelioration of the laboratory data in some instances.

Symptomatic Agranulocytosis by Auto-Antibodies. A few cases of aleukemic leukemia with auto-antibodies having agglutinating properties against leukocytes in the serum have been described. Similar antibodies have also been observed in the serum of patients with acquired paroxysmal hemoglobinuria, acquired hemolytic anemia with cold auto-antibodies, myeloma, lymphosarcoma, Hodgkin's disease,

aplastic anemia etc. All these conditions are known to be possibly complicated by auto-antibodies against red cells.

The simultaneous fall in leukocytes, red cells and thrombocytes in many of these patients is difficult to explain. Anti-platelet and anti-red cell antibodies could be found inconsistently. Some of them show pan-antibodies active only against trypsinized cells. The possibility still remains that the techniques for detection of specific agglutination antibodies are not sufficiently sensitive, that the anti-leukocyte substance has a polyvalent action on a protein substrate common to all three series, or that thrombocytopenia and anemia are produced by some other unknown mechanism.

The L.E. phenomenon and clumping of leucocytes in lupus erythematosus is the consequence of antinuclear antibodies rather than antileukocytic antibodies. In comparative investigations it has been found that serologically, the L.E. factor behaves like an experimental antinuclear antibody. It seems to be a gamma globulin adsorbed specifically and quantitatively upon nuclei, which is eluted again only with great difficulty.

Idiopathic Thrombocytopenic Purpura. Several lines of investigation suggest that some cases of idiopathic thrombocytopenic purpura (I.T.P.) are due to an autoimmune mechanism. Evans and Duane have observed that some patients with acquired hemolytic anemia have persistent neutropenia and thrombocytopenia. Since acquired hemolytic anemia is due to demonstrable agglutinins, they deduced that thrombocytopenia and granulopenia might be due to the same cause. Another argument was that both conditions improve simultaneously in some patients following splenectomy. An observation also suggesting a humoral agent as the cause of the disease is the occurrence of transient thrombocytopenic purpura in more than half of the babies born of mothers with idiopathic thrombocytopenic purpura. The offending factor in the mother's blood passes through the placenta and destroys the baby's platelets. The survival, in the circulation of normal individuals, of transfused platelets from patients with hypoplastic bone marrow or patients with I.T.P. supports the hypothesis of rapid platelet destruction in these diseases. The survival time of transfused platelets in cases with a hypoplastic marrow is 4 to 5 days, in cases with I.T.P. only 1 to 24 hours. The plasma of approximately 30 percent of the patients with I.T.P. transfused into normal individuals causes a temporary thrombocytopenia and even purpura in the recipient.

Although this in vivo demonstration of a platelet depressing factor in the plasma of some patients with I.T.P. provided convincing evidence of the existence of a platelet auto-antibody, there is still much uncertainty. The demonstration of platelet agglutinins in vitro is

technically difficult. Platelets are not so easy to manipulate as, for example, red cells. The normal tendency of platelets is to clump, red cells on the other hand do not agglutinate spontaneously. Moreover, the amount of available platelets in cases of I.T.P. is by definition sparse. It is difficult to demonstrate the presence of adsorbed antibodies on the surface of platelets with the antiglobulin technique, considering that platelets are partly clumped during the repeated washings.

For this and other reasons, more emphasis has been laid on the demonstration of agglutinins in the plasma and serum. The incidence of positive results varies in the published series from 28 per cent to 66 per cent. Many of these cases have not become immunized against platelet types through pregnancy or transfusion. The assessment of platelet agglutinins is so difficult that several workers fail to obtain reproducible results and cross experiments in different laboratories testing the same blood samples have been discouraging. Several modifications of the techniques have been presented (preparation of the serum, choice of the anticoagulant) and even a modified Coombs test (Flückiger, Hassig and Koller) and a hemagglutin test have been described (Kissmeyer-Nielsen). It is probable that the failure to demonstrate platelet agglutinins does not necessarily preclude their presence in the blood of I.T.P. patients. A similar situation occurs in acquired idiopathic hemolytic anemia where free serum auto-antibodies are not demonstrable by any technique, even where there is active disease. If the antibodies fixed on platelets have a low dissociation constant, it will be difficult in many cases to demonstrate the presence of free agglutinins in the plasma. In addition it may be important to include the patient's platelets in studies for autoagglutinins, since there is evidence that auto-antibodies for platelets are specific and agglutinate only autologous platelets.

Not all platelet agglutinins have an additional lytic effect. If the antibody is only an agglutinin, the clumped platelets are lysed in the circulation or within the tissues or may be phagocytosed by tissue macrophages and leucocytes. Damaged platelets are also trapped in the spleen.

I.T.P. may be acute or chronic. In both types there is thrombocytopenia in the peripheral blood, increase in the number of megakaryocytes in the bone marrow and abnormalities in their morphology and a normal or slightly enlarged spleen.

Acute I.T.P. occurs typically in young children where bleeding into the skin and mucous membranes starts suddenly without any previous tendency to bruising. The hemorrhage is often very severe, probably because the vascular wall is injured as well as the platelets and megakaryocytes. Extensive ecchymoses, severe epistaxis or spon-

TABLE 1

	Acute I.T.P.	Chronic I.T.P.
Blood:		
Platelet count	Extremely low. (5,000–20,000/mm³)	Low. (40,000–20,000/mm³)
Platelet morphology	Relatively normal.	Platelets large, bizarre, irregular.
Eosinophilia	Often present.	None.
Lymphocytosis	Often present.	None.
Bone marrow:		
Megakaryocytes	Normal number. Often small, agranular vacuoles, degenerated forms present, immature forms. Prevaling in differential event. No platelet production.	Increased number. Normal size, granularity reduced, mature megakaryocytes. Prevailing in differential event. Diminished platelet production.
Eosinophilia	Often present	None.
Platelet agglutinins	Rare.	In about 50 % of cases.
Thrombocytopenic effect of plasma	Rare.	In about 60 % of cases.
Platelet survival time	Very short (1 to 6 hours).	Short (12 to 24 hs.)

taneous bleeding from other sites are noted. Physical examination is almost negative except the bleeding. The bone marrow shows a normal or slightly increased number of megakaryocytes mostly of the intermediate type. The number of the eosinophils is also increased. The last finding seems to be typical for the self-limited type of disease.

After a few days of intense bleeding, the bruising tendency decreases, purpura disappears and shortly afterwards the platelet count returns to normal. The whole course lasts 2 or 3 weeks to 1 or 2 months. Most patients with this self-limiting disease heal completely but about 10 per cent become chronic.

The chronic relapsing thrombocytopenia occurs most frequently in adults and older adolescents, 64.3 per cent appearing before the age of 21. The incidence of the disease before puberty is the same in both sexes: after puberty the male-female ratio becomes 1:2. A family history of easy bruising is uncommon.

A personal history of ready bruising, bleeding gums and epistaxis over a variable period of time is obtained. A sudden onset of the clinical symptoms is rather rare. The appearance of petechiae and purpura in the skin and mucosa together with spontaneous ecchymoses and suffusions are typical of thrombocytopenia.

The abnormal physical findings are limited to the sites of bleeding with a moderately enlarged spleen in about a fifth of the cases. There is no glandular enlargement and the liver is normal.

The laboratory data reveal normochromic anemia proportional to the blood loss. Long standing bleeding produces a hypochromic picture. The platelet count is low, well under 100,000/cu.mm.; the bleeding time is prolonged: clot retraction is slow or absent. Other coagulation tests giving abnormal results are a slow consumption of prothrombin in the serum, diminished heparin tolerance of the plasma, generation of a small amount of plasma thromboplastin at a slow rate and an abnormal thromboelastograph. The bone marrow shows an increase of megakaryocytes with single nuclei, relatively little cytoplasma and few granules. The main abnormalities are nonlobulated nuclei, the presence of vacuoles and the lack of granules in the cytoplasm. In contradistinction to the acute form of I.T.P., there is minimal injury to the vessels in the chronic type. A special group in the chronic type is seen in women developing thrombocytopenia during pregnancy. Serological studies on 12 mothers with auto-immune idiopathic thrombocytopenia have permitted accurate predictions of neonatal thrombocytopenia in 23 out of 24 of their infants. In 6 additional instances, normal mothers apparently became immunized to the platelets of their fetuses and gave birth to a total of 7 infants with neonatal purpura.

The treatment of acute I.T.P. is positive in two respects and negative in one during the acute phase. Positively, the patient should be helped to survive the emergency period of the disease without surgery. Transfusion of fresh blood, plasma or platelets and administration of prednisone may be life saving. Splenectomy in the active bleeding phase is a dangerous and unnecessary operation. The self limiting character of acute stormy idiopathic thrombocytopenia has always to be kept in mind.

The actual treatment of chronic I.T.P. is based on the well planned use of prednisone and related compounds, transfusion of plasma or platelets and splenectomy. The most important effect of steroids in these conditions is on the vascular fragility. The tourniquet-test often becomes negative or less positive within a few hours of cortisone therapy although the number of platelets may still be low. A temporary increase in platelets is noted after a few days of treatment in some cases. This might be a consequence of the stimulating

effect of the hormone on the bone marrow. No advantage of the intravenous route of administration of steroids has been noted, except for a more rapid effect on the vascular wall. Transfusion of platelet-rich plasma or a platelet suspension is presently possible in larger institutions. It is known that platelets are unstable after contact with a foreign surface such as glass or metal. The coating of needles and containers with water repellent agents f.i. Arquad 2-C (Dicoco-dimethyl-ammonium chloride), Lacquer Silicone or Teflon fluid to metals and silicone to glassware give satisfactory results and a limited platelet loss. The availability of plastic tubes and bags has solved many problems. The usual technique used to concentrate platelets is differential centrifugation. There is still uncertainty about the preserving media to be recommended (dextrose, gelatine, plasma, saline, glycerine). Many investigators prefer therefore the administration of fresh platelet-rich plasma, obtained by low speed centrifugation of compatible blood collected without vacuum in plastic bags. There is no constant direct relationship between survival time of transfused platelets and the improvement of the bleeding manifestations of the patient. Even if platelet counts remain low, it is quite common for a cessation of bleeding to be noted.

Splenectomy is definitely contra-indicated in I.T.P. secondary to drug ingestion, in neonatal purpura and in the acute state of I.T.P. in children, which usually undergoes spontaneous remission. In chronic I.T.P. a six month trial with adequate doses of steroid therapy should be instituted before splenectomy is decided upon. The operation should be done at a favorable time after preparation with steroids and platelet transfusions. About 60 per cent of the chronic cases show an immediate and sustained post-operative rise of platelet level, although some of them may relapse after a few years. About 20 per cent of the cases show a partial favorable clinical response as well as a rise in platelets. In 20 per cent there is no improvement following splenectomy. Some of the last cases may possibly belong to the category of disseminated lupus. It has been stated that splenectomy is usually successful when ribonuclease material is detected by the Feulgen stain in the megakaryocytes and platelets. According to Harrington and Osimura, splenectomy was successful in 68 out of 83 patients with antibodies but in only 5 out of 21 of those in whom a positive test was not obtained.

Supportive measures with steroids and platelet transfusion can be advised to treat bleeding in splenectomised patients. The search for accessory spleens has been disappointing and little advantage has been gained in practice from injecting Thorostrast or by reintervention.

3. Allergic Purpuras

Acute vascular anaphylactoid purpura has been described as hemorrhagic capillary toxicosis of Frank, peliosis rheumatica and Schönlein-Henoch syndrome. Schönlein described a hemorrhagic disease of purpura with acute rheumatic symptoms. Henoch called attention to a similar purpura associated with crampy abdominal pain and melena. The full picture includes symptoms referable to the skin, joints, gastro-intestinal tract and kidney. Anaphylactoid purpura may be considered as a generalized disturbance of small blood vessels in which purpura is only one manifestation. Pathologically, there is a diffuse angiitis of the smaller vessels and capillaries. An active pericapillary inflammatory infiltrate with lymphocytes, polymorphonuclear cells and macrophages is centered around capillaries and in some of them necrotizing arteriolitis has been described. These changes cause an increased permeability of the capillary endothelium. The onset of purpura is sudden and usually commences 1 to 3 weeks after a sore throat caused by a hemolytic group A beta streptococcus. The exciting factor may occasionally be a drug (antibiotics, antihistaminics, menthol, quinine, gold ...), an insect bite or the ingestion of food to which the patient is sensitized (chocolate, tomatoes, eggs, seafood, etc.). In the majority of cases no specific causal agent can be discovered. The infection is probably responsible for the initiation of an immunologic response. The antigen-antibody reaction takes place in the lag period at the vascular level.

This non-thrombocytopenic purpura with the characteristic cutaneous purpura, the digestive symptoms and a microscopic hematuria has been reproduced by several authors by injecting guinea pig vascular endothelial antiserum in dogs and guinea pigs. This experimental syndrome seems to have at least two phases: an early phase immediately after the rabbit-serum injection and a secondary phase around the 9th day. The capillaro-toxic potency of an immunized rabbit serum or of the serum of a patient with the Henoch-Schönlein syndrome is linked to gamma-globulin. Their injection in the presence of added complement produces ecchymoses. Allergic purpura with angiitis of small vessels, perivascular changes of the skin and generalized character of the disease are very similar to periarteritis nodosa where larger vessels are involved. Allergic purpura is considered by some to be one of the collagen diseases. Even the association of allergic purpura with hyperimmune states such as acute idiopathic thrombocytopenic purpura has given some support to the belief that these various conditions may be inter-related.

The purpuric attack is often preceded by malaise, fever and head-

ache. Large purpuric spots in milder cases are usually limited to the extensor surfaces of the limbs, the lower back and buttocks. The trunk and face are rarely affected. The shape of the purpuric lesions is variable, being in general larger and sometimes more confluent than in thrombocytopenic states. There is a symmetrical distribution of the intensely purplish, slightly elevated spots. Hemorrhage in this syndrome is rarely severe and even the purpuric spots are a minor component of the clinical picture. The tendency of the spots to coalesce and their variability in size and shape contrast with the small and regular pinkish petechiae of Werlhof's disease. The skin eruptions begin occasionally with urticarial wheals. The joint symptoms are typical for Schönlein's purpura and are characterized by periarticular effusion and swelling associated with pain. The metacarpal, knee and elbow joints are frequently involved. Hemarthroses never occur. Salicylates are ineffective. The purpura itself is usually slight and may not appear until long after the joint symptoms have become apparent. The patient may run a low grade fever as long as arthralgia is present.

The gastro-intestinal symptoms (Henoch's purpura) occur most commonly in children and adolescents and include abdominal colic with melena; even bright red blood may appear in the stools. The symptoms are caused by edema and hemorrhagic effusion in the intestinal wall, which may simulate intussusception. The mistaken diagnosis of acute appendicitis is not infrequently made.

The renal symptoms may consist of hematuria and hyaline and granular casts may be found. Only microscopic hematuria remains after one week; the persistence of casts indicates a chronic renal involvement with a poor prognosis. Nephritis has been observed in as many as 47 per cent of cases. The renal lesion is the slowest to heal. The autopsy findings in the kidneys are the same as in acute glomerulonephritis. The laboratory findings in allergic purpura are few. Only a moderate increase of the white count is found. Bone marrow aspiration may show an increase in megakaryocytes. Platelet count and function are normal. The tourniquet test is negative or only mildly positive. All other blood clotting investigations are normal. An antivessel precipitin test, using neonatal aorta, may be positive.

The disease is "self limiting" in nature. During the active period the patient should be confined to bed. Articular and intestinal pain are relieved by sedatives. ACTH gives prompt remission of the histologic lesion but seems not to act directly on the renal symptoms. According to several authors the disease fails to respond to cortisone but the clinical symptoms improve with larger doses of prednisone. Only a long -term follow-up will determine whether permanent renal impairment can be avoided by steroid therapy.

4. Hematologic Manifestations of Diseases with a Questionable Immuno-Allergic Etiology

Certain generalized diseases of the mesenchymal structures such as rheumatoid arthritis, lupus erythematosus, scleroderma and periarteritis nodosa are often grouped together under the title of "collagen disease". Though of unknown etiology, these disorders have features which suggest that an immuno-allergic mechanism is operative. Much of the supporting evidence for this belief is supplied by the results of hematologic studies.

In rheumatoid arthritis, it has been possible to demonstrate a serum factor which has a high specificity for this disease. This factor causes the agglutination of sheep red cells which have been sensitized by a sub-agglutinating dose of anti-sheep cell serum prepared in the rabbit. The reaction has some value as a diagnostic test in differentiating rheumatoid arthritis from other diseases, but shows more promise of usefulness in the investigation of the pathogenesis of the condition.

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ALLERGY OF INFANCY AND CHILDHOOD

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When Von Pirquet and Schick first started giving specific treatment of anti-diphtheric and streptococcal serum to children, they observed that a number of them developed a serum disease. Their original description—now translated into English (Von Pirquet and Schick 1951), remains to this day a wonderfully accurate description of a syndrome that became the beginning of what Von Pirquet described as "Allergy".

The capacity to develop the atopic type of sensitivity cannot be induced experimentally, but the induced type of sensitivity as seen in serum sickness and some drug reactions has much in common with the spontaneously occurring type of allergy. The capacity to develop an induced type of sensitivity reaction is in no way confined to the so-called allergic child. An induced sensitivity is probably more likely to develop in someone who is already allergic, as allergic individuals are three times more likely to become sensitive to penicillin injections than the non-allergic. Nor must it be forgotten when considering the serum sickness type of reaction that fever is one of the more frequent symptoms. Asthmatic children often have a raised temperature with the more severe attacks. In the past, it was generally considered that the fever was caused by infection and before the antibiotic era, bacterial vaccines were used to combat infection.

Bruun (1955) gives an account of a child aged one year who died following doses of a bacterial vaccine. It can be easily understood how an extract of an allergen could cause a generalized urticarial rash, asthma and anaphylactic death. It is not so easy to understand how a bacterial vaccine could cause death unless perhaps with each dose the vaccine sensitized the child.

Rhinitis and Nasal Catarrh.

Many children have repeated colds but the term tends to be used as a diagnosis rather than a descriptive term. The colds are described

by some mothers as catarrh and by others as hay fever particularly when associated with much sneezing. Before making any decision as to the possible cause of the nasal symptoms, it is always important to obtain a very careful history of the symptoms. The age at the onset of symptoms must be very carefully ascertained. Some mothers will insist that the child always had a wet nose and tended to be a mouth breather. Others will say "always", but when asked to be more definite, will admit that the symptoms started about the age of five or later. The patient's personality and the parental attitude to the symptoms will emerge as the history is taken. The character of the nasal discharge if present must be noted. Is it watery, mucoid or purulent? Does it change in character? Is it sometimes greenish and thick? When the colour changes are there associated symptoms of cough or headache? Are the symptoms worse at any particular season? The symptoms that are worse in summer are suggestive of a possible allergic cause, if worse in winter of an infective cause. The previous history of infantile eczema or the story of dyspnoea and wheeze, again begin to point in the direction of a possible allergic cause.

It is surprising how often the symptoms that worry the parents seem to cause little trouble to the patient. Anyone who has spent some time in an ear, nose and throat department will know that the large majority of the children sent up for advice by doctors have come about the advisability of removal of tonsils and adenoids. This operation is at last becoming less popular than it used to be. All allergists are only too familiar with the story that asthma began after the removal of tonsils and adenoids. I strongly advise that if a child is thought to be allergic and if the nasal mucous membrane looks allergic, removal of tonsils should not be performed unless there is a definite indication for tonsillectomy. I believe that there are very few indications for removal of tonsils. Repeated colds and blocked nose certainly are not indications for removal of tonsils. Sobel (1953) has discussed adeno-tonsillectomy and its relation to asthma. He points out that there are three schools of thought. (i) The tonsils and adenoids act as a focus of infection and if these are removed the asthma will be improved. (ii) The tonsils and adenoids play an important role in preventing the spread of infection in the upper respiratory tract to the lower respiratory tract and therefore the removal of the tonsils and adenoids may precipitate asthma. (iii) The indications for adeno-tonsillectomy are the same for allergic and non-allergic patients. Sobel studied 100 patients and came to the conclusion that the indications for adeno-tonsillectomy were the same for the allergic as the non-allergic and made no difference to the severity of the asthma.

Migraine headaches can occur in children but a commoner cause of headache is a bilateral (rather than unilateral) headache seen in children with sodden nasal mucous membranes. The causal mechanisms of these headaches in children with non-suppurative sinusitis is often difficult to explain but is related to the interference with ventilation and drainage of sinuses (Protz 1951).

The appearance of the nasal mucosa may have been materially altered by the application of decongestants. The bright red appearance of the nasal mucosa must not be mistaken for a normal or an infected nasal mucosa without first making sure that it is not a "drop treated nose". The nasal mucous membrane is a pseudo-stratified columnar ciliated epithelium which lines the nasal cavities and nasal sinuses. Numerous goblet cells and submucous glands secrete mucus which is kept moving by the cilia in specific directions. In the sinuses it always leads to the ostia while in the front of the nasal cavity the flow is backwards to the nasopharynx. Besides the more obvious allergic and infective causes of nasal obstruction it is a common experience that a sudden fall in temperature or cooling of the body surface will produce nasal obstruction and hypersecretion (Collier 1954).

Emotions play a part in producing changes in the nasal mucosa. Wolf and associates (1949) showed that there were two different patterns of reactions. Fear, sadness and other conditions involving minimal conflict led to vasoconstriction with shrinking of the nasal mucosa. Probably the parasympathetic type of reaction is more common in the type of patient who comes for advice. Emotional situations producing frustration, guilt, anxiety and resentment lead to hyperaemia, swelling of the erectile tissue and increased nasal secretions.

Suppurative sinusitis probably only accounts for 30 per cent of the cases previously labelled sinusitis (Gill-Carey 1950). Non-suppurative sinusitis is a common complaint of children with an allergic background and the suppurative sinusitis following a non-suppurative sinusitis is rare. The seasonal hay fever patient seldomly develops a suppurative sinusitis at the height of the pollen cloud. Many children who have an allergic rhinitis of the perennial type which is so often due to the various components of household dust, have unnecessary nasal operations (Frankland 1958). Whatever the cause of nasal symptoms, antihistamine tablets are worth using in children, although good results are more likely in true allergic rhinitis (Frankland 1957).

Asthma.

It has recently been stated (Overall 1957) that most children do not tend to outgrow their asthma. The natural history and cause of asthma in childhood seems to be unpredictable in most patients. The mother is generally told not to worry about her child's asthma because he will outgrow the complaint if she stops fussing. Presumably doctors who give such advice believe it to be true. A long-term follow-up of asthma in childhood is not easily undertaken though three reports are available (Rackemann and Edwards (1952), Flensborg (1946), Dees (1957)). The most detailed study is that of Rackemann and Edwards, who reported on a follow-up study of 688 patients after an interval of 20 years. Of the children seen before the age of 13 years, 30.7 per cent were apparently "cured", 19.3 per cent were still sensitive but avoided the cause, and another 21.4 per cent no longer had asthma but had some other form of allergy, usually hay fever. 15.1 per cent had mild symptoms, 10.9 per cent still had serious asthma and 2.4 per cent were dead. In those seen after the age of 13 years the general impression was that the asthma was more serious because 21.7 per cent were cured, 25.5 per cent were relieved but were still sensitive, 8 per cent were relieved of asthma but were still allergic, mild asthma persisted in 12.1 per cent, severe asthma in 27.6 per cent and 5 per cent were dead. Flensborg's series in 1946 referred to 298 children who had been seen in the Danish children's hospitals between 1926 and 1939. The attacks had ceased in 40 per cent though nearly one half of these cases reported significant exertional dyspnoea. Grant (1957) noted that among university students 41 per cent of 119 men and 45 per cent of 33 women had become free of attacks of asthma during puberty and early adolescence.

In the Jewish National Home for asthmatic children at Denver, there is a hard core of 10 per cent of children who after 2 years' intensive treatment as well as "parentectomy", still retain an intractable asthma (Tuft 1957).

In any series of asthmatic children that has been followed up not less than 1 per cent die of their complaint. This aspect of the problem has been ignored, since it is more comforting to remember Osler's aphorism that "the asthmatic pants to a ripe old age". Recent experience with the steroid hormones in no way alters the fact that at all ages asthma can cause death. While the mortality rate is impressive, as it kills five times as many as polio in the United States, the morbidity is even greater and the disease certainly incapacitates as many as does poliomyelitis.

Many countries have special centres for the long term study and

treatment of asthmatic children. It may be unwise to generalize about any asthmatic patient from some of the conclusions reached at these asthmatic centres. This is because the children who are referred to these centres are almost always selected cases and generally represent severely incapacitated children.

The Jewish National Home for asthmatic children in Denver, Colorado, started in 1930, seems to have been a first attempt to make a special centre for asthmatic children (Glaser 1956). Some of the special schools, convalescent homes or hospitals for asthmatic children, claim good results because the child is taken up into the mountains, others because the child is taken to the sea, others because the child is taken away from its parents, others from the specific treatment given. In France there is a spa at La Bourboule where children come in thousands in the summer to take the "cure". The centre where fundamental studies are in progress is the Asthmatic Children's Home, "Heideheuvel", Hilversum, Holland. The findings from this centre after the first few years will make interesting reading. (Schoek 1956).

Bacterial Vaccines in the Treatment of Asthma.

It has been a time-honoured custom to use bacterial vaccines as a form of treatment in asthma. A generation ago it was taught that bacterial vacines would help to build up resistance against infective colds and would cut down the incidence of bronchitis. Now we are more interested to know what are the many causes of colds and what organisms are responsible for bronchitis. Whether stock or autogenous bacterial vaccines are effective in any specific way is not easy to decide. Wilken-Jensen (1956) is of the opinion that a stock bacterial vaccine is of help to children with the infectious type of asthma. Schoek (1956) notes that with an infection, asthma will often clear, and therefore doubts whether infection is important as a trigger for acute exacerbations of asthma. If this is so, and it is a common observation that an attack of measles (Morbilli) in a child will clear the child of asthma—then children may differ from adults. In adults there seems to be no doubt that the infective trigger is often the most important cause of an acute exacerbation of a severe asthmatic attack. Frankland and co-workers (1955) have found that an autogenous bacterial vaccine gives no *specific* help in infective asthmatic adults. We did not find, as has been stated, that bacterial vaccines are of no use, we found they gave good results in just over 50 per cent of patients. Saline injections, however, gave equally good results. I do not condemn the use of bacterial vaccines in asthmatic children, sometimes they are certainly worth using.

Case Report.—A patient aged 10 years was seen who had had his tonsils removed "to see whether this would help the asthma". It did not. I was asked by the boy's doctor to prepare an autogenous bacterial vaccine made up from organisms in his nasopharynx. The vaccine was made and the mother was delighted to think her son was going to have a course of injections to help him get through the winter. She wanted everything done to help her son's asthma, yet it was so mild that the boy told me he had not been kept home from school during the preceding year. On reviewing him three years after the vaccine had been given the boy was quite well. The mother was grateful for all the injections that I had ordered, she (but not I) believed that the bacterial vaccine had cured her son.

Tonsils are often removed with the idea that this will lessen the incidence of infective colds. Sometimes asthma apparently follows as a result; rarely, I believe, is asthma helped by the operation. It has been shown in the report of the school epidemic committee of the Medical Research Council (1938) that in Great Britain during one term in a population of 13,709 boys and girls, the incidence of upper respiratory infections was slightly higher in those who had had their tonsils removed than in those who had not. The attitude of parents and the family doctor who sends the child for a consultation with the specialist is that something more must be done. Unfortunately it often does not follow that what is done is necessarily beneficial. Indeed some children not surprisingly become really alarmed at the sight of a new doctor, which means new treatment.

Case Report.—An asthmatic boy aged eleven came to the hospital outpatient department one day, gave one look at me and began to cry. I asked him what was the matter. He said the first specialist he saw ordered his tonsils to be removed, the next his adenoids to come out, the third put him on injections for a year, the fourth sent him to a special school away from home, the next had him in hospital and drained his sinuses. It was not surprising that he wondered what was now going to be advised. He was relieved when told that he must make sure that his mother kept him away from doctors. He was told to have ephedrine tablets handy for any further attacks and to lead a normal life.

The over-treated child is always to be pitied, yet perhaps the under-treated child is almost as pathetic when a little reasoned prophylactic advice and palliative treatment may give such good results.

Infective Factors in Asthma.

One of the difficulties when considering the importance of the infective factors in asthma relates to the definition of terms used. Asthmatic bronchitis is a term that is used by many doctors to describe a clinical syndrome that they believe is quite different from bronchial asthma. The term is applied to paroxysmal attacks of dyspnoea accompanied by physical signs of wheezing and evidence of a respiratory infection. The condition commonly starts as a coryza. There is generally some fever, the blood sedimentation rate is

raised, nasal smears show a preponderance of neutrophils and sympathomimetic drugs usually are not helpful. When asthmatic bronchitis occurs under the age of three years, only a relatively small percentage develops asthma. Occuring over the age of three years most of the children will develop bronchial asthma. Doctors seem to dislike using the term asthma and often prefer to use the term bronchitis in the young. Mortality statistic for bronchitis in different countries in Europe are so very different that one suspects that the differences between Scandinavia and Great Britain, may be due in fact to diagnostic differences in nomenclature. For the same reason the terms bronchitis, asthmatic bronchitis and asthma may in many accounts refer to the same complaint.

When a child has had no previous eczema, the diagnosis of asthma may only be possible retrospectively depending upon further asthmatic attacks. Mention has already been made of the use of bacterial vaccines in asthma. In a recent excellent book "Allergy in Childhood" (Glaser 1956) in the chapters on the management of the child with either acute or chronic asthma, no mention is made of any causal organisms although antibiotics are recommended for the acute attack if this does not quickly subside.

There is certainly no simple relationship between bronchospasm and infection. Much bacteriological work in the past on infection has not taken into account that all sputum specimens are grossly contaminated by nasopharyngeal organisms. Neither has there been, until very recent years, any systematic study on the importance of the viruses. The latter produce epithelial cell destruction in the bronchiole and this favours the growth of bacteria. Nevertheless it is not certain whether the bacteria which give rise to purulent sputum have originated in the nasopharynx. The common cold virus probably gives rise to an increased flow of mucus and this may affect the drainage of the bronchioles. The formation of excessive mucus is one of the cardinal features of chronic bronchitis. Why this may or may not become infected must depend upon many factors most of which are unknown. There are four groups of viruses which may initiate acute attacks or cause relapses in infective episodes of bronchial asthma. There are (1) influenza viruses (2) the common cold virus (3) atypical pneumonia viruses (4) adenoviruses (or A.P.C. viruses). Further knowledge about the common cold virus and more easily available serological diagnostic methods may elucidate some of our present difficulties.

Case Report.—A girl in her teens was referred because of recent onset of asthma. Six weeks before she was seen she had her first illness which her doctor had diagnosed as bronchitis as she had a fever with some purulent sputum and a wheezy cough. The fever subsided, the sputum disappeared but she continued

to cough and wheeze. She finally returned to work but was awakened every night with wheezing and difficulty in breathing. She was referred to hospital 4 weeks after her original illness was diagnosed as asthma. All investigations such as blood counts and chest X-rays were normal. She was referred to me to exclude allergic causes for her asthma. I did not consider from her history that she had bronchial asthma. Skin tests were all negative but her blood serum showed agglutination of a very high titre 1/128 to psittacosis virus. Three months later this had fallen to 1/50. On my advice, the first time I saw her, she got rid of her three pet budgerigars which she said were healthy. This was before the serological report had been received so we do not know whether the birds were infected.

This case illustrates the help obtained by serology and the difficulties that may arise in diagnosing asthma.

Although epidemiological surveys have been made to study respiratory infection and its spread in a community in children, I can find no record where a special study has been undertaken in asthmatic children except that by Schoek (1956) in Holland.

It has been shown in adults (May 1954) that 10–20 per cent of patients with mucoid sputum harbour *H. Influenzae* or pneumococci. Eradication of these organisms produces no clinical improvement. In an acute exacerbation with purulent sputum it seems that 80 to 90 per cent of patients have *H. Influenzae* either alone or in conjunction with the pneumococcus as the infecting organism. (Mulder et al. 1952, May 1954).

Gastro-intestinal Allergy.

Collins-Williams (1954) reviewed the problems of gastro-intestinal allergy in infancy. He pointed out that there are many clinical syndromes in which allergy may play a part. Yet vomiting, diarrhoea, the coeliac syndrome, mucous stools, colic, abdominal pain etc., are common in infants, and it is difficult to assess the incidence due to allergic causes. Rowe (1944) believes that gastro-intestinal allergy is much commoner than is usually appreciated. He uses elimination diets as a means of diagnosis. Although many allergists would not agree with all Rowe's methods and conclusions, it is generally agreed that many food sensitivities will not give positive skin tests. Foods such as eggs, fish or nuts that cause a stinging sensation to the lips, mouth or throat and are automatically spat out by the child will, however, give a positive skin test. There may be fixed antibodies in the skin to fruits, e.g. strawberry, but the testing antigen is so weak and unstable that a positive response cannot be obtained unless fresh fruit juice is used. Skin tests, therefore, for many reasons have only limited value when investigating gastro-intestinal food allergies.

Diet diaries can be used to help the parents to devise a suitable diet, and at the same time the doctor decides whether any food elimination has helped. Removing a suspected food from the diet is

the simplest way of confirming a suspected diagnosis of gastro-intestinal allergy. The symptoms return when the food is put back in the diet. Eosinophilia, when looked for in the faeces or in the mucus of the vomit of an infant, should always suggest a possible allergic cause.

The allergist may be asked whether there is any justification for carrying out protein skin tests in the coeliac syndrome. There is probably no proof to suggest that those coeliac patients who respond to the removal of gluten from the diet are allergic. Collins-Williams and Ebbs (1954) found on testing 28 cases intradermally with wheat as well as the wheat fractions gliadin, globulin, glutenin and proteose, that ten gave positive reactions to wheat or its fractions while eighteen gave negative skin reactions. It is possible that in rare cases the sprue of adults and the coeliac syndrome of children is due to wheat or other food sensitivities.

Milk Sensitivity.

The incidence of milk sensitivity has been variously quoted from 0.3 per cent to 15 per cent. Grules and Sandford (1936) pointed out that seven times as many infants developed eczema on cows' milk as infants fed on breast milk. Ratner (1928) believed that allergic phenomena occurring in infants due to foods were caused by the overindulgence of these foods by the mothers during pregnancy. On these grounds a greatly increased consumption of milk or eggs by the mother is to be deprecated. The allergic mother does not apparently directly sensitize her child, because skin sensitizing antibodies (reagins) of the mother cannot be demonstrated in the cord blood taken from infants of such mothers (Bell and Eriksson 1931). Neither are reaginic antibodies to pollen found when skin testing the newborn infant of the mother with hay fever. We must therefore presume that the capacity to react allergically in the infant is dependant on genetic rather than on any passively induced mechanism. Although heredity probably does play a role in allergy, this has never been proved. (Frankland 1958).

As breast feeding becomes more unpopular, mixed feeding is often started earlier and one therefore expects that cows' milk sensitivity will become commoner. No allergic history is complete without enquiry into the diet during the first year of life. Fries (1952) found that in allergic children with nausea, vomiting, epigastric distress or abdominal pain starting a few minutes after the ingestion of offending foods, the most common finding radiologically was pylorospasm and this resulted in gastric retention. I have observed that in marked cases of cows' milk sensitivity a retrospective diagnosis of a

pyloric stenosis operation can quite often be made. This does not mean that pyloric stenosis is commonly due to allergic causes but undoubtedly it is one of the rarer causes. Addition of cereal and cows' milk may have heralded so-called teething eczema and bronchitis. Nor must it be forgotten that orange juice or fish oil may allergically upset the infant. Occasionally cows' milk can cause very acute symptoms of shock, vomiting, diarrhoea and croup. Collins-Williams (1955) reviewed 30 such cases, two of which were fatal. Clein (1951) reviewed the symptoms of cows' milk allergy in infants and found that in 24 per cent of 140 infants, diarrhoea was present, 6 per cent passed mucus in their stools, 5 per cent had chronic constipation, and many had colic. The milk-sensitive infant may belong to one of four categories: (i) he may be sensitive to the species specific factor of cow lactalbumin. This group of cases does well on goats' milk. (ii) he may be sensitive to a factor common to animal (but not human) lactalbumin. (iii) he may be sensitive to casein as well or (iv) to casein alone (Hill 1935).

Prophylactic Injections and the Allergic Child.

Parents will often enquire whether there is any danger for their allergic child to have a prophylactic injection. When giving advice it is always wise to point out that any injection carries a risk but that it is negligible. This does not mean that the doctor does not know the risk but he must be able scientifically to use his judgement as to the risk of any injection in a particular patient.

Infants with eczema should not be vaccinated because of the danger of a generalized vaccinia developing. No harm will be done by waiting a few years for the eczema to clear and then performing the vaccination. It is particularly important that the eczematous child should be immunized against diphtheria and tetanus so that the corresponding antisera need not be given should there be a danger of these infections. An eczematous child seems particularly liable to be sensitive to horse scurf and about 40 per cent of such children are sensitive to horse serum. Before giving an antitetanus serum a skin test should be performed. This is easily done by pricking through a drop of the undiluted serum. This will introduce about five millionths of a ml. (Squire 1950). If no positive skin response occurs, then it is safe to give a small dose (0.05 ml.) intracutaneously. A control test should be done at the same time. If after fifteen minutes there is no positive response then the full prophylactic dose can be given. Such a scheme can be carried out in half an hour. A positive prick or scratch test is a definite indication that a severe anaphylactic response may occur from a full prophylactic dose.

It is well to remember that an intradermal test as generally carried out introduces 20,000 times greater an amount of fluid than the prick test. An intracutaneous skin test using antitetanus serum has been known to kill a patient from anaphylaxis. I have only once seen a large immediate local urticaria following a prophylactic dose of tetanus toxoid. As at present prepared, it must be one of the safest, the most effective and the most important of the prophylactic vaccines.

Whooping cough, besides carrying its own mortality, is important as a disease in infants because it will often trigger off the onset of asthma. It appears as though the chest has been damaged or changed so that asthma, for a variety of reasons, begins to make its appearance. Whooping cough vaccine is worthwhile giving and by itself is relatively safe. The alum-precipitated diphtheria-pertussis vaccine carries a small but definite risk of precipitating paralytic poliomyelitis in about 1 in 37,000 inoculations. (Med. Res. Council 1956). Diphtheria prophylaxis is usually given in combination with pertussis and tetanus. Death following a diphtheria injection has occurred. Various viral and rickettsial vaccines are cultured on egg embryos. Ratner and his associates (1952) have described the various reactions that may follow giving such vaccines. These reactions may include fatal anaphylaxis, severe anaphylaxis with recovery, serum sickness-like reactions and local immediate and local delayed reactions. When in doubt a test dose of 0.05 ml. of the vaccine should be performed and any large local or systemic reaction would be reasonable grounds for withholding the vaccine.

Mansmann (1954) pointed out that when using influenza virus vaccine, patients sensitive to chicken were particularly liable to large local reactions.

Many parents are now enquiring whether it is safe or wise for an allergic child to be given injections of a poliomyelitis vaccine. In America probably about 15 million children had received the Salk vaccine by 1956 and no serious anaphylactic reactions had been reported (Bierly 1956). I have heard (Brum Negreiros 1957) of a doctor's child who unaccountably died suddenly two days after a poliomyelitis injection. Urticaria, angioneurotic oedema, erythematous rashes and febrile reactions after injections have been reported, but all are rare. In addition to the poliomyelitis virus protein and nucleoprotein, the vaccine contains small amounts of many substances which could sensitize and might cause a sensitivity reaction in someone already sensitive. These substances are (i) the medium that supplies the nutrients for tissue culture growths in vitro, (ii) horse serum—less than 1 part in 5 million, (iii) Phenol red 0.002 per cent, (iv) soluble monkey protein from blood or kidney, (v) Antibiotics

—penicillin, polymyxin, neomycin and dihydrostreptomycin, (vi) formaldehyde 1 in 4,000, (vi) preservatives which vary according to the manufacturer.

The penicillin content varies from 15 units to 0.005 units per ml. depending upon the manufacturer. As 10 units of penicillin can cause severe anaphylaxis it is possible for the vaccine to do this also. Yet patients have been known who have had poliomyelitis vaccine subsequent to a penicillin urticaria without any reaction. In general, the incidence of penicillin sensitivity in children is not high and the poliomyelitis vaccine so far has for the most part been limited to the younger age group.

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VASCULAR HEADACHE OF THE MIGRAINE TYPE

Its Relation to Histamine and "Allergic" Headache

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The "migraine" headache may be defined as a periodic, recurrent headache, commonly unilateral but often becoming generalized before the episode is ended, and frequently associated with nausea and vomiting. In 5–10 per cent of instances, it is preceded by visual disturbances and is significantly modified by vasoconstrictor agents. Perhaps 10–15 per cent of the population seek medical aid because of the severity of migraine attacks (1). We have recently examined a group of sixty healthy young men, not one of whom had been completely free of headache throughout his lifetime. The "migraine" headache in one or another of its many and varied forms comprises approximately half of those clinically encountered. The symptoms of the migraine attack may well be the commonest complaint heard in the physician's office.

It has often been stated that the migraine type of vascular headache is an allergic disorder, i.e. consequent upon an antigen-antibody reaction. In this chapter we will consider this thesis as it deals with the phenomenology of the migraine attack. Moreover, since histamine is postulated by some to mediate many of the results of the antigen-antibody reaction, the relation of histamine to headache will be evaluated.

The features of the migraine attack are conveniently divisible into those phenomena which are intimately linked with changes in the structure and function of cranial vessels and those which are not so related. Changes in the cranial circulation occur in three phases. In the preheadache phase, often accompanied by cranial vasoconstriction, and in the absence of pain, there are transient sensory and motor disturbances. During the headache phase, local pain, tenderness, edema and cranial vasodilatation are present. Finally, in the late headache and post-headache phase, the local scalp and periarterial edema and tenderness are more prominent. Uncommonly, dysfunction of the cranial nerves passing through the orbit also occurs. Any

or all of the latter features may and usually do outlast the headache itself. The pain, local edema, and tenderness are intimately linked with the large and minute vessel dilatation and the probable presence of substances in tissue fluid at the site of the headache that lower pain threshold, augment pain due to vasodilatation and damage tissue (2).

Those phenomena which are associated with the headache but are unrelated to change in cranial vessels will be discussed after consideration of the vascular dysfunctions.

Pre-Headache Phenomena.

As stated earlier, 5–10 per cent of migraine headache attacks are preceded by visual disturbances. Such visual alterations have a duration of a few minutes to an hour, on rare occasions lasting longer or remaining permanent. In some instances they may not be followed by headache and rarely may occur in a setting of headache. When of long duration, they may still be present at the time the headache begins and then diminish in intensity during the subsequent few minutes or hours.

The pre-headache visual disturbances take various forms. There may be blind spots, either black or gray, arrayed in simple arrangements or in homonomous, non-homonomous, or incongruous visual field defects. Bright flashes of light, multicolored balls, stars, serrations and fortification phenomena are sometimes vivid, i.e. "I see tinsel and cobwebs", "It's like looking through a waterfall", or "Like many colored balloons drifting across my eyes".

A study of the mechanism of scotomata at the New York Hospital was initiated by a physician who experienced predictable pre-headache phenomena and who was able to make accurate and rapid records of his own visual field defects. When at the onset of the field defects, the subject inhaled the vasodilator amyl nitrite in amounts so small as not to lower blood pressure, the field defects were entirely eliminated (Fig. 1). Shortly after cessation of inhalation of amyl nitrite, the field defects recurred. Inhalation of the same cerebral vasodilator again was followed by restoration of normal fields (3). Subsequently, it was observed that inhalation of 10 per cent carbon dioxide, another cerebral vasodilator, had a similar effect on this pre-headache phenomenon (4). Superficial temporal artery constriction measured plethysmographically also occurred during scotomata (5). A patient, subject to migraine headaches, was studied during a headache-free period. The intravenous infusion of levarterenol (an agent having vasoconstriction as its sole significant effect) at a rate sufficient to raise blood pressure 50 mm. of mercury systolic and 30 mm. diastolic induced scotomata. The patient saw a black

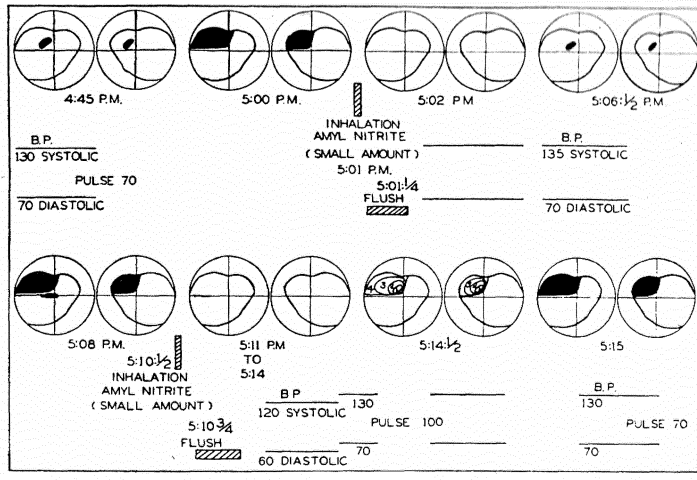

Figure 1.

Effect of inhaling a small amount of amyl nitrite on pre-headache scotomata in a subject with migraine. The amount was insufficient to cause a drop in blood pressure or 'lightheadedness'.

and white mosaic, and black circles in areas involving both eyes, scotomata such as she had seen preceding some headache attacks in her past (Fig. 2). Within two minutes after cessation of infusion, the scotomata were gone (6). The association of scotomata with spontaneous cranial vasoconstriction, their amelioration by vasodilators and induction and intensification by vasoconstrictor agents led to the inference that the mechanism of scotomata is intimately linked with cranial vasoconstriction.

The relationship between the site of dysfunction and type of scotomata was studied in nine healthy subjects. Retinal ischemia was induced by sustained manual pressure on their eyeballs to levels above diastolic levels. In every instance, the ensuing scotomata were largely black, white or gray, and simple in outline, consisting of dots, squares, mosaics, geometric forms, simple abstract design, and amorphous forms. Movement was usual and four subjects reported blue, green or violet colors as background. In no instances were complicated structural arrangements or elaborately colored images reported. One hypertensive woman with retinal occlusive disease predictably experienced images resembling a heavy snowfall with large, slowly moving flakes drifting downwards across her visual field and obscuring it.

On the other hand, another woman who often experienced paresthesias and syncope before headache, predictably saw as a pre-headache visual phenomenon an iridescent pear-shaped object surround-

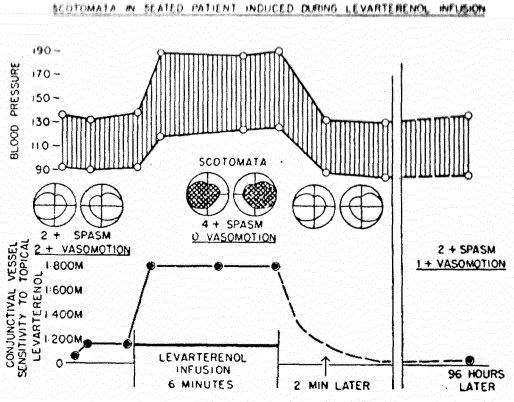

Figure 2.
Scotomata in a headache-free migraine patient induced during intravenous infusion of levarterenol.

ed by multicolored zig-zag flashes. One patient with cerebral hemangiomatosis described visual hallucinations resembling moving and exploding rockets. Visual experiences during vertebral angiography which modifies occipital lobe circulation are likewise complex and multicolored.

These observations support the thesis that simple and sombre-hued scotomata may originate in the retina or pre-chiasmatic optic nerves, and that more elaborately structured and brightly colored visual disturbances arise in the occipital and adjacent portions of the hemisphere. Patients' descriptions, the observations of Ferris, Engel and Romano (7), and those of Bärtshi-Rochaix (8) support the inference that the occipital hemisphere is an important site of disturbance. Thus as suggested above, the vasoconstriction during the occurrence of scotomata commonly involves two zones. The circulatory defect may be either (a) in the retina, i.e. retinal or ophthalmic artery, or (b) in the occipital portion of the cerebral hemisphere.

The small vessels of the bulbar conjunctivae have been studied by means of an ophthalmic slit lamp at a magnification of 47 × and appropriate photographs made. The responsiveness of the arterioles and minute vessels to the topical application of levarterenol, a potent vasoconstrictor agent with minimal metabolic effects, was assayed. This agent was dissolved in an isotonic phosphate buffer at a pH of 7.2 and used immediately after preparation. The concentration of levarterenol required to blanch capillaries was determined and was called "the sensitivity". When persons subject to vascular headache were studied, no defect in the bulbar conjunctival vessels by this method of examination could be detected during the headache-free

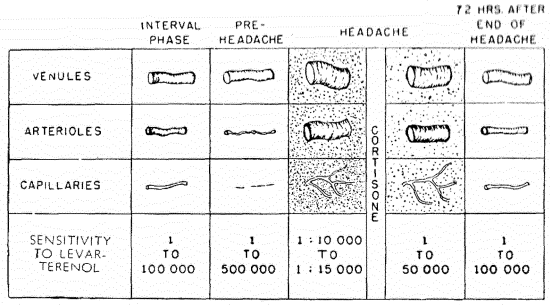

Figure 3.
Schematic representation of function and sensitivity to topical levarterenol of bulbar conjunctival blood vessels on side of migraine headache.

periods. Seven patients were studied just before and at intervals of several hours preceding headache attacks. In five of these seven subjects, the appearance and behavior of these minute vessels were normal. Specifically, the rate of flow was moderately rapid, there was no sludging and minimal periodic interruption of flow. The sensitivity of levarterenol was in a range of 1–50,000 to 1–100,000. In two subjets, however, there were arteriolar constriction, sludging and increased rate of rhythmic interruption of flow, and the levarterenol sensitivity increased to 1–200,000 to 1–400,000. These observations support the inference that an euvascular state in the smaller cranial vessels may be usual during the interval between and even shortly before migraine headache attacks (Fig. 3).

Although cranial vasoconstriction does not invariably precede the onset of the migraine type of vascular headache, an attempt was made to ascertain whether there might be a causal relationship between the pre-headache vasoconstriction and the subsequent cranial vasodilatation. Levarterenol was infused intravenously at rates which caused ischemia of the conjunctival minute vessels and a high degree of narrowing of extra-cranial arteries. Although in four persons subject to headache such infusions were continued for periods of up to three hours, no headache occurred after cessation of infusion. Hence it is unlikely that the painful vasodilatation of headache is merely a sequel of or reaction to previous ischemia.

Far less common than scotomata, are other pre-headache phenomena which also are probably related to intracranial vasoconstriction. These are syncope, paresthesias, and hemipareses. They also are usually of short duration and the effect is completely reversible, commonly terminating before the onset of the headache attack. Rarely, however, they persist for weeks or months.

Scotomata have been reported immediately following and as a

result of the ingestion of certain foods (9). In these instances, however, the visual disturbances were not followed by headache and were predictably associated with the acute onset of severe neurologic disorders, namely convulsions and/or hemiplegia. Such scotomata did not occur in patients subject to migraine headache, but rather in those with histories of allergy. The ischemia leading to scotomata may be induced by a variety of stimuli which are not related, i.e. manual pressure on vessels, certain chemical agents and vascular disease. One cannot conclude that scotomata induced by allergens are identical with those preceding the migraine headache attack.

Headache Phenomena.

Often, in a person experiencing a migraine type of vascular headache, the temporal artery and its branches on the side of the headache can be seen to be conspicuously enlarged and throbbing. The photograph of such a patient demonstrates this phenomenon as well as the diminution in the size of the vessel after administration of a vasoconstrictor agent, ergotamine tartrate. A record of the pulsations in the temporal artery was made during this headache and revealed a very high amplitude of pulsations measured plethysmographically at the beginning of the attack (Fig. 4). With the introduction of ergotamine tartrate intravenously, the amplitude of the pulsations decreased rapidly and dramatically as the headache terminated (10). Thus an alteration in amplitude of temporal artery pulsations is associated with the change in the intensity of the headache. When this vasoconstrictor agent is administered intramuscularly, instead of taking 12½ to 15 minutes to reduce the amplitude of pulsation and eliminate headache, it may take fifty minutes or an hour. To the extent that dilatation and distention of the artery are reduced, as reflected in decreased amplitude of pulsations, there is a reduction in the intensity of the pain. Likewise, levarterenol decreases the intensity of or terminates headache while reducing the amplitude of pulsation of the relevant extra-cranial arteries (11). This agent, when administered in a dose of 4 cc. of a .2 per cent solution in a liter of 5 per cent dextrose in water by intravenous infusion at a rate sufficient to raise systolic pressure by 20–40 mm. of mercury, commonly alleviates headache in 10–60 minutes. In general, the more intense the headache, the longer the time required for its elimination.

Many features of the migraine attack resemble localized allergic responses. In the migraine type of vascular headache, bulbar conjunctival vasodilatation and edema are predictable occurrences and often of sufficient magnitude to be seen with the unaided eye. The microscopic details of these changes will be described subsequently.

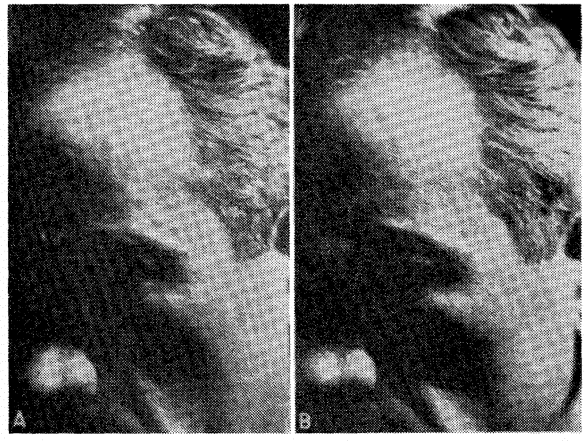

Figure 4.
Appearance of the temporal artery before and after termination of migraine headache by ergotamine tartrate. Photograph A was taken while the patient was suffering from a left-sided migraine headache. The temporal arteries stood out clearly. Photograph B was taken under identical conditions twenty minutes later. In the interim the patient had received ergotamine tartrate (0.4 mg.) intravenously, and his headache had been abolished. The temporal vessels were then much less prominent.

Similarly, conjunctivitis induced by exposure to air-borne allergens in certain sensitized persons exhibits edema and hyperemia. In the latter, there may be a periorbital sensation of fullness, discomfort or ache. Both the migraine and the allergic conjunctival inflammation are promptly terminated by locally applied vasoconstrictor agents.

Certain differences, however, are apparent. The allergen induced vasodilatation is equal in magnitude in both eyes. Whereas, in migraine, while the contralateral eye exhibits some arteriolar and capillary dilatation, such changes are more prominent in the eye on the side of the headache. The periorbital discomfort in allergic conjunctivitis is seldom as severe as in the migraine attack. Moreover, cortisone alone either topically or systemically inhibits the allergic response but has little or no effect on the vascular changes in migraine, other than to potentiate the vasoconstricting effect of levarterenol, as described hereinafter.

The mucous membranes within the nose may also participate in the vasodilatation of migraine. There are local edema, hyperemia, and increased secretion. Dull ache and sometimes burning pain in and about the nose occur. Such changes, including the local aching sensation, are also a part of allergic rhinitis and may be induced by exposure to specific pollens (12). As in the eye, however, the nasal mucosal changes are more prominent on the side of the headache,

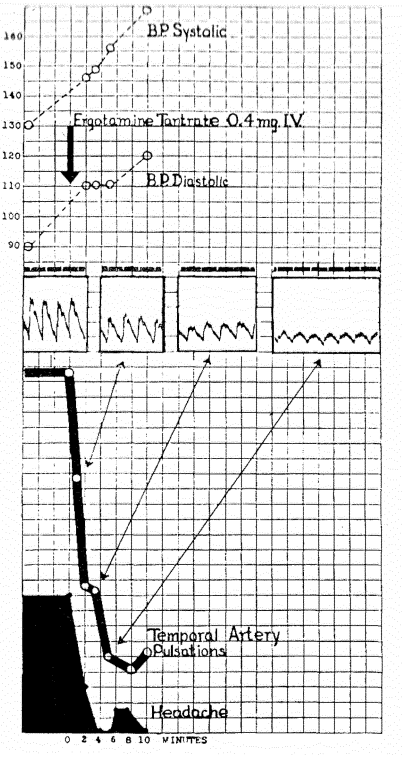

Figure 5.

Relation of the amplitude of pulsations of the temporal artery to the intensity of headache after administration of ergotamine tartrate. The sharp decrease in the amplitude of pulsations following injection of ergotamine closely paralleled the rapid decrease in intensity of the headache. Representative sections of the photographic record are inserted. The average amplitude of pulsations for any given minute before and after administration of ergotamine was ascertained by measuring the individual pulsations from the photographic record. The points on the heavy black line represent these averages, expressed as percentages. In this record and those in the accompanying figures the initial or 'control' amplitude was taken as 100 per cent. The interrupted line represents intervals of one second.

while they are bilaterally equal in the allergic disorder. Sneezing is common during allergic rhinitis but unusual during a migraine headache attack.

It can be concluded that although vasodilatation, edema and hypersecretion in the eye and nose are a part of the migraine attack and certain allergic disorders, there are fundamental differences in distribution of the lesions, in the responses to certain agents, and in the phenomenology associated with the attack.

Patients commonly report that there is a soreness or tenderness

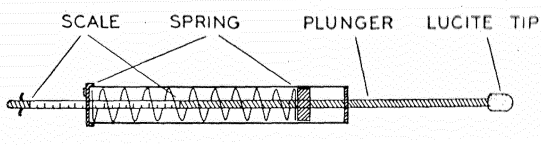

Figure 6.

Diagram showing the principle of the Hardy deep pain dolorimeter. The lucite tip is placed on the test site, and pressed against the subject's head at a standard rate. The pain threshold is expressed as the number of units representing grams of pressure of the coiled spring when the subject first perceived deep aching pain.

of the scalp in areas of headache. Combing the hair, putting on a hat, or pressing the scalp are painful experiences. These phenomena have been explored through a study of deep pain thresholds of the scalp during headache and headache-free periods by means of a lucite-tipped metal plunger capable of applying measured and predictable amounts of a pressure to the scalp (Fig. 6). This instrument was also helpful in assaying the amount of local scalp edema present in association with headache. Briefly, it was found that local edema and lowering of deep pain thresholds almost invariably were present at the headache site during the headache episode, but not preceding it (Fig. 7). When headache was allowed to terminate spontaneously, these local tissue alterations often persisted for hours or days. However, when headache was eliminated through the action of ergotamine tartrate or levarterenol, the pain threshold returned promptly to normal and local edema was dissipated.

The observation that the small bulbar conjunctival vessels are very often dilated during headache led to a further explanation of local tissue phenomena during headache. In the hours preceding headache, an euvascular state was common, although moderate arteriolar and venular constrictions were occasionally noted. During headache, the arterioles and venules dilated, the number of patent capillaries increased, and conjunctival edema and burning pain in the eye were common (Fig. 8).

These changes were most marked on the side of the headache, but were present to a lesser extent on the contralateral side. The sensitivity to topical levarterenol during headache was 1–5,000 to 1–10,000 on the headache side, and 1–10,000 to 1–25,000 on the headache-free side (Fig. 9). Headache-free patients usually gave sensitivity values of 1–50,000 to 1–100,000. Topical 2½ per cent cortisone suspension partially restored the sensitivity to levarterenol. On two occasions when headache was allowed to terminate spontaneously, dilatation of the small vessels of the eye with decreased sensitivity to levarterenol, local edema of the scalp about the eye, and lowered deep pain thresholds in the scalp in the same area all persisted and then ter-

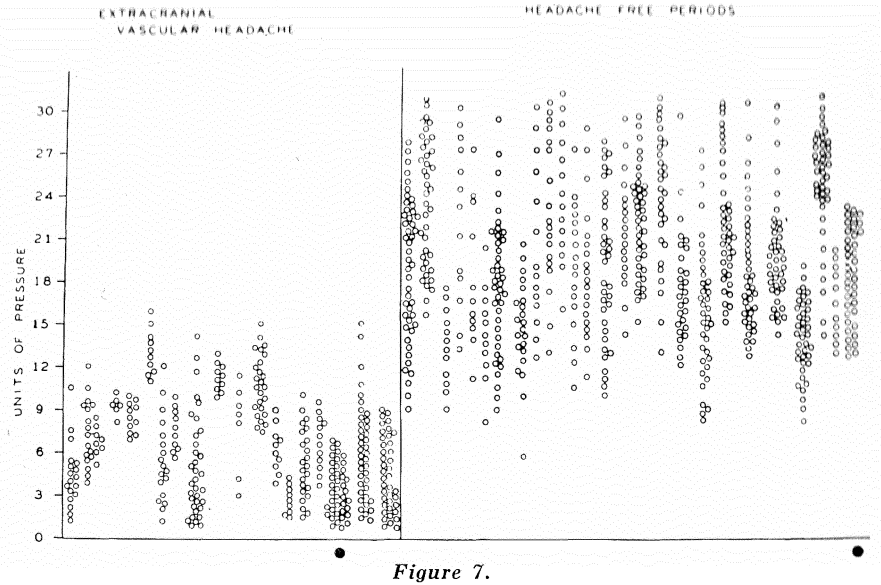

Figure 7.

Deep pain threshold measurements made in the zone of headache during migraine attacks in 10 subjects compared with deep pain threshold during headache-free periods. The two black dots identify measurements in one person.

minated together about 72 hours after the ending of the headache. When levarterenol was administered intraveneously during headache, there occurred constriction of conjunctival minute vessels, reduction of conjunctival minute vessels, reduction of conjunctival edema, and elimination of burning pain in the eye at the same time that the headache was diminishing. On the basis of these observations, it is postulated that small vessels, as well as large vessels, participate in the headache attack. They may contribute to the attack by altering hydrostatic pressure in the capillaries so that water and all lower weight molecular substances accumulate in the surrounding tissue in greater than normal amounts. Among these lower molecular weight substances are agents which have the capacity to lower pain thresholds and damage tissue.

In twelve migrainous subjects, temporal arteries were biopsied under general anesthesia during a migraine headache attack involving them. These vessels were embedded in paraffin, sectioned and stained with hematoxylin and eosin and Weigert's connective tissue stain. Edema of the adventitia and surrounding areolar tissue was the only predictable finding (13). There was no collagen swelling, no tissue necrosis, and no cellular infiltrate. This is in distinct contrast to the collagen changes, necrosis, and cellular infiltration in those arterial diseases of presumed allergic origin, i.e. periarteritis

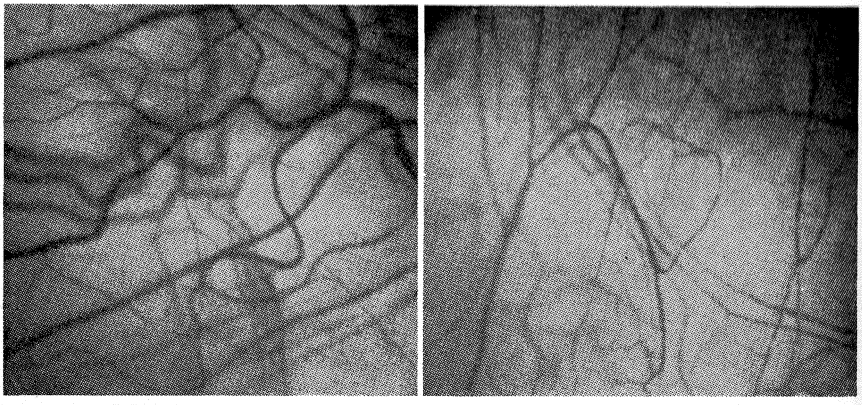

Figure 8.
Contrast in appearance of vascular structures in right and left bulbar conjunctivae during right-sided headache. Conjunctival vessels in the eye on the headache side are increased in diameter and exhibit great tortuosity. On inspection through the slit lamp the walls of these vessels are 'blurred', there are relatively few red cells within their lumina, and blood flow is slow.

nodosa, thromboangiitis obliterans, etc. Moreover, the local lesion in migraine differed from certain urticarial hypersensitivity reactions, in that the latter commonly exhibited eosinophilic cellular infiltration (14), while none was present in the temporal artery biopsies[1].

That cranial artery dilatation is a predictable and prominent phenomenon during migraine headache attack is well established. It is equally clear, however, that cranial vasodilatation either occurring spontaneously or induced, as by getting into a hot bath, may be unaccompanied by headache. Furthermore, many of the local features of the migraine headache attack, namely the edema, lowered deep pain thresholds, bulbar conjunctival injection, burning pain and minute vessel hemorrhages are not readily attributable to large artery dilatation. The following data support the inference that during the migraine attack there is present locally, a pain threshold-lowering and tissue-damaging agent which is more immediately relevant to the above-mentioned features of the headache attack.

In three subjects, the injection of 300 TR units of hyaluronidase in 2 cc. of sterile isotonic saline into a tender scalp area during headache, was followed by a quadrupling in size of the area in which

1 According to M. E. Jorg of Buenos Aires, Argentina (personal communication) the examination 'with microchemical techniques for connective tissue' of biopsy specimens of the meninges from two patients with long-standing vascular headaches, revealed 'oedema, fibrilar dissociation and catabiotic changes in arteriolar walls' ... 'resembling the features found in collagenoses.'

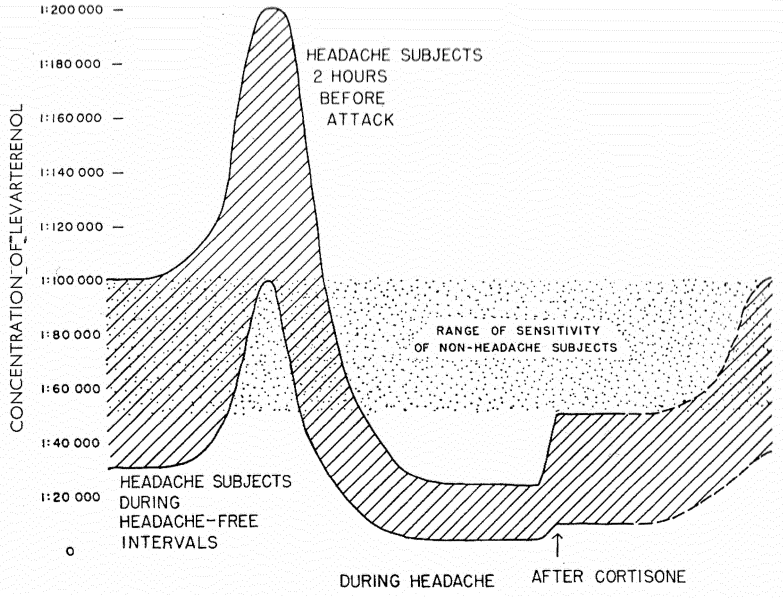

Figure 9.
Sensitivity to levarterenol of conjunctival vessels.

pain thresholds were lowered and by a slight fall in the pain thresholds themselves. The non-tender scalp of headache-free subjects was injected on two occasions in the same way. Pain occurred on one occasion, but this terminated promptly and was not followed by any lowering of deep pain thresholds, either at the site of injection or in the neighborhood.

Since Armstrong et al. (15) had shown that blister fluid has the capacity to initiate pain on an exposed blister base, the possibility that pain threshold-lowering agents of the type existing in blister fluid might be relevant to headache was investigated in the following series of observations. On ten occasions, five subjects were immersed in water at 109° to 110°F. until bilateral temporal artery dilatation was evident. No headache was present at this time. All fluid was removed from a blister prepared by burning the forearm two to four days before. The usual volume of blister fluid obtained was .2 cc. Fluid was allowed to remain in contact with a glass syringe for at least seven minutes, since this is the time required to activate bradykynine, one of the allegedly significant pain-producing substances. The fluid was then injected subcutaneously within a few mm. of one temporal artery and an injection of sterile isotonic saline made alongside the other temporal artery. Subjects remained in water for another 10–15 minutes during which time no headache appeared. In

all instances, however, 20–60 minutes after the injection, headache indistinguishable from the migraine type of vascular headache occurred at the site of the blister fluid injection and persisted from 1 to 12 hours.

Since serotonin is also present in blister fluid and might therefore be relevant to the experience of pain, the capacity of serotonin to lower superficial and deep pain thresholds was assessed in four subjects. As little as .05 mg. diluted in .2 cc. isotonic saline predictably lowered superficial and deep pain thresholds and evoked vasodilatation in the skin. The immersion experiments were repeated using serotonin. After immersion under similar circumstances, .05 mg. serotonin in .2 cc. isotonic saline was injected periarterially into the scalp on one side and .2 cc. sterile isotonic saline in the other, without the subjects' knowing which was saline. A low intensity headache occurred at 5–8 minutes after serotonin injection about the site of the injection in two subjects and persisted for 1½ to 4 hours. The intensity of pain was reported as greater than that induced in the same subject by the injection of an equal amount of saline in the same area.

That a combination of induced extracranial vasodilatation and naturally-occuring pain threshold-lowering agents may produce headache is significant. However, a latent period of some minutes between injection and headache indicates a degree of dissimilarity between this contrived situation and true migraine headache. In the latter syndrome, pain thresholds fall at the same time as the extracranial dilatation appears and headache begins. A latent period may represent time required to activate or produce another agent locally by enzymatic means.

In two subjects, the capacity of the extracranial edema fluid to lower pain threshold in the skin was assessed by a crude method. Pain thresholds in both forearms were determined in these subjects by means of the Hardy, Wolff, Goodell dolorimeter. At the time of the headache of the migraine type, 5 cc. of sterile isotonic saline were injected subcutaneously into the area of the headache and also into a headache-free area, and as much of the fluid withdrawn as possible, usually .1–.2 cc. This withdrawn fluid was injected intradermally in the forearms immediately contiguous to the sites where these thresholds had been previously determined, and threshold determinations repeated. The fluid from the headache site was injected into one forearm and that from the headache-free site into the other. In both patients there was more erythema about the site of headache fluid injection and a threshold-lowering of 20–30 millicalories as compared to the opposite side. These differences, while small in magnitude, support the inference that there is an agent in

the tissue fluid on the headache side, present to a lesser degree or not at all on the non-headache side, which promotes lowering of pain thresholds and local vasodilatation.

Attempts were made by means of paper chromatographic techniques to identify the relevant agent. Utilizing #1 filter paper, phenol-water, and lutidine-colidine systems with ninhydrine staining, a purple spot with an RF of .37 in phenol-water and .17 in colidine-lutidine predictably appeared in all areas made from fluid obtained from headache sites. Those spots made with headache fluid were deeper-staining and larger in area than others made with material from headache-free patients or the headache-free side in subjects with headaches. The precise chemical nature of these spots has not been determined. The increased amounts of ninhydrine-staining agents present during headache may be due either to their greater accumulation in the local edema fluid or to breakdown of larger protein or polypeptide substances occurring as a part of the local tissue reaction during headache. Such breakdown could presumably occur through the action of enzymes released locally as a result of changes in cell membrane permeability.

The earlier observations of Babkin, Gibbs, and Wolff (16) and subsequent studies of Hilton and Lewis (17) have established that the vasodilatation produced in the salivary glands after chorda tympani stimulation is probably not due to the action of vasodilator nerves. Hilton and Lewis conclude that chorda tympani stimulation does not directly provoke release of a vasodilator substance, but that activation by neural means produces changes in the gland cells which permit the escape into the interstitial fluid of an intracellular enzyme. The enzyme acts in turn upon the tissue proteins to form a vasodilator polypeptide having the pharmacological and physical-chemical properties of bradykynine. Their thesis was based on studies with salivary gland perfusate. That a similar mechanism may also be operative locally in a migraine-type vascular headache is an attractive thesis and supported by many of the observations included herein.

Assuming that the eye extracranial subsurface tissue, and assay studies have all dealt in a different way with the same agent, the following statements about its properties can be made. It has the capacity to lower deep and superficial pain thresholds, and to induce vasodilatation. It spreads rapidly in tissue, such spread being facilitated by hyaluronidase. It is soluble in isotonic saline and stable at room temperature for at least 7–10 minutes. Its effects are not blocked by antihistamines or anticholinergic agents. It occurs in the local edema fluid present in vascular headache of the migraine type, and it is probably withdrawn from tissue via the blood stream

through the action of vasoconstrictors more rapidly than occurs spontaneously.

When a saline extract of tissue fluid removed from an urticarial swelling induced by exposure to ice in a patient subject to cold urticaria was injected intracutaneously into one forearm, it lowered pain thresholds significantly as compared to the effects of a saline extract of tissue unexposed to cold injected into the other forearm. It is likely, therefore, that a pain threshold-lowering agent exists in the tissue fluid of urticarial lesions.

According to Duke (18) the mechanism of cold allergy may be due to the development of a new substance in the tissues of the sensitive person under the stimulus of cold similar to the new molecules produced when proteins are subjected to these physical agents in vitro. The proteins thus altered may act as autogenous antigens. Alexander (19) has suggested that nerves may elaborate histamine and thereby evoke such cold responses.

It has long been postulated that the effects of antigen-antibody reactions are mediated through certain chemical agents or 'anaphylatoxins'. Of such agents, histamine has received the most serious consideration, since in certain species, it produces a syndrome resembling anaphylactic shock.

Histamine is ubiquitous in tissue, occurring in high concentrations in blood platelets, leucocytes, and most cells. Moreover, trypsin, as shown by Rocha e Silva and Andrade (20), can release histamine from biologic substrates in vitro. Fell (21) demonstrated that animals made allergic to a histamine horse serum antigen are relatively refractory to anaphylactic shock as compared to a non-sensitized group, a finding supporting the thesis that histamine is linked with anaphylaxis.

Not all the evidence is in favor of histamine as the mediator of anaphylaxis. Histamine does not induce the prolonged blood coagulation time that always occurs in anaphylactic shock (22). Campbell and Nicoll (23) have shown that rat uteri unaffected by ordinary doses of histamine in the tissue respond to some other substance released by sensitized guinea pig lung during anaphylaxis. Moreover, Schild (24) demonstrated that the sensitized guinea pig uterus responded to a specific antigen after it had ceased to contract following application of histamine.

It is therefore not possible at present precisely to define the role of histamine in antigen-antibody reactions. The consensus is that it is significantly linked with anaphylaxis (10). Its relevance to migraine headache will be considered subsequently.

Bronfenbrenner has postulated that the union of antigen and antibody results in activation of serum trypsin with subsequent

digestion of certain serum proteins. Breakdown products of these tissue proteins then mediate the development of the anaphylactic reaction. Moreover, serotonin has recently been linked with anaphylaxis in certain species.

To recapitulate, in migraine and proven allergic reactions, specific chemical agents have been implicated. Substances with properties like those of histamine as well as protein tissue breakdown products have been linked with both disorders. In neither case has the precise relevant agent been identified, and one cannot assume at present that the same substance or substances underlies both disorders.

Late Headache and Post-Headache Effects.

A rare type of vascular headache pattern is referred to as ophthalmoplegic migraine. The pain in ophthalmoplegic migraine is experienced as in the usual migraine headache behind or over the eye. It is commonly limited to one side of the head and is on the same side as the ophthalmoplegia. The headache usually precedes the extraocular paralysis, the latter appearing 6–10 hours after the onset of the headache or with subsidence of the attack. More rarely, from 1 to 10 days may elapse between the headache and the palsy. The III, IV, VI, or even portions of the V cranial nerve may be involved (Fig. 10). Occasionally all of them may be involved, presenting a complete external ophthalmoplegia. In partial III nerve palsy, the external musculature alone may be involved, resulting in differences in size of the pupils, paralysis of accomodation and defects in convergence. When the pain is intense, nausea and vomiting occur. In addition to the headache, the previously described pre-headache visual disturbances occur. It is usual for the paralysis to be transient, lasting a few days with complete recovery. But paralysis may persist for months with certain palsies, ultimately becoming permanent. Since the vasoconstrictor agent, levarterenol, which has the capacity to constrict large and small vessels and reduce local edema, was effective in reducing the ophthalmoplegia in two patients seen very early during the eye weakness, it is likely that in some instances, opthalmoplegic migraine is the result of pressure exerted on cranial nerves by greatly dilated or thickened walls and periarterial edema associated with the headache attack. The proximity of the III, IV, V and VI cranial nerves to the anterior and middle cerebral arteries and of the III nerve to the posterior cerebral and posterior communicating arteries suggests the site of the damage leading to the palsies. On the other hand edema of the contents of the orbit could equally well explain the weakness in some instances.

As stated during the discussion of scotomata, coma, convulsions

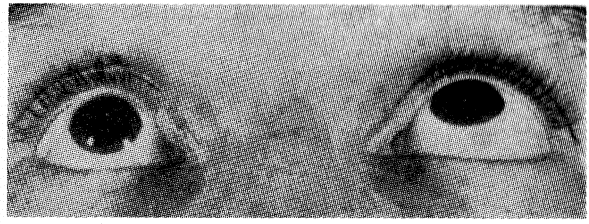

Figure 10.
Permanent third nerve weakness and pupil dilatation after a right-sided attack of ophthalmoplegic migraine.

and hemiplegia have on rare occasions occurred as part of an allergic reaction. The neurologic lesions in these cases persisted for months or were irreversible. Moreover, they did not involve the nerves passing through the orbit, and no relation to ophthalmoplegic migraine is evident.

Phenomena Associated with Headache.

In addition to the alteration in the structure and function of the cranial vessels during migraine headache, there may be disturbances involving other body systems. Certain individuals with vascular headaches go through extraordinary fluctuations in their body weight. About half of 134 patients experienced weight gain preceding headache of from 2 to 17 pounds, followed by diuresis with weight loss during the period of dwindling intensity of headache. There was frequent retention before headache of sodium, potassium and corticosteroids, as well as water, with outpouring of these substances during diuresis (25) (Fig. 11). It has further been observed that diuresis can be provoked during the period of weight gain without affecting the ensuing headache (Fig. 12), and that weight fluctuations may be prevented through the use of oral carbonic anhydrase inhibitor diuretics (Fig. 13) without altering the frequency or severity of headache. Also, weight gain may be provoked in migraine patients by hormonal means without producing headache (Fig. 14). It can be concluded that headache and over-hydration are concomitant phenomena, but are not causally related. A period of special alertness and driving activity often underlies both headache and the fluid accumulation. It should be made clear at this point that the local scalp edema present during headache is unrelated to the generalized edema just described. The generalized edema precedes headache and is usually diminishing by the time the local edema appears (Fig. 15).

Disturbances in bowel function occur in association with the migraine attack but much less commonly. There may be a period of

Figure 11.
Fluid and Electrolyte Excretion in Subject M.S.

Phase	H_2O cc./min.	S.D.	Na µeq./ min.	S.D.	K µeq./ min. D N	S.D.	Cr. mg./ min.
Average of 47 Asymptomatic Days	0.76	±0.17	96	±20	54	±5	
2 days before Headache	0.45		31		23 18		0.920
2 days with Subsiding Headache ...	1.48		130		72 —		1.014

A comparison of fluid and electrolyte excretion in Subject M.S. during 3 periods: 1) without headache, 2) two days before headache and 3) during headache.

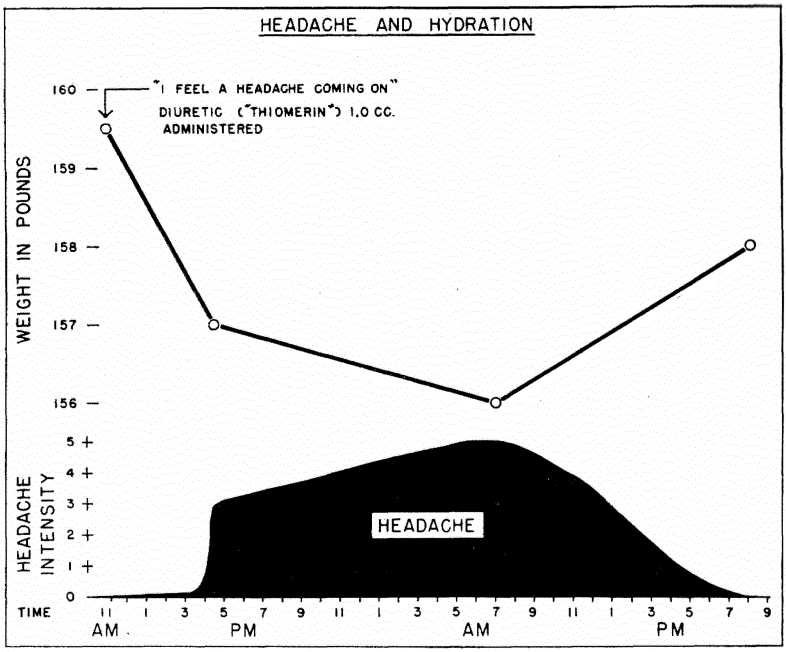

Figure 12.
Headache and hydration. Failure of induced diuresis to prevent a migraine headache atack.

constipation during the several days antedating headache, followed by diarrhea during the period in which the headache is diminishing in intensity. Robertson has shown that distending the rectum or the bladder in persons accustomed to headache and constipation, as well as those without such experience, does not induce headache (26). These data lend further to support the view that at least the mechanical factor of distension in constipation is not related to the phenomenon of headache.

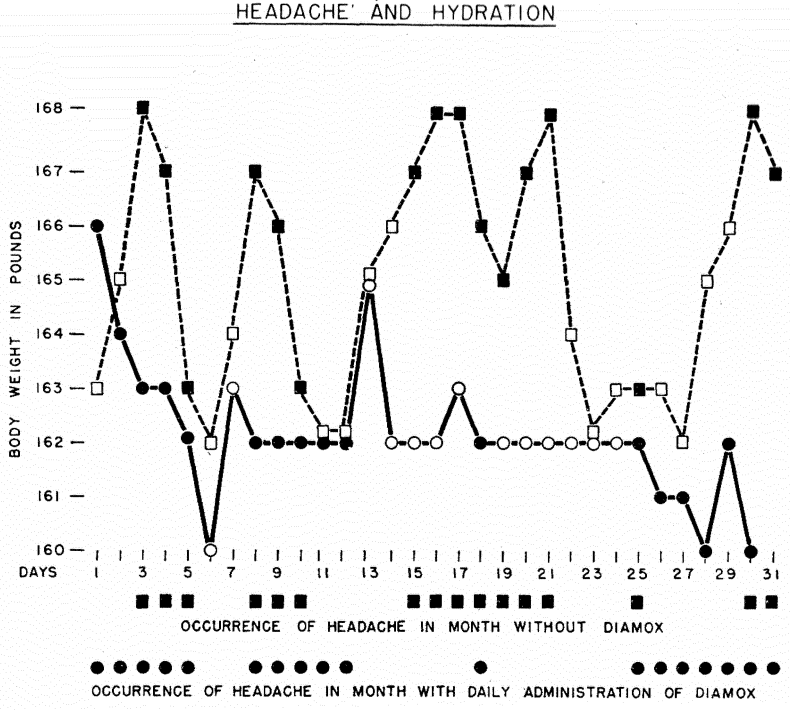

Figure 13.
Occurrence of headache with and without induced diuresis.

Histamine Headache and "Allergic" Headache.

Some years ago it was discovered that if one inadvertently injected histamine intravenously into a subject, he had a headache lasting five or ten minutes which in many ways resembled headache observed at the bedside and which left him quickly with no untoward effects. This headache has been used for experimental exploration and therefore, when the phrase—histamine headache—is used, it means a headache which has been induced experimentally for the express purpose of studying some of the facts concerning the natural history of vascular headache.

If one injects histamine phosphate intravenously in sufficient amounts, one produces a headache all over the top of the head which is pulsatile and throbbing in quality and lasts a few minutes. In analyzing this headache, certain interesting phenomena present themselves. A needle was put into the lower back of a subject, permitting the cerebro-spinal pulsations to be amplified through an air system and recorded on a moving film in a camera. Likewise, temporal artery pulsations were recorded by means of another air sys-

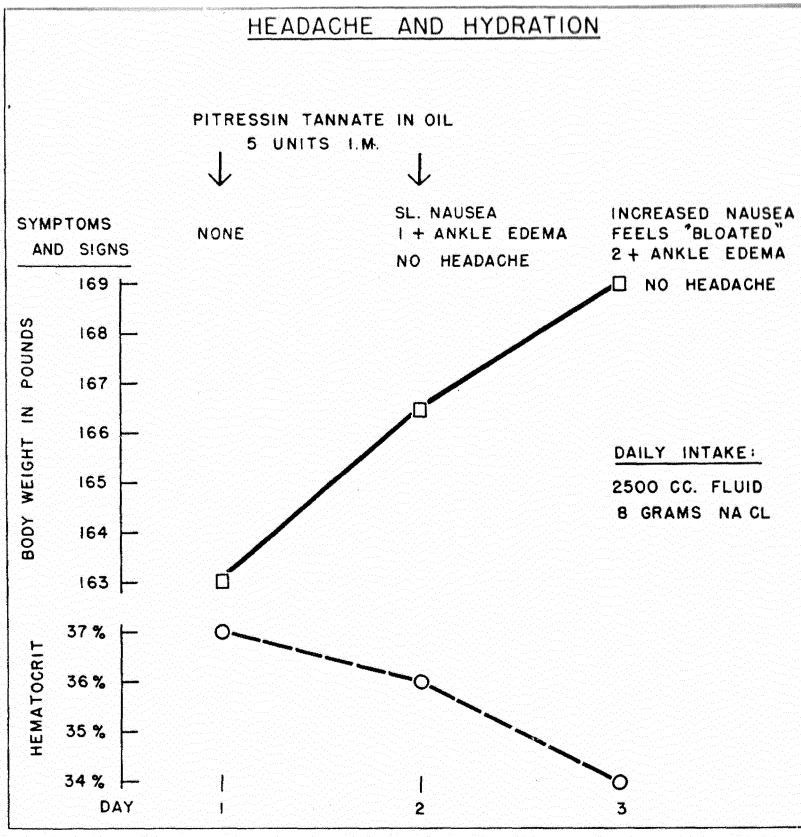

Figure 14.
Failure of induced hydration to precipitate headache.

tem amplification. Immediately following injection of histamine, there was a drop in blood pressure which quickly returned to normal. It was at this point that headache began (Fig. 16). During this experimentally-induced headache, the amplitudes of pulsations, both intra- and extra-cranial, were greatly increased, subsiding to control levels with termination of the headache. It was concluded that increased amplitude of pulsations after injection of histamine actually represented an increased stretch of dilated intra-cranial vessels with each cardiac systole (Fig. 17). This conclusion becomes particularly significant when it is recalled that dural vessels, dural sinuses, and the larger pial vessels are important pain-sensitive structures. The question must be asked, "Perhaps the histamine directly stimulates end organs having to do with pain?" If that be so, histamine headache should be most intense when the amount of circulating hista-

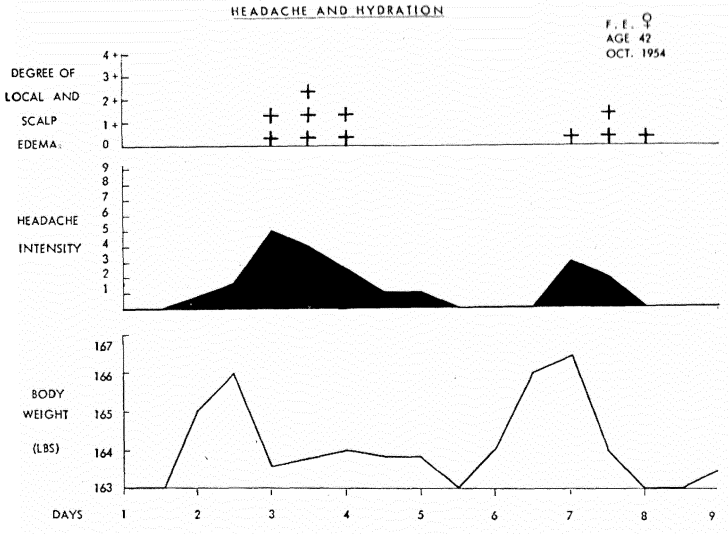

Figure 15.

Headache and hydration. Note the disparity in time between the occurrence of local edema and general accumulation of fluid.

mine is greatest, i.e., during an infusion period. Therefore, histamine was infused for nine minutes but there was no headache during that period although there was a maximum histamine content in the blood and a falling blood pressure. During infusion there was not much change in the amplitude of intra- or extra-cranial pulsations. When the infusion was stopped, however, the blood pressure returned to its normal level and exceeded it for a brief moment. There was a coincident rise in the amplitude of pulsations and the headache began. Thus, amplitude of pulsations increased and pain began with diminishing concentration of circulating histamine and when the blood pressure had returned to normal. It is postulated that the full impact of each cardiac systole upon the relaxed blood vessels which directly stimulated sensory end organs in and about their walls, resulted in a flood of afferent impulses interpreted as pain. It was further observed that raising intracranial pressure by means of saline run into the subarachnoid space greatly reduced or even eliminated the experimentally-induced headache. It was as if increased intracranial pressure acted as a dampener of vascular dilatation or supported them so that the vessels could not be painfully dilated.

Lecomte found that approximately 25 % of patients given a histamine liberator developed headache during the subsequent reaction (27). The headache was throbbing, generalized, not hemi-

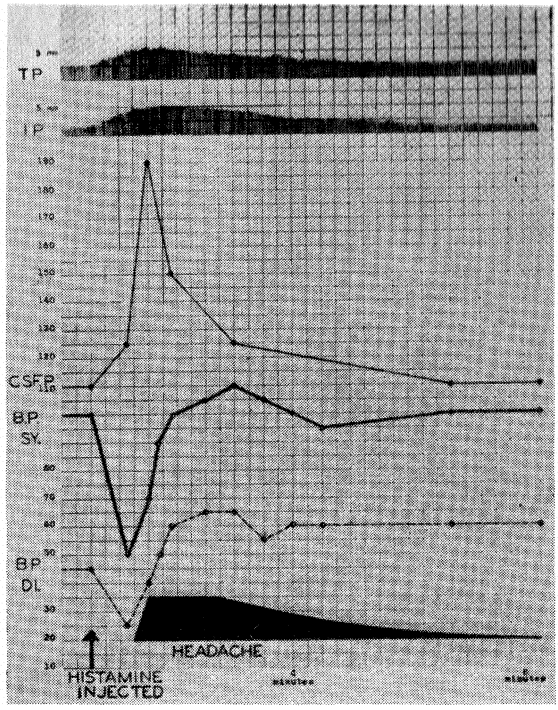

Figure 16.

Diagrammatic representation of the course of events during headache produced by histamine in subject G. The headache was most severe with rising blood pressure, and it should be noted that at this time the cerebrospinal fluid pressure is returning to its resting level from the high point reached after the injection of histamine. Increase in amplitude and rate of the temporal pulse (T.P.) and of the intracranial pulsation (I.P.) are indicated in the upper two shaded areas. The line C.S.F.P. indicates the cerebrospinal fluid pressure in millimeters of Ringer's solution. Systolic blood pressure is indicated by the heavy black line at B.P.SY., and the diastolic blood pressure is indicated by the broken line at DI.

cranial, and occurred in both those subject to headache and those who were not. The fact that an individual experienced such headache once did not indicate that another histamine liberator reaction would include headache.

We have shown that administration of 50–60 mg. of Diphenhydramine (Benadryl) intravenously completely blocks the hypotensive effects of .1 mg. histamine intravenously and the subsequent headache as well (11). Furthermore, the administration of a 1–800 dilution of the antihistaminic tripellanamine, topically instilled in the bulbar conjunctivae, prevents the vasodilatation which follows similar administration of 1–1,000 histamine. However, in two subjects

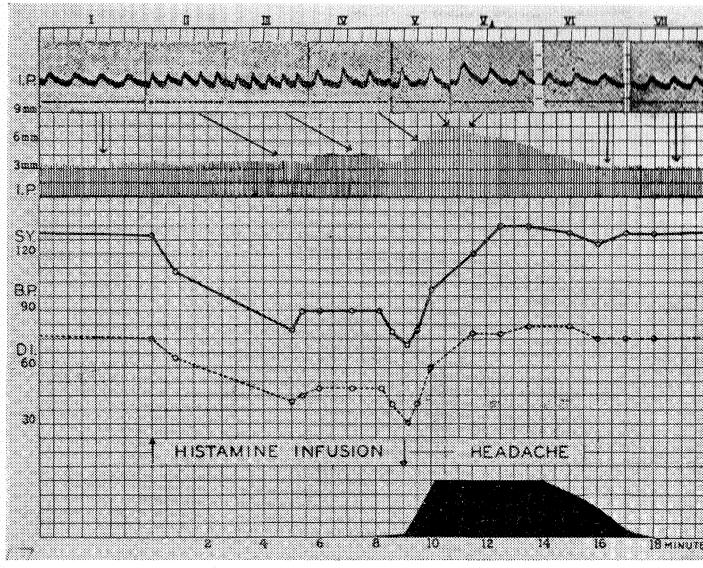

Figure 17.

Diagrammatic and photographic representation of the course of events in the experiment in which histamine acid phosphate (0.1 mg. per minute) was infused continuously during nine minutes. Systolic blood pressure is indicated by the heavy black line SY. and diastolic pressure by the broken line D1. At I.P. the variations in rate and amplitude of the intracranial pulsation are represented and the top line I.P. is made up of approximately corresponding sections from the photographic record of the intracranial pulsation. Arrows point from the photographed intracranial pulsation to the corresponding pulsation represented diagrammatically. It should be noted that the slow rate of pulsation during the height of the headache and at the maximum amplitude of oscillation is exceptional to this case. The pulse rate is usually more rapid during the height of the headache.

seen while they were experiencing scotomata and acutely anticipating the migraine headache attack, the intravenous administration of 60 and 70 mg. of diphenhydramine and the topical administration in both eyes of 1–800 tripellanamine did not affect either the subsequent headache or unilateral bulbar conjunctival vasodilatation which appeared as they always had in the past. It is therefore unlikely that endogenous histamine in increased amounts is relevant to the great majority of clinically encountered vascular headaches of the migraine type.

Pagniez, Pasteur Vallery-Radot, and Nast (28) in 1919 were among the first to implicate an allergic mechanism in migraine. The reports of De Gowin (29), Rinkel (30), Balyeat and Brittain (31), Hahn (32), Hamburger (33), Gonzales Suarez (34) and others followed. Vaughan's work is representative of these publications (35). On the

basis of a clinical history of attacks after certain foods and positive skin tests to these foods, he concluded that hypersensitivity was a factor in 70 % of cases. In half of his patients some relief was afforded by an appropriate elimination diet. The chief offenders have varied in different studies, being wheat, milk and eggs in the opinion of Balyeat and Brittain and celery, pea, and onion in the paper of De Gowin.

Some workers (36) have advanced a step further in performing experiments which attempt to link migraine attacks with an allergen. In two subjects, Unger not only induced headache by feeding allergens which gave positive skin reactions but also failed to provoke headache after administration of harmless extracts presented to the patients as the known offending allergen.

In all of the above studies and most of the subsequent ones, a critical experiment has been omitted. If the allegedly offending foodstuff had been administered without the patient's being aware that it had been given and headache then predictably induced, the evidence would be more conclusive. When this step was carried out at the New York Hospital with chocolate disguised in capsules or milk given through a stomach tube, the results did not confirm the earlier work.

Moreover, Mary Loveless gave in disguised form, milk, corn, arrowroot and tapioca, as well as placebo feedings, to persons alleged to have had headache attacks precipitated along with other symptoms by the ingestion of these foods. She noted in her well controlled study no predictable relationship between the administration of these substances and the occurrence of headache (37).

The many difficulties in the interpretation of skin tests make the problem of their relevance to migraine a difficult one. There may be a positive skin response to an allergen which is not actually absorbed as such from the gastro-intestinal tract into the blood stream. A positive skin test, moreover, may outlast the clinical allergic state or even precede it. With respect to food allergy, it is noteworthy that, although the gastro-intestinal tract is most permeable to food allergens in the very young, the incidence of migraine in children (38) is at most one-third to one-half that in the adult population.

The relief of migraine attack by elimination diets cannot be relied upon as supporting the relevance of ingested allergens to migraine. The list of allegedly therapeutic regimens in migraine is a long one. One can only conclude that a factor inherent in every treatment situation is the agent which effects the ending of symptoms. There is much evidence to support the thesis that the interest and good will of the physician and the expectation of relief on the part of the patient may effect relief through neural mechanisms (39).

Mary Loveless ascertained the occurrence of headache as well as other effects of overdosage of allergens among 177 pollen-sensitive persons (37). Headache, when it occurred in these subjects after allergen overdosage, was generalized and not hemicranial. It occurred both in those with and without histories of frequent headache attacks. The 177 subjects experienced 925 overdosage reactions. Twelve of the 177 subjects had headaches as part of such overdose reactions on one or more such occasions. Indeed, these 12 persons experienced 26 headaches during 121 overdosage reactions, or 21 % of the time. For the entire group, the incidence of headache as an aspect of allergen overdosage effects was 2.8 % and then always as part of a widespread allergen overdosage syndrome, including urticaria, rhinitis, asthma, and hypotension. In this study, headache never occurred as an isolated phenomenon during induced antigen-antibody reactions.

However, Kallós has demonstrated that a small, highly selected group of patients with migraine as well as urticaria, rhinitis and asthma linked with sensitivity to specific allergens, had apparently true migraine headaches induced by the parenteral injection of such allergens although in no instance were visual or other pre-headache phenomenon induced (40). Further, he showed that associated with the headache were always such other effects as rhinitis and asthma. The occurrence of the latter was prevented by the administration of antihistaminic agents just before the injection of the allergens, whereas headache was not prevented. On the other hand, the previous administration of ergotamine tartrate did not prevent the occurrence of the nasal and chest manifestations, but did prevent the occurrence of the headache. Granting that ergotamine tartrate inhibits the effects of many vasodilator agents, these observations nevertheless indicate that as a part of the reaction to specific allergens to which the patient is sensitive, those subject to migraine may have an attack precipitated by the administration of such an allergen.

In conclusion, the phenomenologies of migraine and of certain allergic responses are similar in many respects. In both, attacks are paroxysmal, featured by edema and hyperemia, probably mediated by tissue breakdown products, or histamine-like substances, and terminated by vasoconstrictor agents. But at most points of such a comparison, fundamental dissimilarities are apparent. The cellular infiltration prominent during allergic reactions is absent in migraine; antihistaminics have no therapeutic effect in migraine and have value in treating certain allergic reactions. The responses to adrenal steroids are different in the two disorders and finally, there is no conclusive evidence that histamine or ingested allergens can

produce a vascular headache of the migraine type or that migraine commonly results from the ingestion of such allergens as part of the antigen-antibody reaction.

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REACTIONS TO DRUGS

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Fifteen years ago the boundaries of the field of "Drug Allergy" could easily be defined and the subject one fairly simple to encompass. Many of the drugs then in use possessed single or few actions. Attention was then focused on the obvious clinical reactions. We have only to imagine medical treatment without present-day multiple purpose, multiple action, anti-microbial, anti-malarial, anti-convulsant, antihistaminic, anti-arthritic, anti-tubercular and anti-hypertensive agents and no tranquillizing drugs to realize how simple the problems truly were. Today we are not as certain as to what is or is not drug allergy and almost all discussions of the subject include much of what was at one time termed "Drug Reactions".

But, because approximately ten per cent of the drugs we use today, although they date back more than twenty years, continue to be prescribed, the naive classifications of two decades ago can usefully be repeated from text to text, although they will not stand the critical scrutiny of present-day knowledge.

For the purposes of this Chapter it must be stressed that any substance taken in any form, by any route to modify any body cell or body invasion of any type, is by definition legally, medicolegally and medically, a drug, as are vitamins, vaccines, and for that matter, pollen extracts for the treatment of pollinosis.

Since a drug is any substance used to combat, (to comfort the patient) or to mitigate or cure any disorder or disease, the definition of reaction has also been broadened to include every type of present-day recognizable response, from the immunological to the organic and psychological levels. Precise definitions are as yet impossible, and this Chapter cannot, therefore, in any reasonable or practical way, discuss the entire field of drug reactions, but only such aspects as are related to understanding one subdivision, namely, what is commonly termed drug allergy, although its boundaries also are by no means clear.

Allergy has been defined as any alteration in the capacity of tissue

cells (single or when combined together in an organ) to react specifically on exposure or re-exposure to the same substance or an immunologically related substance. It was until recently believed that the reaction had to be of a "specific" type. For purposes of convenience only, however, some patterns of reaction are termed "allergic" using the word in its broadest connotations, while other types of responses are, for the moment, not so labelled. The so-called "allergic" reaction is occasionally termed "atopic" and in some of the literature "immediate". Advances in knowledge and critical study have also proved these terms to be inadequate descriptions as what happens when cells react to drugs.

Although toxicity relates the similar effects as seen in all members of a species, the states of allergy and toxicity certainly overlap, as when an allergic reaction results in death, although the death may follow a sequence of events marking it as a particular type of final dissolution. The states of allergy, intolerance, idiosyncrasy, and untoward reactions similarly may overlap. Side reactions and secondary effects operate by means of a different reaction mechanism. In the Shwartzman and Jarisch-Herxheimer reactions, the responses are mediated once again by what appear to be totally different processes. The so-called allergic reaction can perhaps best be understood if other types of reactions, when present in typical form, can be defined and excluded.

A toxic drug may be used remedially and safely in controlled quantities as is either digitalis or curare. Larger doses of these same drugs and others used similarly are truly toxic and the effects seen are properly so termed. An occasional patient will respond to normal dosage schedules as though toxic amounts had been administered. In many of these, slower-than-normal excretion can, as a cause, be eliminated. Nevertheless, there is no satisfactory term to apply to such patients. A drug known to possess such toxic effects in a small percentage of patients, may deliberately be administered to others for the same effect, but for the treatment of another abnormality. A drug generally avoided because of its tendency to cause toxic leukopenia in ordinarily sick patients, may be used with success in those suffering from leukemia.

Side effects are like weeds which are often described as plants which grow either in the wrong places or for which no useful purposes have as yet been found. The somnolence seen with some antihistaminic agents is certainly neither toxic nor allergic any more than is the appetite-depressant effect of the amphetamines. Neither of these is a side effect when the antihistaminic agent is given to induce sleep or the amphetamines as part of a reduction diet.

Secondary effects are more easily classified than recognized. When

the drug is not a direct cause of, but rather indirectly initiates a series of changes and the effects are due to such changes, the term secondary is particularly apt. A prime example is superinfection or the so-called "choleriform syndrome" following antibiotic agent administration. Moniliasis, similarly caused, is another example. The body changes seen when a drug interferes with vitamin absorption, as in the ingestion of mineral oil, itself acting merely mechanically, can truly be termed secondary effects.

The Shwartzman phenomenon can also easily be separated from all other groups of reactions. The cells affected must have been exposed to bacterial filtrate and subsequently to an intravenously administered toxin to which the response is initial vasoconstriction, associated with the formation of plugs of leucocytes and platelets followed by local vasodilatation and capillary rupture. The mechanical effect of loss of blood supply involves many cells not equally sensitized, if at all, by either the initial or the second challenge.

The Arthus Phenomenon is also easily taken out of the discussion because of its special characteristic development. The local cells must have been exposed to a toxic (to them) substance which obviously has not affected them. The injection of the same or a related substance causes local necrosis.

There is no convenient term for an apparently related phenomenon. A substance may, in the present state of our knowledge, be innocuous at the clinical level, but when it is injected with smallpox vaccine, or when the site of injection is exposed to solar or roentgen radiation, a reaction occurs. The photosensitizing reaction seen when blond patients were given the first sulphonamides may also be of this type. The present-day sulphonamides only rarely cause such photosensitization. It would seem that, loosely speaking, these might be termed secondary reactions, in which case the phrase must be broadened and redefined. It is also seen in animals. Mice injected with Hemophilus pertussis acquire, for example, a decreased tolerance for histamine.

The Jarisch-Herxheimer reaction is again, in a special sense, secondary. The term is applied to those reactions due, not to the drug, but in infected states to the effects of the toxins released by the bacteria the drug has affected. Such bacterial endotoxins may also act as allergens. What differentiates the Jarisch-Herxheimer reactions from others, is the fact that the re-administration of the same drug to the same patient in the absence of infection causes no similar reaction. The alert clinician will look for the Jarisch-Herxheimer reaction following the use of penicillin for syphilis, of Aureomycin® for brucellosis, and Chloromycetin® for typhoid fever.

The term idiosyncrasy occurs frequently in the literature describ-

ing drug reactions, allergic or non-allergic in type. It has been used loosely to describe many different types of responses. It is best applied to qualitative abnormal reactions paradoxical by nature. We know that in cats morphine administration causes excitement while dogs behave as humans usually do with sedation. There are patients in whom barbiturate ingestion causes both excitement and wakefulness. There are those whose insomnia can be treated by coffee. It has been postulated that, in the latter, the hot drink induces sleep before the caffeine effects occur, but in one of the author's patients, caffeine in tablet form at any time is equally successful, causing sleep within minutes, while with placebo tablets, the patient stays awake for several hours. Since sleep occurs naturally in time, such experiments are not always crucial. The most paradoxical of the idiosyncratic effects is noted when patients suffering from urticaria have an immediate increase in the number and extent of their hives following treatment with antihistaminic agents. In some rare cases, this has been traced to the excipient, but in some of my patients, the injectable and liquid preparations caused equal reactions, due perhaps to selective withdrawal of the antihistaminic agents by some cells protecting themselves, permitting the histamine or similar agents present to affect other cells in greater concentration.

Intolerance is perhaps best defined as a quantitative deviation from the normal response. Sialorrhea and bronchorrhea from small doses of iodides, and cinchonism following normal doses of quinine fall into this category. The effects are usually those of pharmacological overdosage, due in part perhaps to rapid absorption and body transportation mechanisms. They are not usually difficult to recognize, since they are pharmaco-dynamic in nature. Such patients can often tolerate the minimal doses of the same drugs, if such small doses are sufficient for therapeutic purposes. When quantitatively the dose must be too small, then substitute drugs must be given.

None of the reactions included so far can be classified as "allergic". They may be secondarily, but are certainly not primarily, due to toxic, pharmaco-dynamic, or cumulative effects.

The classic allergic reaction is generally characterized by the fact that normal doses may initially be taken with safety, but that minute amounts of the drug may subsequently cause one or several types of reactions not so far described. Classically, the first exposure should cause no reaction. Clinically, however, it is sometimes seen in patients whose history apparently shows no previous administration. The explanation usually advanced is that previous exposure may have been unwitting, as by penicillin in poliomyelitis vaccine or in milk, or the use of tetracyclines as preservatives for fish or chicken. In some cases, cross-sensitization may explain such reactions. When we

can uncover sensitization to substances of similar nature or related origin, this explanation usually suffices. An example is the presence of a reaction to an initial injection of horse anti-tetanus serum in an atopic patient sensitive to horse dander. Unfortunately the relationship is rarely so obvious. Paradoxical as an allergic reaction to the first supposed administration of a drug may be, some comfort can be drawn from the fact that we rarely possess complete histories of our patients and perhaps the drug or a similar remedial agent may have been administered in the past. Certainly, few patients know the composition of previously ingested or injected drugs.

Particularly distinguishing allergic reactions from all others are smooth muscle spasm and generalized mucous membrane edema associated with urticaria and angio-edema, which may affect local areas of mucous membrane and of the skin, the latter being clinically more obvious. On the skin, undifferentiated rashes may also occur and be described by morphological characteristics as maculopapular, or by clinical resemblances as scarlatiniform or morbilliform.

In the past such reactions have been differentiated as they were immediate or delayed in type. Each was supposedly a different sort of reaction. It may be true, but evidence to the contrary is beginning to appear to show that the two types of reactions are not as different as previously supposed.

It has also been said that when the sensitization affected not only the so-called shock organ but also an adaptation elsewhere in the body of an organ with an enzyme system concerned with the synthesis of globulins, then and then only were there measurable circulating antibodies, and, therefore, so-called "positive" tests seen. When the changed enzyme system resided only in the shock organ and when the tissue cells of such an organ were not involved in globulin production, there was no blood stream evidence of allergy and no tests in the skin or elsewhere.

It would now appear that, as in tuberculin sensitivity, all the cells of the body may be sensitized and yet that antibodies need not be recoverable from the blood stream. All the cells of the body react, but some to so slight a degree that the reaction is ignored and some to so great a degree that attention is turned upon them.

There are several other explanations for the supposed lack of antibodies. They may be present, but by today's relatively coarse techniques not measurable. They may be difficult to demonstrate because a blocking antibody may concurrently be present. In the tuberculin-sensitized guinea pig, sensitivity may be carried by a fraction of the alpha globulin and blocking antibody in the gamma globulin fraction. The picture becomes even broader, as when hypersensitivity of special type is described as existing in Negroes in whom ingestion of

primaquine causes hemolysis. In a small number in whom this occurs the abnormality was shown to be inherited and not due to previous exposure. In other words the patient is "allergic" to the drug but the allergy so-called lies outside the classical definition of allergy. Epidemiological studies may in time uncover similar types of "non-allergic-allergy".

It is believed that the immediate type of reaction is more often seen in patients with atopic disorders such as Atopic Dermatitis and upper and lower respiratory tract allergy, a constellation of syndromes in which there is a strong hereditary factor. An examination of the available data shows that these disorders may be present in patients in whose forbears there were, by present standards, no clinical atopic disorders. This does not mean that parents now alive may not at present suffer these disorders in subclinical form or subsequently not develop them. There are two other relationships to bear in mind.

Such hereditary factors are often present in a group of disorders which, by present standards, are often regarded as nonatopic, as for example infectious asthma. In this group there is not only a frequent familial history of allergy, but it is, itself, known for its special reactions to acetylsalicylic acid. On the other hand, studies have also shown that drug sensitivity is three times more common in an allergic (atopic) as compared to a non-allergic population.

Not to be ignored is the fact that many of the reacting drugs have been available for less than ten years and that neither do we know whether there are constitutional types of reactors nor what the future of present non-reactors or of their progeny may be. To my knowledge, no epidemiological studies of second generation children of reactive parents have as yet been made. Nor will such studies be practical for some years.

A recent survey of the literature shows that the whole problem of antibodies as regards drug sensitivities needs critical review.

First and foremost, as has been said elsewhere (Brown, 1955), "there are neither gross organic changes nor microscopically recognized tissue alterations that are *per se* invariably pathognomonic of allergy, either drug-induced or otherwise. The body cells apparently respond to many different types of stressors with a limited number of reaction patterns. The apparent diversity of reaction can be explained by quantitative effects as regards to how much of any tissue or how widespread the reaction among organs may be, and with the qualitative effects on the organs themselves. The responses need not be sequential because the order of the organs affected varies from patient to patient and from disease to disease. In this regard the state of the patient's disease may also be an important factor.

Until recently it was believed that each antigen was specific and acted as a template for antibody formation from gamma globulin. One type of antigen gave rise to the development of one type of antibody, and confusion could occur only when related antigens caused the development of closely similar types of antibodies. The differently located reactive sites on the molecule of such related antibodies accounted for some of their differences. It is now known (Talmadge, 1957), that "antibodies to the same as well as to a different antigen have been found to vary in (a) physicochemical property including N-terminal amino-acid sequence, (b) ability to produce secondary reactions such as hemolysis, (c) fixation of complement, skin sensitization, agglutination, precipitation, and Arthus reactions, (d) avidity for the injected antigen, (e) cross-reactivity with related antigens, (f) rate of metabolism, and (g) distribution between blood and tissues". Talmadge says that "the only properties common to all antibodies are (a) their protein nature, (b) an increased production following exposure to antigen and (c) affinity for the antigen".

Of the three present-day theories of antibody formation, the antigen template and the change in globulin synthesis have been most widely held. The third is that the antigen *"selects"* from the Globulin Synthesizing Units available "those with which it has the greatest 'affinity' and '*induces*' them to produce antibody and to replicate". The words "selects" and "induces" have been italicised from the rest of Talmadge's statement to draw attention to the anthropomorphism and teleology which can hardly be applied to such reactions but which are seen frequently in the literature. In another review, another author writes of a drug that "it had long enjoyed a sinister reputation in causing reactions". What happens to this "reputation" when in carefully chosen patients no reactions occur?

The chief criticism of the template theory is the fact that antibodies continue to be formed long after the antigen, as such, by our present standards of identification, has left the body.

Campbell (1957) says, "...it is now evident that even soluble antigens, or more likely, fragments of such antigens persist in tissue cells for long periods of time after injection". Campbell believes that the fragments mentioned contain configurations foreign to intracellular enzymes and cannot therefore directly be broken down any further. But an explanation must be found for the fall in antibody titer which follows cessation of antigen injection. Under such conditions it is postulated that the fragment may form a fairly stable complex with a component of the cell and would therefore dissociate very slowly, decreasing its participation in protein synthesis. Undetectable levels of antibody production would thereafter probably continue. With

renewed injection of the antigen, fragmentation into antigenic templates occurs more rapidly, accounting for the anamnestic response.

If we agree with Haurowitz (1952, 1956) that there are perhaps not more than 50,000 types of antibodies, then any antigen can be coupled to an antibody sufficiently close to its configuration as to require little change to become "specific". On this basis we can agree with Talmadge's brilliant analysis and dispose of the antigen template theory on the basis of the work of Burnet and Fenner (1949) and of Jerne (1952, 1955), who show that the template hypothesis is faulty when we note the specific anamnestic response, the avidity of antibody (which increases with continued immunization), the rise of antibody (which is exponential), and its production for long periods of time and lastly "the dominant part played by the surface of particulate antigens in determining the specificity of the antibody molecules found".

If we follow along with Jern's theories, the extracellular union of an antigen with a naturally occurring antibody is rapidly replicated intracellularly. This would be true of "true" antigens as well as those haptenically produced.

But, in all of this, there is no answer to the question as to why in one patient sensitive to penicillin, an intracutaneous test is positive and in another, it is negative, although both patients respond to an injection by urticaria.

There are undoubtedly many other unknown factors involved. Until recently (Ackroyd, 1954), it was not realized that some types of Sedormid® reactions required the presence of normal platelets. In hemolysis the antigen must be absorbed or attached to the surface of the erythrocyte. Either the antigen or the antibody may in their breakdown, release toxins which affect distant sensitized cells. Or, as I have mentioned elsewhere (Brown, 1955), a distant enzyme system may be activated or inactivated, in the one case releasing toxins or in the other, failing to neutralize such toxins, thus causing ill effects.

Our studies are hampered by the fact that in human beings, studied clinically, reactions can only be noted when they have occurred at the clinical level, usually in patients otherwise ill, in which case we attempt to study the patient, as it were, retroactively. In those patients in whom we attempt sensitization so that laboratory studies can be made as they occur, we are limited in the types we can induce. To my knowledge no one has given large numbers of normal, nonatopic, non-diseased subjects injections of penicillin in courses designed to induce urticaria. In other words, in clinical drug sensitivity we are always working backwards and using what we find today to reconstruct what happened weeks or months before.

It must be remembered also that the majority of studies with which we have to work are at what must be termed the gross or macroscopic clinical level. The drug is given to the patient for a purpose as it were, to combat infection. It may do so and, in the process, do something else; in other words, cause urticaria. It is possible that the particular patient's body has done something to the drug. In some cases the breakdown of the drug by the body leads to the formation of substances of greater potency than the original medication.

Usually we seek to determine the effects of drugs in separate frames of reference. The clinician is interested in how the patient's disorder can be remedied. He wishes among other things to kill microbes, to restore, decrease or increase organic function or perhaps lessen pain.

The pharmacologist wants to know what the tissue cells will do as regards alterations of permeability, electric potential of cell surfaces, the crystallization-decrystallization of cell systems, the selective effects of electrolyte interchanges, and the elevation or depression of intramural or extramural electrolyte movement. He wonders whether it can react on two systems as on the cell surface of one tissue and intracellularly on another. He wishes to discover whether the drug can compete on the cell surface when it is faced with mutually-presenting substances, one of which is harmful and the other, harmless, as do the antihistaminic agents. When there is no reaction he wonders whether the cells may not be able completely to neutralize its effects, as does atropinesterase when a rabbit is given atropine to which it is immune. Does the drug cause an initial production or increased production of cell enzymes not only in themselves toxic but incapable of completely breaking down the foreign protein so that its end products such as peptones may be toxic? Does it affect cell metabolism and cause changes in desoxyribonucleic acid content or configuration? He knows it may act by changing the number of interacting molecules or by changing the strength of the bond between the protein molecule and the substance. Actually it may quantitatively affect the energy of combinations of molecules.

As a result of any of these, the patient may respond macroscopically apparently not at all. This, too, is a response. We term it tolerance. If we are dealing with toxic agents we term the response resistance. The type of response may successively pass through stages of hypersensitivity, sensitivity, tolerance, dependence or in the reverse order. We may then have metabolic disturbances, derangements in growth, carcinogenesis, signs of allergy, or of stress.

In any one organ at the enzyme level, the agent may evoke the development of an enzyme which reacts with the agent to form a new complex. This may cause the development of another self-

perpetuating multi-catalytic enzyme system which again reacts with the new agent. This, in turn, may call forth another enzyme system to react with it.

But the same enzyme may be present in two different types of tissues, as in the brain and in the nerves. A drug as, for example, morphine, not only acts differently with each, but differently on different parts of each. The cells, as it were, "learn quickly" not to respond with respiratory depression and muscular weakness. The effect on pain changes slowly with habituation, but the pupil and the gut never cease to respond in their typical fashion.

We have no explanation for the temporary irreversible actions of some drugs whose effects persist long after their excretion as with reserpine and dicoumarol.

I have discussed briefly elsewhere what I have termed "transport mechanisms". Wherever its site of deposition, part of the drug is bound and part unbound. One portion is being absorbed, with another being retained as such, while one portion may be transformed, while another is being excreted. At the surface or within each tissue cell such action takes place. Absorption and excretion may be independent or interdependent. It has been long known that localization in special tissues occurs, but recent work implies that this effect may be greater than we had suspected. It has been shown that when Dromoran® is injected intraveneously in dogs it appears in the gastric juice in a concentration forty times that of the plasma. Although acidic drugs do not appear in the gastric juice in measurable quantities, others given as their bases, such as acetanilid, theophylline, aminopyrine and quinine, do. The fact that forty times may be a constant may be due only to the speed of circulation.

Microscopically it appears from recent work that there may be barriers within the individual cell, that is, intracellular in type. In homogenized tissues, enzyme action can proceed to completion, whereas in the intact cell, relationships between iproniazid, monoamine oxidase and serotonin demonstrate that selective action can occur. Brodie and Hogben (1957) give examples of how this occurs and also examples of how so-called detoxification, although it results in "less active compounds", may nevertheless by bio-transformation change the drug into one more active. It can also be changed into compounds as active as the parent drug as well as into others less active. The reactions to any of the three may be allergic or non-allergic.

The problem appears to grow ever more complex. Meyler's review of the world's literature on the "Side Effects of Drugs", although it makes much information readily available, compounds the confusion for anyone who would attempt to make a pattern or classification of drug reactions.

When aminophylline is listed as causing convulsions, vomiting and albuminuria, we are certain that these are not allergic responses. But amphetamine ingestion is listed as causing restlessness, tremor, palpitations, insomnia, perspiration, dry throat, itching, congestion, dizziness, anxiety, nausea and vomiting. One of these reactions, pruritus, is also common to an early, typically allergic reaction, except that it occurs with normal pharmalogical doses, and previous safe ingestion is not noted.

A patient is described as responding with what seems to have been a typical allergic type of reaction to butobarbital, since there were red macules with central hemorrhages, purpura, pigmentation and arthralgia.

A tablet of Sedormid® is described as causing hemorrhagic diathesis and a reduction in thrombocytes to 40,000 with thrombocyte agglutinating antibodies. With the use of carbomal there are described purpura, erythema, pigmentation, arthralgia and capillary fragility.

With Dilantin® there may not only be the usual exanthematous and gingival reactions but hyperchromic anemia and hypertrichosis. With Mesantoin® there may be the same exanthemata but aphthous stomatitis, pigmentation, pruritus with no visible lesions, swelling of the lymph glands and edema of the face.

Following Thiomedan® administration, morbilliform rashes have been seen but also leukopenia, agranulocytosis and myxedema. With a drug like phenylbutazone, the types of reactions are so many and so diverse that the investigator finds it difficult to discover any common denominator, since several types may occur concomitantly in the same patient. In the cardiovascular system there can, understandably, be decompensation, hypertension, and angina due to sodium and water retention. An interstitial "allergic" type of myocarditis is described. Hemorrhages into the skin and mucous membrane have been noted, as well as hematuria. In one patient a second course of phenylbutazone caused anaphylactic shock and death. Postmortem findings included adrenal hemorrhage. Re-activation of peptic ulcer and edema of the gastric membrane have been described. One patient responded to 25 tablets given during 22 days with fever, rash, purpura, nausea, vomiting and stomatitis, dying on the 44th day of exfoliative dermatitis. Liver necrosis and multiple gastrointestinal tract ulcerations were found. Another patient developed fever, purpura, erythroderma, enlarged liver with jaundice, splenomegaly and eosinophilia, all responsive to ACTH. Many other types of dermatological reactions are listed as well as effects on the liver, the kidneys, the nervous system, sensory organs and the thyroid gland.

In the present state of our knowledge it is impossible to classify these reactions, especially when the types overlap to so great a degree in the same patients.

All that we can say is that although individual drugs are more noted for one type of reaction than another, all drug reactions, however limited for one drug or one patient, will in the greater number, if the response is allergic, fit somewhere into the picture of serum sickness, the atopic disorders, atopic eczema, respiratory tract effects and urticaria, anaphylactic shock, the skin rashes, the serum disease-like syndrome, the blood dyscrasias and (in a different category) the contact dermatitis.

We do not know why the drug causes one or more manifestations of these and not others. With the injection of serum there may be, for example, among other types of reaction, arthralgia, whereas with another drug, as for example pollen extract, an injection may cause an anaphylactic type of response but never arthralgia.

If the reaction due to the drug itself varies with colloid as compared to crystalloid structure, the response may also vary due to conditions inherent in the patient. If he responds chiefly with the canine form of anaphylaxis the reaction will be one of shock, whereas with the guinea pig type of anaphylaxis, pulmonary spasm will be seen. If the nature of the reaction is of the horse or cow type, there may be lung spasm, but also increased peristalsis, generalized severe perspiration with angio-edema and urticaria affecting skin and mucous membranes. Both the primate and rabbit type of anaphylaxis affect the heart; the first with dilatation of both auricles and ventricles and the second with distention of the right ventricle due to contraction of the pulmonary arterioles succeeded by hypopiesia and bradycardia. In the feline type there will be renal and gastrointestinal effects. Each of these (in whole or in part) and in overlapping syndromes, have been noted in reactions of human beings, depending entirely on the organs chiefly affected by arteriolar spasm. The permutations and combinations of the properties of the drug and of the different types of patient-responses explain the multitudinous varieties of reactions seen.

It may be that serum, being colloid in nature and animal in origin, contains more antigenic fractions which can affect more tissue cells or body systems, while many of the drugs are, by comparison, relatively simple crystalloid substances capable of affecting few types of cells. But this explanation falls short of telling us why serum does not cause blood dyscrasias or why the crystalloid drugs, although they rarely cause the appearance of the whole picture of serum disease, are nevertheless capable of causing, albeit separately, almost every one of its individual characteristics, although in dif-

ferent patients. Equally difficult to understand is the phenomenon of changing sensitivity as seen in the same patient, who may on one occasion present evidence of idiosyncrasy with a small dose, allergy to repetition and toxic reactions at a later dose, and then for no obvious reason (spontaneous hyposensitization?) no reaction whatsoever.

Although some drugs are undeniably more often associated with some types of reactions then are others, as for example iodides causing iodermas and aspirin causing asthma, it must nevertheless be stressed that any drug can conceivably cause any type of reaction so far recognized as well as others awaiting recognition.

The inquiring physician will want to know what drugs most often cause what reactions. The grouping of drugs on the basis of types of reactions is not to be taken as implying that they act by similar mechanisms, as, for instance, the furunculoid disorders following either bromide or ACTH administration. Only the most frequently occuring reactions are listed. Single unconfirmed reports have not been included.

Pruritus alone may follow the use of acetylsalicylic acid, aminopyrine, antibiotic agents, atropine, codeine, emetine, the mercurials, the opium derivatives, phenobarbital and the sulphonamides.

Acneiform, furunculoid and erysipelas-like eruptions may follow the use of ACTH, bromides, chloral hydrate, iodides, oils and tars.

Eczematous eruptions may follow the use of anesthetic agents (local), antibiotic agents, arsphenamine, atabrine, chloral hydrate, ephedrine, formalin, mercurials, procaine and quinine.

Erythema multiforme-like responses may follow the use of acetophenetidin, antibiotic agents, antipyrine, barbiturates, iodides, phenolphthalein, salicylates and sulphonamides.

Erythema nodosum-like eruptions may follow the use of bromides, iodides, salicylates and sulphonamides.

Fixed eruptions may be due to acetophenetidin, antipyrine, arsphenamine, Atabrine®, atropine, acridine, acriflavin derivatives, bismuth, cinchophen, emetine, gold salts, mercury, phenacetin, salicylates and sulphonamides.

Purpuric eruptions have been seen with the administration of arsphenamine, barbiturates, carbamides, ephedrine, guanidine, iodides, mercurials, salicylates, sulphonamides and thiouracil.

The drugs which may cause contact dermatitis are too numerous to list.

The following drugs are known to cause depression of the bone marrow or thrombocytopenic purpura, or both: acetanilid, acetophenetidin, aminopyrine, anesthetic agents, antibiotic agents, antihistaminic agents, arsenicals, Atophan ®, barbiturates, Gantrisin®,

gold salts, iodides, mercurials, para-amino-salicylic acid, phenolphthalein, sulphonamides, thiosemicarbazone, thiouracil and Tridione®.

Those drugs known to depress the bone marrow but not cause thrombocytopenic purpura include Dilantin®, dinitrophenol, hydantoin, phenurone, procaine amide and urethane.

Those drugs known to cause thrombocytopenic purpura but not depression of the bone marrow include acetylsalicylic acid, bismuth, cortisone, the estrogens, digitalis and quinine.

In patients presenting rhinorrhea or bronchospasm, the drugs most frequently incriminated are: acacia, acetylsalicylic acid, ACTH, anesthetic agents, antihistaminic agents, argyrol, arsenicals, Atophan®, atropine, asthma powders, cocaine, cortisone, derris root, Demerol®, digitalis, emetine, heparin, hyocyamus, insulin, iodides, ipecac, karaya gum, liver extract, lycopodium, the mercurials, morphine, Pantopon®, para-aminosalicylic acid, penicillin, pollen extracts, Privine®, quinine, sera, streptomycin, sulphonamides, Takadiastase®, tannic acid, tetraethylammonium bromide, thiamine, and vaccines.

The drugs known to cause urticaria or angio-edema, or both, include: acetylsalicylic acid, aminopyrine, amphetamine, anesthetic agents, anticonvulsants, antibiotic agents, arsenicals, Atophan®, atropine, Aureomycin®, barbiturates, belladonna, bee venom, bismuth, bromides, chloral hydrate, cinchophen, codeine, digitalis, dinitrophenol, Diodrast®, emetine, ephedrine, estrogenic substances, gold salts, heparin, insulin, iodides, karaya gum, liver extracts, mercurials, morphine, para-aminosalicylic acid, penicillin, pentothal, phenolphtalein, phenylhydrazine, pollen extracts, quinidine, sera, streptomycin, sulfobromophthalein, sulphonamides, tannic acid, thiamine, thiocyanates, thiosemicarbazone, thiouracil, tridione, and vaccines.

It also appears that certain types of patients are more often affected by some drugs rather than by others. Patients with acne, acneiform eruptions, pyodermas, moniliasis and monilids, react more often than does the general population to iodides and bromides. Patients with recurrent herpes simplex will react also to salicylates. Those with acne, pyodermas and hypertrichosis are more allergic to androgenic substances. Individuals subject to purpuric and hematological disorders may respond allergically to arsenicals, barbiturates, gold salts, salicylates and sulphonamides. Those prone to seborrheic diseases, intertrigo, infected or impetiginized eczematoid eruptions respond adversely to arsenicals, gold salts, penicillin and sulphonamides. Patients with past or present epidermophyton infections are more likely to repond allergically to penicillin and other antibiotic agents.

The majority of the reactions described will, depending on their type and distribution (and occasionally on their cause), respond to epinephrine, ephedrine, the antihistaminic agents and the steroid hormones.

Those associated with jaundice, yellow atrophy of the liver and nerve damage will respond less or not at all to these remedial drugs. Reactions which in the present state of our knowledge cannot with certainty be labelled as either allergic or toxic, since they might equally be caused by both types of reactions, as granulocytopenia, thrombocytopenia, polyneuritis and anemia, due perhaps to an associated, infected state should, as the case may be, be given treatment with anti-allergic drugs, the corticosteroids and ACTH.

It is obvious from this brief review that a number of medications are associated more frequently than the laws of chance would suggest with certain types of patient reactions. These reactions are not frequent, but occur sufficiently often, and with such severity, as to be the concern of any conscientious physician. Their occurrence cannot in most cases be predicted and much of the evidence for their relationships is *post hoc propter hoc*. When the reaction is immediate, typical, and recurrent as in aspirin-caused bronchospasm, neither the physician nor the patient can ignore the relationship. But when atypical or delayed such supposed drug reactions can be a source of much concern.

The first rule to follow, since there is no method of knowing in advance that a drug will cause reaction, is not to repeat the use of the drug when the cause of any disorder does not conform to the classical pattern. The actual number of proven serious reactions is small. In some cases the physician who first suspects the drugs in use as causing an atypical clinical course will be wrong, but it is surprising also how often he will be right.

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