Allergy and Tissue Metabolism

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William Heinemann Medical Books Limited
London

First published 1964

***Printed** in Great Britain by The **Whitefriars** Press Ltd*
London and Tonbridge

Foreword

During the last fifteen years, research relating to allergic disease processes has penetrated into many areas covered by the basic medical sciences of physiology, pharmacology, biochemistry, and experimental pathology. This has expanded a large volume of scientific literature into a voluminous one. Thus, one of the difficulties now experienced by the interested observer of this research effort is the apparently disconnected character of individual research communications relative to the field as a whole.

The present monograph represents an assessment of some of the more important features of the current state of knowledge in the relevant areas of the basic medical sciences. Emphasis has been given to the interdependence of these discrete areas of knowledge in the belief that such a survey of the "growing points" of allergy research will prove to be a valuable aid to practising allergists and physicians as well as interested workers in the scientific disciplines involved.

Sunderland, Co. Durham W. G. S.

1963

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Chapter I

The immunological basis of allergic disease

During the period when the body is recovering from certain infectious diseases it becomes more resistant to the organism responsible for the infection. This increased resistance is known as acquired immunity. Its duration depends upon the nature and severity of the infection; so that it may be weak and transient on the one hand or substantial and lifelong on the other. The immunity acquired in this way is associated with the appearance in the blood of substances called antibodies, which have properties enabling them to combine specifically with the infecting organism or a toxin produced by it. The first clear demonstrations of the formation of antibodies were made during the last ten years of the last century, and soon shown to be examples of a general phenomenon in which a large variety of foreign cells and simpler entities like protein molecules stimulate the production of specific antibodies if they are injected parenterally into the mammalian body. Substances that stimulate the formation of antibodies in this way, and react with them specifically, are known as *antigens*. Conversely, a substance that appears in the blood or body fluids as the result of the parenteral administration of an antigen, and that reacts specifically with that antigen, is called an *antibody*.

Early observations showed that when the antigen is a soluble substance such as a foreign protein, its combination with specific antibody contained in an antiserum often led to the formation of a precipitate. The antibodies were then termed precipitins. When the antigen was a constituent of foreign cells, such as erythrocytes from another species of animal, the combination of antigen and antibody caused the cells to agglutinate. The antibody was then called an agglutinin. It is now clear, however, that a single antibody can be involved in either the formation of a precipitate or the agglutination of cells according to the situation of the specific antigen with which it reacts.

Unfortunately, the production of antibodies does not always have beneficial results. It may have the very reverse effect when the body cells experience an antigen for the second time, resulting in severe symptoms and even death. This phenomenon, whereby an *immunological response* involving combination of antigen and antibody is the cause of reactions which are damaging to cells, is called *allergy* or *hypersensitivity*. Hypersensitivity can occur in a large number of conditions, some produced artificially, others occurring naturally, and a number associated with infective disease. The relationship between the hypersensitive state and the production of antibodies is in some cases quite clear, but

in others, antibodies have not as yet been detected and the immunological basis for the conditions can only be inferred indirectly. It seems quite probable that in all infective disease of long enough duration to allow an immunological response, symptoms due to hypersensitivity to bacterial or viral products are present, superimposed on those due to the direct effects of the infecting organisms themselves.

The relationship between hypersensitivity and antibody production can be most clearly demonstrated where the hypersensitive state is produced artificially; a condition known as *anaphylaxis*. This term is compounded from the Greek and suggests that guarding (phylaxis) is reversed (ana). It was first used by the French physiologist Richet[1] in 1902 who later wrote:

"While endeavouring to determine the toxic dose (of extracts of sea anemone), we soon discovered that some days must elapse before fixing it; for several dogs did not die until the fourth or fifth day after administration or even later. We kept those that had been given insufficient to kill, in order to carry out a second investigation upon these when they had recovered. At this point an unforseen event occurred. The dogs which had recovered were intensely sensitive and died a few minutes after the administration of small doses. The most typical experiment, that in which the result was indisputable, was carried out on a particularly healthy dog. It was given at first 0·1 ml. of the glycerin extract without becoming ill; twenty two days later, as it was in perfect health, I gave a second injection of the same amount. In a few seconds it was extremely ill; breathing became distressful and panting; it could scarcely drag itself along, lay on its side, was seized with diarrhœa, vomited blood and died in twenty five minutes."

A somewhat similar observation had been made in England at about the same time by Theobald Smith in guinea pigs used for the assay of diphtheria antitoxin. Animals injected with neutral mixtures of toxin and antitoxic serum, and which therefore survived, became very ill and often died after receiving a second injection some days later. Theobald Smith communicated his results verbally to Ehrlich, and later, Otto[2] in Ehrlich's laboratory investigated more fully what he described as the "Theobald Smith phenomenon". He was able to show that it was not confined to mixtures of diphtheria toxin and antitoxin and readily invoked by a foreign protein like horse serum. Subsequent work has clearly defined the conditions which will lead to the development of the state of anaphylaxis or, as it is often called *anaphylactic shock*.

Anaphylactic shock in animals

To produce anaphylactic shock, the animal must previously have had experience of the antigenic protein. After the first administration of the

protein, certain changes take place in the body which is then said to be sensitised to the particular protein concerned. It is necessary for sensitisation that the antigen molecules reach the body cells in an unaltered state. Sensitisation is thus most conveniently brought about by parenteral injection, although inhalation and even ingestion are often effective. In the last case much of the protein will be destroyed in the alimentary canal, but the mucous membrane is apparently permeable to some extent to unchanged protein[3] and since incredibly small amounts of antigen will sensitise the guinea pig (e.g. 1 μg of egg albumin or 0·000001 ml. of horse serum),[4] it is only necessary for small quantities such as these to escape digestion and penetrate the alimentary mucosa. The size of dose required for sensitisation depends on the species of animal. Very small doses are effective in guinea pigs, but larger doses are needed for rabbits and dogs. On the other hand, excessively large doses may delay sensitisation or even prevent its occurrence.

Anaphylactic shock occurs when a second injection of antigen is given after a certain period of time. This latent period varies with different species and with the degree of sensitisation. A period of at least a week is required for all species, and with some a period of three to four weeks is preferable. Once this period has elapsed the resultant sensitivity may persist for an almost indefinite period. Shock is only produced if antigen reaches the sensitised cells in a relatively high concentration. Doses larger than those required for sensitisation are usually required and often the required concentration in the tissues can only be achieved by administering the antigen intravenously.

Animal species also differ one from the other in the signs, symptoms and pathological lesions of anaphylactic shock. Whereas the blood pressure in the rabbit and guinea pig rises, at least initially, in the dog it falls progressively. The guinea pig dies of asphyxia with signs of acute respiratory distress; the rabbit dies of acute right sided heart failure; while the dog dies of circulatory failure following the segregation of much of its circulating blood in the hepatic portal circulation. Nevertheless it is now generally believed that the main manifestations of anaphylactic shock are due to two main effects—contraction of smooth muscle and increased capillary permeability.

In the guinea pig the main symptoms are attributable to an intense contraction of bronchial smooth muscle, which in that animal is particularly well developed throughout the lung. Within a few minutes of the intravenous administration of antigen to a sensitised animal, there are signs of severe respiratory difficulty. When bronchial muscle contracts it is expiration that becomes difficult; this is seen in human asthmatics. A guinea pig in anaphylactic shock develops a syndrome very similar to a human asthmatic attack.[5] It becomes extremely cyanosed and dies within ten minutes. The post mortem picture shows over-inflated lungs, occluded bronchioles and local hæmorrhage in the

lungs and also other tissues. There is a considerable accumulation of polymorphonuclear leucocytes in the lung capillaries.

In the dog the predominant signs of anaphylactic shock are different. Death never takes place in less than 1 to 2 hours unless the animal is exceptionally well sensitised and may not occur at all. The most prominent symptom is prostration and weakness due to a profound fall in systemic blood pressure (e.g. from 120 down to 30 mm. Hg). This startling fall in blood pressure is due to a segregation of a large proportion of the circulating blood in the liver and hepatic portal circulation. This is brought about by an intense spasm of the smooth muscle in the walls of the hepatic vein. Not only is the liver the main organ to show changes in a dog undergoing anaphylactic shock but it is apparently responsble for most or perhaps all of the pathology of shock. Exclusion of the liver by ligature will prevent the onset of shock.[6]

The rabbit also shows distinctive features in anaphylaxis. This species is difficult to sensitise. Death following a challenge dose of antigen is caused by acute right heart failure. The right side of the heart is enormously dilated as a result of an intense contraction of the pulmonary artery. It is not only the pulmonary artery which contracts, however. Sudden blanching of the ears due to constriction of peripheral arterioles is a noticable feature of anaphylaxis in this animal, and arterioradiograph studies have shown that general arterial contraction occurs throughout the body.[7]

In all three species, the blood becomes less coagulable. Leucopenia (decrease in number of circulating leucocytes) in the peripheral blood is apparent and due to the accumulation of leucocytes in the capillaries of the lungs. A fall in the number of circulating platelets is also observed. Platelets appear to be segregated with the leucocytes in the lungs. In the dog, they are also found in the liver.

The antigenicity of the sensitising agent, the identity or immunologically specific relationship between this and the time required for sensitisation all point to the involvement of antibody in the anaphylactic reaction. This is made quite conclusive by the finding that sensitisation can be transferred passively. The transference of sensitivity with serum transferred from one animal to another has been noted for some time. It has also been shown that the degree of sensitivity produced by the transferred serum is related to its content of antibody.[8] It is thus clear that the production of anaphylactic shock requires two components, namely antigen and antibody, to be present in the body at the same time and must therefore, be presumed to depend upon some interaction between the two.

The manifestations of anaphylaxis which have just been described as those which occur when an animal is injected with antigen on two occasions. The first injection stimulates antibody production and is termed the *sensitising dose.* The second injection of antigen, which

brings about anaphylactic shock, is termed the *challenge dose.* Since under these experimental conditions the animal reacts to the challenge dose of antigen with antibodies of its own manufacture the resultant reaction is called *active anaphylaxis.* When an unsensitised animal is injected with serum from an actively sensitised animal the antibodies which that serum contains will sensitise the tissues of the unsensitised recipient. When this animal is given a challenge dose of antigen the resultant reaction is described as *passive anaphylaxis.* The reactions of passive anaphylaxis can be localised by injecting antibodies into a restricted area. A common example where restricted areas of skin are sensitised by intradermal injections of antibody and then challenged with antigen is *passive cutaneous anaphylaxis.* The terminology of anaphylactic reactions and the techniques by which they are produced has recently been lucidly described by Davies.[53]

Allergy in humans

Whilst anaphylactic shock in experimental animals is a highly artificial condition brought about by the injection of antigen into the circulation of a previously sensitised animal, there are, however, a number of natural diseases for which there is evidence for an underlying mechanism essentially similar to that responsible for anaphylactic shock. These diseases which have been studied almost exclusively in man are the *allergic diseases.* Although some authorities make a clear distinction between these various diseases, there is a tendency nowadays to divide them into two groups. The first group includes those forms of allergy in which antibody can readily be demonstrated in the patient's serum, and which give rise to an immediate urticarial reaction when antigen (sometimes called allergen) is injected locally and in which the symptoms can be related to contraction of smooth muscle and changes in the permeability of blood capillaries. *Serum sickness, serum allergy, serum anaphylaxis* and *atopy* are examples of this group. The second group includes allergies in which no antibodies have been demonstrated in a form free of cells, in which a delayed, indurated more cellular reaction is demonstrated by local skin injection of antigen, in which all cells are sensitive and in which there is no contraction of smooth muscle. This group includes *contact dermatitis* and the tuberculin type of *allergy of infection.*

Serum sickness is a term first used by von Pirquet and Schick[9] to describe the signs and symptoms which followed the injection of a large dose of therapeutic horse serum antitoxin in man. The earliest sign, which appears about a week after injection is an urticarial rash around the injection site, soon followed by indications of increased capillary permeability i.e. generalised urticaria, enlargement of lymph glands draining the injection site, and œdema of the lips and eyelids.

There is a rapid fall in the numbers of circulating leucocytes which is coincident with the onset of symptoms. It is due to leucocytes congregating in œdematous tissues.[10]

The disease is due to antigens present in the antitoxic serum and is unrelated to the content of antitoxin. Since foreign proteins are eliminated from the body very slowly, seven days after injection there is still a high proportion of the dose present in the circulating blood. At this time, however, body cells have produced antibody in response to the antigenic stimulus provided at the time of injection. It is now believed that the cause of serum sickness is a union of circulating antigen to fixed antibody in tissue cells. Symptoms come on when antibody first appears in cells and abate when sufficient circulating antibody has been produced to neutralise the antigen still remaining.

Serum sickness thus resembles anaphylaxis in that it is dependent upon an antigen-antibody reaction; fixed tissue antibody and circulating antigen react on tissue cells, the one large dose of antigen functioning first as a sensitising and then later as a shocking dose. The disease differs from anaphylaxis in that it never involves contraction of smooth muscle, and the onset of symptoms is always slow.

Serum allergy describes a condition having essentially the same cause as serum sickness but with a much accelerated or even immediate onset. In addition, unlike serum sickness, there are manifestations of contraction of smooth muscle. The condition is confined to individuals who have been sensitised to horse serum by previous injection or those with a hereditary or natural hypersensitivity to horse products. Symptoms vary from urticaria at the site of injection, or immediate serum sickness, to general serum anaphylaxis identical with that seen in animals. The signs and symptoms may resemble guinea pig, rabbit or canine anaphylaxis. Spasm of the smooth muscle of the bronchioles, pulmonary artery or hepatic veins is therefore a prominent feature. Œdema of the glottis may also be a cause of death.

Atopy is a term used to describe a group of hypersensitivity diseases in which hereditary factors are known to be involved. It is well known that some individuals are unable to eat common articles of food without suffering from acute symptoms which vary from urticarial rashes to gastro-intestinal disturbances and asthma. Others are especially sensitive to the inhalation of dust from animal or vegetable sources. Hay fever, due to the inhalation of grass pollen during the height of summer is a well known example of this type of allergy. It is not confined to naturally occurring substances, but can also be caused by drugs, of which common examples are aspirin, quinine and the sulphonamides. Drug allergy must not, however, be confused with drug idiosyncrasy, a heightened sensitivity to the normal pharmacological actions of a drug which has no immunological basis.

The reactions of atopy are often very specific. A person can be

sensitive, for instance, to strawberries grown only in one particular locality. On the other hand, multiple hypersensitivity is not uncommon. Hay fever sufferers, for instance, are rarely sensitive to only one type of pollen. The tissue most affected by contact with allergen usually depends upon the route of administration. Substances which are inhaled tend to produce nasal œdema and/or bronchiolar spasm, while substances which are eaten produce gastric and intestinal disturbances. In some cases, the reaction varies within an individual. Eczema of infancy may give way to asthma in childhood or hay fever in later life.

Atopy has two important diagnostic features. It is frequently accompanied by an increase in circulating eosinophils (eosinophilia) in the circulating blood. It imparts skin sensitivity to allergen so that intradermal injections of it invoke well characterised reactions which are sometimes helpful in discovering the particular allergen responsible for a given condition, especially as the skin response can be obtained in conditions where skin reactions are not involved, e.g. asthma. The response to an intradermal injection of allergen in a sensitive individual consists of an urticarial wheal surrounded by erythema at the site of injection. Allergens to which the individual is not sensitive show little or no reaction at all. One important feature of this reaction is the fact that it is imitated by intradermal injections of histamine in both normal and hypersensitive individuals.

It is often found that one or both parents of an individual suffering from atopy are also hypersensitive. However, it is not sensitivity to a particular allergen but the predisposition to become hypersensitive that is inherited. The hereditary element could be the result of a predisposition of atopic individuals to either make large quantities of antibody in response to an antigenic stimulus or to produce antibody in response to casual rather than unusual contact with allergen. It has been suggested that in atopic, but not in normal, subjects, the cells of the respiratory or intestinal tract which come into contact with the allergen are particularly liable to produce a sensitising type of antibody. The hereditary factor, although important, is not essential for the development of atopy. In many typical cases of asthma and hay fever, no hereditary factor has been found to be involved. Some allergens produce hypersensitivity in normal individuals in small doses. An example is diptheria toxoid. Once induced, the sensitivity of normal individuals to allergen does not noticeably differ from that of individuals in whom a definite family history of atopy has been established.

In patients who are specifically hypersensitive to a single allergen, it is very likely that sensitisation has been brought about by a previous contact with the allergen. Evidence of that contact is, however, often extremely difficult to find. Pollen and dusts of animal origin, to quote only two examples, are very ubiquitous materials. In cases of atopic drug allergy on the other hand, the history of first contact may be quite

evident. Mere external contact with allergen can be sufficient to induce general hypersensitivity. Many examples of penicillin hypersensitivity in medical and nursing staffs of hospitals bear witness to this.

In cases where no previous history of contact with an external allergen has been obtained, it has been suggested that hypersensitivity is the result of allergens produced endogenously. The phenomenon is then described as autosensitisation. It has been discussed in some detail.[12] Sometimes the incidence of hypersensitivity by such means is well established, as in sympathetic ophthalmia in which hypersensitivity to uveal pigment is brought about by absorption of the pigment following trauma to the uvea. Patients suffering from this condition show a positive skin reaction to intradermal injection of uveal pigment. Hypersensitivity to hormone secretions of the endocrine glands are in many cases endogenous in origin. The best documented reactions of this type are those involving insulin. Local urticarial reactions which have appeared around an injury some ten days afterwards have been interpreted to be the result of hypersensitivity to denatured protein from the damaged tissue. There is also evidence that certain physical allergies, i.e. those following exposure to cold, heat, pressure etc. are due to hypersensitivity to the patient's own protein.

Most allergens are proteins, whose activity is destroyed by proteolytic enzymes or by heating. Horse and other animal danders are of this type, while eggs and milk, the most common food allergens, depend upon their protein for their allergenic nature. Occasionally it is not the food as eaten that is the allergen, but some metabolic product of it. In such cases the symptoms appear some hours after ingestion of the food.[13] Some allergens contain carbohydrate. Examples are grass pollens, house dust, and some bacteria (meningococcus, hæmophilus influenzæ, shigella and mycobacterium tuberculosis). Drugs which induce atopy contain neither protein nor carbohydrate. However, aspirin or sulphonamides do not produce skin reactions in sensitised subjects unless first mixed with normal serum or the patient's own. It is thus considered that drugs function as allergens only when bound to protein. Direct evidence for this has been obtained[14] in a patient who developed a local reaction to an intradermal injection of an aspirin-protein complex isolated from his urine.

In most cases, atopic hypersensitivity can be transferred from one individual to another by blood transfusion. However, the antibodies responsible cannot be detected in the donor plasma, by "in vitro" precipitin or agglutination tests. In this respect they are different from antibodies which impart anaphylactic sensitivity to animals. For this and a number of other reasons, the antibodies of atopic hypersensitivity are known as reagins. The amount of reagin in a sensitising serum can only be determined by the Prausnitz–Küstner Reaction.[15] Küstner was hypersensitive to certain species of cooked fish. If some of his serum

was injected intradermally into the skin of Prausnitz, 24 hours later an injection of fish extract induced a local wheal and flare reaction within 1½ hours. A site prepared in this way remains sensitive for as long as a month after the preparing injection, but immediately loses its sensitivity after a positive Prausnitz-Küstner reaction (P–K reaction).

The differences observed between anaphylactic antibodies and reagins were once considered to be important, but it is now currently believed that these differences are not of a fundamental character and are due largely, if not entirely, to the low content of reagin in serum from individuals with atopic hypersensitivity. The sera of highly sensitive individuals contain only very small amounts of reagin. Reagins do not precipitate with allergen "in vitro", but anaphylactic antigens and antibodies do not always do so.[16] Reagins will not sensitise guinea pigs to anaphylactic shock, but this failure has been explained on a quantitative basis.[17] For instance, the serum of some individuals naturally sensitive to diptheria toxoid was highly effective in preparing sites for a P–K reaction, but contained only 1/2000th of the amount of antibody necessary to sensitise guinea pigs to anaphylactic shock. Reagins are not transmitted from mother to fœtus; hence passive sensitisation "in utero" cannot take place. Whilst many anaphylactic antibodies can induce passive sensitisation in this way, certainly not all of them are able to do so. It is also commonly stated that whereas reagins are destroyed by heating at 56°C for 4 hours, anaphylactic antibody is more thermostable. It has been shown, however, that such heat treatment does not necessarily destroy reagin, but merely alter its ability to prepare a skin site for a P–K reaction[17]—the only means of detecting it.

Contact dermatitis has been defined as a manifestation in the skin of an inflammatory reaction due to a hypersensitivity acquired by previous contact with a specific sensitising substance. It occurs particularly in workers in the chemical, agricultural and confectionery industries. In contrast to atopic hypersensitivity there is no hereditary predisposition. The sensitising agents are usually simple chemical compounds, although union with skin protein appears to be a necessary requirement for sensitisation to occur.[18] No antibodies have been demonstrated in human contact dermatitis but there is indirect evidence that a diffusible factor of the nature of a skin sensitising antibody is present since the whole skin becomes hypersensitive after application of the sensitising agent to only a small area. There is also the possibility that the reticulo-endothelial cells of the skin produce antibodies of a type strongly adsorbed to cells.[19] The reaction of contact dermatitis occurs 7 to 21 days after sensitisation and takes 24 hours to fully develop. This is in sharp contrast to the immediate weal and flare of the atopic skin test and hence is termed a delayed hypersensitivity.

The second delayed type of hypersensitivity is that displayed by

allergy of infection which has been most effectively studied in tuberculosis. Early experiments of Koch demonstrated the extreme sensitivity of the tuberculous animal to reinfection with the tubercle bacillus or the injection of tuberculoprotein. A dose of tuberculoprotein which is non toxic to normal animals may rapidly kill tuberculous animals. Very small doses given intradermally elicit a typical tuberculin reaction. This makes its appearance after 12 to 18 hours and reaches maximum intensity about 6 hours after its appearance. It consists of a raised indurated erythematous nodule which often shows papules in addition. Necrosis of variable degree may occur. The tuberculin reaction can be demonstrated in tissues other than skin, e.g. the conjunctiva, serous and mucous membranes and parenchymatous organs.

It must not be confused with the Arthus reaction[20] which is a local manifestation of a hypersensitivity reaction of the immediate or anaphylactic type brought about by a reaction of antigen injected locally with free circulating antibody. It was first observed in rabbit skin but can be invoked in any organ.[21] The reaction causes immediate damage to capillary endothelium, extravasation of blood and necrosis. Although an immediate reaction, its macroscopic manifestations take 18 hours to develop in their entirety. Hence the possible confusion with the tuberculin reaction.

The tuberculin reaction is not induced by sensitising doses of tuberculoprotein. This material is highly antigenic and it will sensitise guinea pigs to anaphylactic shock. Until recently it was assumed that whole organisms of mycobacterium tuberculosis were necessary to induce tuberculin type sensitivity, but it is now known that this type of sensitivity depends upon certain fatty substances of the organism which can be extracted with fat solvents.[19] The active substance is a lipid-polysaccharide complex. Its action is not confined to tuberculin sensitisation, for when other proteins, for example egg albumin, is injected with this lipid-polysaccharide complex a delayed tuberculin type hypersensitivity is induced which is specific for egg albumin.

There is no experimental evidence for the involvement of circulating antibody in tuberculin type hypersensitivity. Passive transfer of this type of sensitivity cannot be achieved with serum, although successful transfer has been accomplished using suspensions of cells.[22] This is interpreted as evidence that the antibody involved in tuberculin type reactions is fixed to the cells. It has been suggested that the cells which are transferred continue to make sensitising antibody or in some way induce the recipient's cells to make it.

Rich has collected evidence that large or repeated injections of antigen or allergen in both man and animals can lead to the development of lesions of the type observed in diseases known as periarteritis nodosa, lupus erythematosis and rheumatic myocarditis.[23] Collagen degeneration is a characteristic of such lesions. It is also found in the

Arthus reaction. A survey of the recent literature shows that there are a number of other diseases, which are believed to have some hypersensitivity component. These include ulcerative colitis,[24] rheumatoid arthritis,[25] glomerulonephritis,[26] allergic encephalomyelitis.[27, 28]

Although anaphylaxis and the hypersensitivity conditions in man which have so far been considered have many distinguishing features, it is not unlikely that all known hypersensitive states are merely variations of an essentially single immune response to an antigenic stimulus.[29] This hypothesis considers that the various form of hypersensitivity are due to the complete or partial arrest of the immune response at some stage. Arrest at the first or cellular stage, before any antibody is found in the circulation leads to the delayed type of hypersensitivity. Arrest at the next stage leads to a condition characterised by reagin type antibodies which have a high affinity for cells, especially skin, and which are found in the circulation in only low concentration. Finally, in the last stage, precipitating antibody is found in larger quantity in the circulation in addition to that fixed by cells. This unitarian hypothesis of hypersensitivity is supported by observations that guinea pigs show delayed type hypersensitivity before they develop circulating antibodies in response to a sensitising dose of antigen,[30, 31] and observations that guinea pigs can produce any one of the three types of antibody in response to a single antigen.[17, 19]

The effects of antigen–antibody reactions in hypersensitive tissue

Having now concluded that hypersensitivity depends upon the simultaneous availability of both antigen and antibody in tissue, there remains the problem of how these two components interact to produce the signs and symptoms of the hypersensitive state. Before considering this problem, however, a few pertinent comments must be made about the nature of both antigens and antibodies.

It is not possible to list precisely the chemical properties that impart antigenicity to a molecule. Size is important since all known antigens are large molecules. It is also known that most antigens consist either entirely of protein or contain a substantial protein component. Polysaccharide and lipid-polysaccharide complexes can be antigenic, but such antigens are less common than those of protein structure. Among proteins, there are considerable variations in antigenic potency. Egg albumin is a potent antigen; hæmoglobin is only a weak one; whilst gelatin is not antigenic at all. Because of the complexity of proteins and the difficulties encountered in determining their detailed structure, only imprecise information exists about the relationship between chemical structure and antigenicity in pure proteins. It was suggested as long ago as 1906 that antigenic specificity is influenced largely by the content and arrangement of amino acids containing

aromatic residues.[32] Another suggestion has been that only rigid protein structures are antigenic.[33]

More precise information has been obtained by coupling non-protein structures to a protein moiety and studying the effects of varying chemical structure in the non-protein portion on the antigenicity of the complex as a whole.[34] These studies have included a number using carbohydrates.

Little was known about the nature of antibodies 20 years ago. Today, there is no doubt that they are members of the serum globulin proteins. They are usually γ-globulins, and like normal serum γ-globulins consist of a family of related substances. It is not known, however, exactly how antibody globulins differ from the corresponding normal globulins. The way in which they are formed is also uncertain. It has been suggested that antigen acts as a mould for antibody globulin, forming on the globulin a shape complementary to a part of its own surface.[35] This particular characteristic is considered essential for the subsequent union of antigen and antibody in the circulation or tissues of a hypersensitive individual exposed to a shocking dose of antigen.

The union of antigen and antibody has been studied in some detail and on a quantitative basis. Most of these studies originate from the work of Heidelberger and Kendall[36] and deal with the "in vitro" precipitin reaction. This work has led to some interesting discussions of the combining forces between antigens and antibodies and the structure and composition of antigen–antibody precipitates. It has not explained why the union of antigen and antibody sometimes has beneficial results (as in immunity to infection) and sometimes quite harmful ones (as in hypersensitivity).

Early workers who turned their attention to this problem regarded the circulating blood as a source of some anaphylactic poison to which they gave the name anaphylotoxin. The first anaphylotoxin to be described in the literature was that produced by Friedberger in 1909[37] by adding antigen–antibody precipitate to guinea pig serum. The specific precipitate was formed "in vitro" by mixing antigen and serum containing antibody, isolated, washed, incubated with fresh serum and removed by centrifugation. The clear supernatant was injected into a guinea pig intravenously whereupon the animal presented all the characteristic symptoms of anaphylaxis. At post-mortem examination the animal showed distended lungs (due to bronchiolar constriction) with emphysema and œdema. The name anaphylotoxin was given by Friedberger to the substance formed in the serum as a result of incubating it with specific precipitate. Heating fresh serum to 56° C prior to incubation with specific precipitate destroyed its capacity to produce anaphylotoxin, so Friedberger inferred that complement was involved in its formation.

Almost immediately other workers demonstrated that anaphylo-