CLINICAL ASPECTS
OF IMMUNOLOGY

EDITED BY

P. G. H. GELL
M.B. M.R.C.S.

Professor of Immunological Pathology
University of Birmingham

AND

R. R. A. COOMBS
M.R.C.V.S. B.Sc. Ph.D.

Reader in Immunology in the
Department of Pathology, University of Cambridge
Fellow of Corpus Christi College, Cambridge

SECOND PRINTING
REVISED

CHAPTER THIRTEEN

THE CLASSIFICATION OF ALLERGIC REACTIONS UNDERLYING DISEASE

R. R. A. COOMBS & P. G. H. GELL

INTRODUCTION

In the minds of many practising physicians, the term 'allergy' though a useful and indeed a fashionable one, implies no precise concept; it is used as a rough and ready label for all conditions in which the active reaction of a patient's own tissues, rather than a disordered physiological process like cancer or diabetes, or the direct damage by an invading organism determines the manifest lesions of the disease, or at least a large part of them. Side by side with this rag-bag of generally obscure conditions are those diseases normally dealt with by the clinical allergist — serum

sickness, drug sensitivities, hay fever and asthma, various dermatological conditions – and empirically used tests such as the tuberculin and Schick tests, which are immunologically determined.

A great deal of fairly intelligible and co-ordinated knowledge has been accumulating in recent years, as the result of laboratory studies both in experimental animals and in human patients, on most, though not all, of the several distinct mechanisms which come under the general head of allergy. In most diseases, in fact, it ought to be possible to say, not merely that they have, vaguely, an 'allergic basis', but that such and such a well-defined process underlies the lesions. Where we find that we cannot say this, the realization of our ignorance provides a stimulus to find out more. A main stumbling-block to clear thinking lies in the use of the words 'immunity' and 'immune' – implying as they do by their common meaning absolute protection against a noxious agent, or at least the occurrence of some process strictly advantageous to the organism. In many reactions 'with an immune basis' the 'immune' process actually constitutes the disease, while in others, such as tuberculin sensitivity, one cannot say for sure whether in the long run they are disadvantageous or not.

Von Pirquet's Original Concept. To evade this source of confusion, and to set out the newer knowledge to the greatest advantage, it is essential to build on a sound semantic foundation. It is our feeling that this is most easily achieved today by going back to the original concept of von Pirquet, expressed with the greatest clarity in his paper published in 1906. The whole of this classical paper is translated in Appendix A. The following extracts from it are strictly relevant to the present discussion:

'*The vaccinated person behaves ... in a different manner from him who has not previously been in contact with such an agent. Yet he is not insensitive to it. We can only say of him that his power to react has undergone a change.*

'For this general concept of a *changed reactivity* I propose the term *allergy ...*

'The vaccinated, the tuberculous, the individual injected with serum becomes *allergic* towards the corresponding foreign substance. A foreign substance which by one or more applications stimulates the organism to a change in reaction is an *allergen.* This term – not quite in accordance with philological usage – traces its origin to the word antigen (Detre-Deutsch) which implies a substance capable of giving rise to the production of antibody. The term allergen is more far-reaching. The allergens comprise, besides the antigens proper, the many protein substances which lead to no production of antibodies but to supersensitivity.

'*The term immunity must be restricted to those processes in which the introduction of the foreign substance into the organism causes no clinically evident reaction, where, therefore, complete insensitivity exists*; whether this be due to alexins (natural immunity), antitoxins (active and passive immunity in diphtheria and tetanus), or even to some kind of adaptation to a poison (Wassermann and Citron).'

Thus the term 'allergy' should be taken to mean the specifically altered state of a host following exposure to an allergen. This altered *biological* state or allergy has in itself no implied connotation as regards the production of either *clinical* hypersensitivity or *clinical* immunity; it may entail either, or both simultaneously in the same individual. 'Hypersensitive' and 'immune' are descriptive terms only, useful in indicating a clinical state, and are not mutually exclusive.

Von Pirquet's clear foresight in putting forward such an untethered basic concept allows without any difficulty the inclusion of actively acquired tolerance amongst the allergic phenomena. We would, however, suggest that 'transplantation allergy' would be a more precise designation than 'transplantation immunity' and likewise 'auto-allergic diseases' rather than 'auto-immune diseases'. Moreover, if we can be persuaded to accept the concept of allergy as it was originally stated, it will be seen that the scope of the subject broadens to contain examples not usually dealt with in text books of allergy. Besides the phenomena of true 'immunity' (protection), and the recognized hypersensitivity reactions, there must be included transfusion reactions, haemolytic disease of the newborn, iso-'immune' neonatal purpura, the tentatively grouped 'immuno-pathological' diseases such as allergic thyroiditis and rheumatoid arthritis, the reactions of homograft rejection and finally the experimentally produced runt disease and actively acquired tolerance.

A Rational Basis for Classification of Allergic Conditions. The conventional basis for classification of diseases, in terms of a clinical syndrome, of an anatomical or a biochemical lesion, and so on works well enough in practice, for the purpose of sorting out patients into their appropriate wards, and deciding whether to subject them to the tender mercies of a physician or a surgeon. But as von Pirquet realized a number of quite distinct though all fundamentally 'allergic' processes may be going on simultaneously in one patient, and even in the one local lesion. Therefore, if we are to apply an *aetiological* classification to the conditions discussed in this section of the book, we must first distinguish the sorts of allergic process which may be occurring. This has to be done mainly on the basis of experimental work on animals, where the variables can be properly

controlled. The next stage is to attempt to sort out which of these processes are going on in any patient with a particular clinically classified disease. In all too few of the diseases considered here is only one kind of allergic process involved; and it is an easy error to assume that, even when one given process is demonstrable, this process, and only this, is responsible for the whole trouble, or indeed for any of it.

We feel that any illuminating classification, which is surely necessary for the physician faced today with allergic manifestations seen not only in the allergy clinic but also in general medicine, must indicate and indeed be founded on the mechanism involved. For this reason we set forth a fairly simple, yet we hope comprehensive, scheme which does not divorce the clinical from the academic and laboratory side. As the basis of this classification we have chosen the circumstances of the initial reaction between allergen (or antigen) and antibody or specifically modified cells (as far as this is known), subgrouping subsequently on other secondary phenomena. Hence this is primarily a classification of initiating mechanisms and not of the subsequent events or the diseases themselves.

CLASSIFICATION OF ALLERGIC REACTIONS WHICH MAY BE DELETERIOUS TO THE TISSUES AND HARMFUL TO THE HOST

We consider here only the kinds of allergic reaction which may do damage of some kind, whether or not the effect in the long run may be beneficial. There are four main pathways or modes of response (see Fig. 13.1) by which the animal or individual, 'sensitized' by a previous experience of the allergen, may react and, if the reaction is intense enough, suffer as a result of the allergic state.

DEFINITION OF THE FOUR TYPES OF REACTION

TYPE I REACTION OR RESPONSE ('ANAPHYLACTIC')*

Initiated by allergen or antigen reacting with tissue cells passively sensitized by antibody produced elsewhere, leading to the release of pharmacologically active substances. Included in this category:

(a) General Anaphylaxis in Man and Animals

This may be dissected, as it were, and the separate components of the reaction observed; examples under (b).

* The phrase in parenthesis gives the conventional nomenclature, but because of historical and common usage does not always allow of consistency.

TYPE 1

TYPE II

a

b

COMPLE-
MENT

COMPLEMENT
ACTIVATED

TYPE III

NO SERUM
ANTIBODIES

TYPE IV
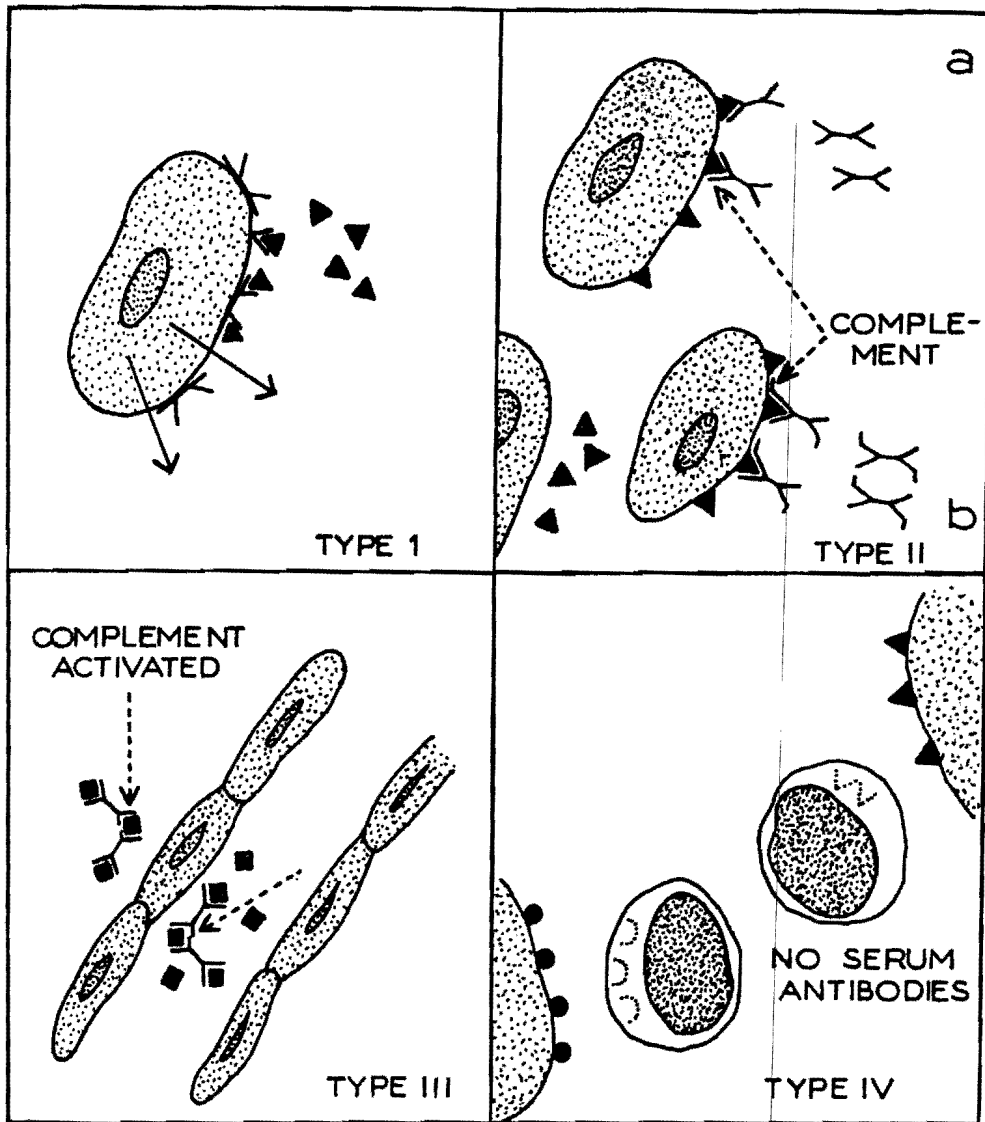
KEY,

● ▲ ■ ANTIGENS.

⟶ LIBERATION OF HISTAMINE AND OTHER PHARMACOLOGICALLY ACTIVE SUBSTANCES.

>⟩< ⟩< ANTIBODY.

---⟶ SITE OF INVOLVEMENT OF COMPLEMENT.

⟩ ⟩ MECHANISMS IN MONONUCLEAR CELLS DIRECTED AGAINST TWO SPECIFICITIES.

FIG. 13.1. Highly diagrammatic illustration of the four types of allergic reaction which may be deleterious to the tissues and harmful to the host.
Type I. Free antigen reacting with antibody passively sensitizing cell surface.
Type II. Antibody reacting with (a) cell surface or (b) with antigen or hapten which becomes attached to cell surface: complement plays a major destructive role.
Type III. Antigen and antibody reacting in antigen excess forming complexes which, possibly with the aid of complement, are toxic to cells.
Type IV. Specifically modified mononuclear cells reacting with allergen or antigen deposited at a local site.

(b) Local manifestations of Anaphylaxis

(i) *Local Anaphylaxis in the Skin.* Seen clinically in man as urticaria: experimentally in generalized skin oedema in, e.g. the rat. In more local form in diagnostic skin tests and Prausnitz-Küstner tests in man; passive cutaneous anaphylaxis reaction in laboratory animals.

(ii) *Local anaphylaxis in the respiratory tract. In vivo* as a component of general anaphylaxis in some species, such as guinea-pig and man; seen clinically in man in hay fever and asthma. Possibly the cause of 'cot-death' in infants. *In vitro* demonstrable as the 'isolated bronchial chain reaction'.

(iii) *Local Anaphylaxis in the Gastro-intestinal Tract and Other Organs. In vivo* as a component of the general reaction seen in some species more than others, e.g. dog, rat, guinea-pig, man. Seen clinically in man, in more isolated form, in certain forms of food allergy. *In vitro* demonstrable as the Schultz-Dale reaction.

TYPE II REACTION OR RESPONSE (CYTOLYTIC OR CYTOTOXIC)

Initiated by antibody reacting with *either* (*a*) an antigenic component of a tissue cell *or* (*b*) an antigen or hapten which has become intimately associated with tissue cells. Complement is usually, but not always, necessary to effect the cellular damage.

Examples of (a)

(i) Transfusion reactions due to antibody reacting with red cells, white cells or platelets.

(ii) Haemolytic disease of the newborn and iso-allergic neonatal thrombo-cytopenia.

(iii) Auto-allergic haemolytic anaemia.

(iv) A component of other auto-allergic diseases, i.e. cytotoxic antibody in allergic thyroiditis.

(v) Possibly a serum antibody playing a role in homograft rejection.

(vi) Reaction produced by injection of anti-Forssman serum into guinea-pigs, or applied to chick embryo.

Examples of (b)

(i) Involved in purpura, haemolytic anaemia and possibly agranulocytosis due to drug hypersensitivity.

(ii) Possibly involved in aetiology of acute nephritis following strepto-coccal infections.

TYPE III REACTION OR RESPONSE (ARTHUS REACTION AND TOXIC-COMPLEX SYNDROME)

Initiated when antigen reacts in the tissue spaces with potentially precipitating antibody, forming microprecipitates in and around the small vessels causing damage to cells secondarily; *or* when antigen in excess reacts in the blood stream with potentially precipitating antibody forming soluble circulating complexes, which are deposited in the blood-vessel walls and cause local inflammation.

(a) Arthus Reaction

Local Arthus reaction in laboratory animals after repeated injection of antigens: a similar reaction may be rarely seen in man, as after injections of antitoxin.

(b) Serum Sickness Syndrome

Responsible for many of the lesions seen in clinical and experimentally produced serum sickness, with accompanying arthritis, glomerulonephritis and so-called allergic arteritis. Probably a component in many diseases with an, as yet, obscure but strongly suggestive allergic background.

TYPE IV REACTION OR RESPONSE ('DELAYED' OR 'TUBERCULIN-TYPE' SENSITIVITY)

Initiated essentially by the reaction of specifically modified mononuclear cells containing a substance or mechanism capable of responding specifically to allergen deposited at a local site. The exact mechanism of this type of reaction is still uncertain, but it is manifested by the infiltration of cells, probably mainly of reticulo-endothelial origin, at the site where the antigen is.

Examples

(a) Delayed skin reactions of the tuberculin type.
(b) Contact dermatitis.
(c) Probably responsible for some elements in the lesion of auto-allergic diseases such as thyroiditis, and certain infectious diseases, e.g. tuberculosis, parasitic infestations.
(d) Probably involved in the rejection of homografts.

In presenting this schematized approach to the allergic reactions a few cautionary remarks are necessary. No dogmatic classification can be

expected to fit perfectly all the intricacies of allergic responses in man and animals; the case for its adoption must depend largely upon its usefulness and simplicity. It must be stressed that the circumstances in which any of these four basic types of reaction may be studied in an uncomplicated form may be very special, and may, in fact, be seen only in certain animal species under quite strict experimental conditions. Again it must be emphasized that the pattern seen in any one human disease is often complex, involving not just one but several of the above pathways or responses. Finally caution is required in defining pathogenesis, since the demonstration of an immunological event, such as antibody production, for example, may be only partly or not at all related to the actual aetiology of the disease under study.

Each of the four main allergic responses will now be discussed in further detail.

DISCUSSION OF THE FOUR TYPES OF REACTION

TYPE I REACTION OR RESPONSE (ANAPHYLACTIC REACTION)

Care has to be taken in the use of the word 'anaphylaxis' or 'anaphylactic'. Although a Type I response is the essential underlying mechanism in anaphylaxis, the word has, on occasion, been applied to Type II and even Type III reactions. For instance the Type II cytotoxic reaction produced as a generalized reaction or locally in the skin of a guinea-pig by the injection of Forssman antiserum has been called passive reversed anaphylaxis (see Redfern 1926). Again the Type III (Arthus-type) reaction produced in the skin of a rabbit (and which may also be produced in man) after repeated injections of antigen and the development of circulating antibody, was referred to as an anaphylactic reaction by Arthus himself and was also referred to as 'localized anaphylaxis' by Richet (cf. Arthus 1903).

ANAPHYLAXIS IN THE GUINEA-PIG AS A MODEL FOR A TYPE I REACTION

This is the experimental model which has received the most study, and fortunately for our purpose is fully comparable with the Type I reaction in man. It is initiated by antigen reacting with antibodies attached to and passively sensitizing cells. The reaction may be local or generalized, depending upon how the antigen is administered to the sensitized animal, i.e. intradermally or intravenously, and on the amount given. After passive sensitization, the nature of the reaction also depends upon how much antiserum was given and where it was fixed.

Intervening Steps between Sensitization of Tissue Cells and the Clinical Syndrome

1. Antibody becomes intimately associated or passively absorbed on to the membrane of tissue cells.

Notes (a) Not all antibodies have this property of passively sensitizing cells. This is a problem of active research.

(b) Which cells become sensitized is still not known for certain; possibly all mesenchymal cells.

(c) Even in an actively sensitized animal the tissue cells discussed under (b), are probably passively sensitized by antibody produced by the plasma cells and liberated into the tissue fluids and circulation.

(d) There is good experimental evidence that competition occurs between antibody and 'normal' γ-globulin for the site of fixation on cells (Biozzi *et al* 1959).

2. Antigen coming into contact and reacting with antibody passively sensitizing tissue cells, 'injures' the cells, which then liberate histamine and other pharmacological mediators into the tissue fluid and circulation.

Notes (a) The exact mechanism by which histamine is liberated is complex and still obscure (see Chapter 15).

(b) Histamine is to be found mainly in the mast cells which are scattered throughout the tissues. These cells may be passively sensitized and disrupted directly in the presence of antigen or they may be disrupted by a secondary process.

(c) Histamine is not the only pharmacological substance liberated as a result of the antigen–antibody reaction. In the guinea-pig and man 'slow reacting substance A' is also very important (see Chapter 15). Another mediator is 5-hydroxy-tryptamine or serotonin. Other less important mediators are acetyl-choline, heparin, bradykinin and other permeability factors. The importance of these is that they may not be inhibited or antagonized by anti-histamines.

3. Histamine has two dominant pharmaco-physiological activities:
(i) It produces dilatation of the capillaries which results in oedema and a fall in blood pressure.
(ii) It produces contraction of smooth muscle.

Notes (a) The localized dilatation of capillaries at the site of a passive transfer test in guinea-pig skin is seen by injecting a dye at the same time as the antigen, the passive cutaneous anaphylaxis test developed by Ovary (1958).

(b) The contraction of smooth muscle of a sensitized animal on addition of antigen or histamine is seen in the Schultz-Dale reaction.

4. The liberated histamine and other mediators produce the clinical syndrome by virtue of their pharmacological activity. In the guinea-pig the unusually well-developed bronchiolar musculature produces intense constriction of the bronchioles with the result that the animal is unable to force air out of its lungs; this is sufficient to cause death by suffocation. In less acute cases where the animal is not rapidly asphyxiated there is time for the other effects of general hormone release to become manifest. Clinically this is seen as generalized shock.

As briefly mentioned already, various local manifestations of the anaphylactic reaction in the guinea-pig (as in man) can be studied independently by experimental means either *in vitro* or *in vivo*. The contraction of the isolated ileum or uterus of a sensitized animal in the Schultz-Dale test is well known. Less known perhaps is the *in vitro* contraction of a chain of bronchial rings on the addition of antigen (Schild *et al* 1951).

The so-called passive cutaneous anaphylaxis reaction developed by Ovary (1958) is not only a valuable technique for demonstrating the presence of very small amounts of tissue sensitizing antibody (about 10 mcg rabbit antibody protein/ml serum), but is also a counterpart to the Prausnitz-Küstner reaction in man (see Chapters 1, 6 and 14 for details).

TYPE I REACTIONS IN MAN

It is not our intention to discuss the Type I reactions in man in any but very general terms, since the clinical pictures are presented in later chapters. There are, however, one or two considerations on the antibodies responsible in man which are of importance.

First there are certain individuals, given the name atopic by Coca & Grove (1925) who produce a type of antibody which has *par excellence* the property of passively sensitizing tissue cells, the so-called reagin or atopic antibody. As yet, this antibody cannot be demonstrated or measured* by any routine serological test *in vitro*. *In vivo* it has very pronounced biological activity, initiating histamine release from passively sensitized cells in the presence of antigen and it may be shown to be present in the serum by means of a passive transfer test, the well-known Prausnitz-Küstner (P-K) test. Unfortunately this human antibody will not produce a reaction in the skin of the guinea-pig and the reluctance, in this country at least, to do passive transfer tests in normal persons with

* See pages 38 and 40; also Shelley, W. B. (1962) A new serological test for allergy in man. *Nature, Land.* **195**, 1181

human serum (for fear of serum hepatitis) makes investigations on this antibody difficult.

There would also appear to be uncertainty whether human antibody other than the 'atopic reagin', i.e. whether potentially precipitating antibody, can passively sensitize human cells to initiate a Type I reaction: there is evidence which can be assembled both for and against this supposition. We feel ourselves that non-atopic antibodies also are able to initiate such a reaction, as is the case in lower animals.

General Anaphylactic (Type I) Reaction in Man

The syndrome is one of profound generalized shock. If the patient does not die rapidly, more local signs are manifest such as bronchial asthma, pulmonary oedema and urticaria. Somewhat different patterns may result according to the type of antibody involved, atopic reaginic or potentially precipitating, and depending on whether local reactions such as oedema of the glottis or bronchial asthma precede the more generalized involvement.

Such a reaction could result from antigen reaching the circulation of a highly sensitized person in the course of serum or drug therapy, from desensitization procedures with pollen extracts, after bee or wasp stings or from the classic example of hydatid cysts burst during operation. Should 'cot death' in infants be proved to be a modified anaphylactic reaction (Parish et al 1960) then absorption of antigen via the lungs must be considered another hazard.

Local Anaphylactic (Type I) Reactions in Man

As examples of this we have the ordinary prick and scratch diagnostic skin test where a local wheal results around the small site where antigen is introduced into the skin. Hay fever and allergic asthma are again local manifestations of a Type I reaction. These reactions are localized because of the local access and action of the antigen or allergen. It must be remembered that the person nevertheless has a general sensitization which would be revealed if excessive amounts of antigen were absorbed.

What is not understood is why some people with such a general sensitization experience only hay fever symptoms or none at all when naturally exposed to the antigen as an inhalant, while others experience asthma. This is hard to explain simply as a quantitative effect. Rather it suggests the influence of as yet unknown local predisposing factors.

Extensive urticaria may be an expression of cutaneous anaphylaxis. The Prausnitz-Küstner reaction is the comparable reaction in man to that

M

of passive cutaneous anaphylaxis in the guinea-pig, no dye, however, being needed as the histamine wheal is seen clearly in human skin.

Finally, as will be seen from Chapter 15, histamine is by no means the only mediator liberated from cells by the Type I reaction in man, so one must not expect all the symptoms and signs of these reactions to be inhibited by more or less specific anti-histaminics.

TYPE II REACTION OR RESPONSE (CYTOLYTIC OR CYTOTOXIC)

In this type of reaction we have antibody reacting directly through its combining receptors with either an antigenic component of a tissue cell or with an antigen or hapten which has become intimately associated with the tissue cells. The antibody is usually of classical type but may be incomplete. The mechanism of destruction depends partly on the nature of the antibody and partly on the kind of cell; complement is frequently involved.

ANTIBODY REACTING WITH AN ANTIGENIC COMPONENT OF TISSUE CELLS

Transfusion Reactions

There is a wide familiarity with the lysis of red cells by antibody and complement *in vitro*. In the body under the circumstance of incompatible transfusion lysis may occur intravascularly, or the sensitized cells, either with or without the participation of complement, embarrass the reticulo-endothelial system. White cells of the blood may be similarly involved.

In most books on blood transfusion, reactions due to previous sensitization and red cell incompatibility are not described as 'allergic' although according to v. Pirquet's definition they surely qualify. In these books the use of the term 'allergic' is generally confined to those reactions following transfusion which are characterized by urticaria, oedema and bronchial spasm, i.e. to those reactions thought to be caused by traces of soluble foreign antigens in the donor's plasma reacting with atopic reaginic antibody in the plasma of the recipient or *vice versa*. In our way of thinking this latter situation is a Type I reaction, while the reaction due to cell incompatibility and destruction, is Type II; both, however, are allergic reactions.

Haemolytic Disease of the Newborn

This disease of man and of many other animal species (Roberts 1957) in which the mother produces antibodies which, on gaining entrance into the foetus or newborn, cause destruction of the red cells, must, by the

same reasoning, be considered an allergic disease. Iso-allergic neonatal thrombocytopenia (see Chapter 18) is a comparable situation.

Homograft Rejection

The extent to which a cytotoxic reaction involving antibody and complement is concerned in homograft rejection is still an open question. Much may depend on the nature of the tissue grafted (see Chapter 22).

Lesions Produced in Tissues by the Action of Antibody and Complement

Antibodies against surface components of the cell may, in the presence of complement, produce specific cell damage (cf. Goldberg & Green 1959). This type of reaction could well play a role in many of the auto-allergic diseases; auto-allergic haemolytic anaemia is an obvious example. However, in auto-allergic thyroiditis Irvine (1960) considers a Type II reaction to play a role. Also in experimental auto-allergic aspermatogenesis (see Chapter 27) humoral factors may be concerned.

Lesions produced in Forssman positive animals upon injection of anti-Forssman sera may also be considered as resulting from a Type II reaction. The guinea-pig has the Forssman antigen on its tissue cells but not on its red cells. Injection of anti-Forssman produces marked vascular damage and haemorrhages. Redfern (1926) studied both the generalized reaction and the lesion produced locally in the skin following intra-cutaneous injection. He pointed out that the reaction was quite distinct from anaphylaxis and was produced by a direct cytotoxic action of the antibody on the vascular endothelium. Although a good example of a Type II reaction, it may not be a perfect prototype because of the presence also of a soluble form of this antigen in the tissue fluids of the guinea-pig. Anti-Forssman serum and complement together are also lethal for the embryo of the chick whose tissues contain the Forssman antigen (Witebsky & Neter 1935).

It has been postulated that acute nephritis following streptococcal infection is due to an antibody to a bacterial product cross reacting with a tissue antigen in the kidney. Such a mechanism might conceivably be operative in other tissues.

ANTIBODY REACTING WITH ANTIGEN OR HAPTEN ADSORBED ON OR COMBINED WITH TISSUE CELLS

Possibly of great importance in connection with Type II allergic reactions and disease is the rendering of tissue cells temporarily susceptible to the

cytotoxic action of antibody and complement by adsorption of an antigen (bacterial product) or hapten (drug) on to such cells. Reaction of the bacterial antibody or antibody to the cell-drug complex might then bring about cellular destruction.

Cytotoxic Reactions in Drug Hypersensitivity

The generalized purpura, which is the form in which the hypersensitivity reaction to the drug Sedormid manifests itself and which has been worked out by Ackroyd (see Chapter 19) is a clear example of a Type II reaction as defined by us.

A comparable syndrome with haemolytic anaemia, instead of generalized purpura, may follow the use of drugs showing an affinity for the red cell (Muirhead, Holden & Graves 1958; Freedman, Barr & Brody 1956). Some such mechanism involving the white cells may also underlie certain forms of drug-induced agranulocytosis (Moeschlin 1958; see Chapters 19 and 28).

Acute Nephritis

Another possible mechanism, still Type II, which is postulated as an explanation for acute nephritis following streptococcal infection, is that certain cells of the kidney combine with a bacterial product and then become a target for a cytotoxic reaction mediated by complement and antibody against the bacterial product. This has been discussed by Wright (1957). Other situations can also be envisaged where localization of a bacterial product could result in tissue damage by such a process.

If the antigen is not in actual association with the cells, reaction with antibody could still produce tissue damage, but this, according to the present classification, would be a Type III reaction which is described in the next section.

It may seem unorthodox to group together under one heading haemolytic transfusion reactions, the reaction produced in guinea-pig skin on injection of anti-Forssman serum and purpura due to Sedormid hypersensitivity but in each case the underlying mechanism is essentially the same, i.e. antibodies of a specifically sensitized or allergic individual reacting with cells and damaging them.

Not only should this realignment clarify the way of thinking about these reactions, but it seems very probable that in the next few years further examples will be found to fall under this heading when mechanisms producing *in vivo* tissue damage receive closer study.

TYPE III REACTION OR RESPONSE: ARTHUS TYPE REACTION; TOXIC COMPLEXES

Basic to the modern conception of this type of reaction is the observation that complexes between antigen and antibody formed *in moderate antigen excess* are locally toxic to the tissues, probably with the participation of complement (for full discussion see Weigle 1961). The mechanism of such damage is multiple; hormonal, vascular, and cytotoxic elements are all involved, and the exact histological site where the complexes are produced or lodge entails differences in the overall pattern. The work upon which this generalization is based is mainly recent, and still a field of active research; thus a reconsideration of the whole approach may be needed, as new data are produced. Nevertheless we feel that some such simplification and generalization is essential and timely; and for the sake of clarity it is better to state it dogmatically.

Complexes between antigen and antibody in which antigen is in excess may be formed in two situations; firstly, in the blood stream, when large amounts of antigen are circulating and antibody is beginning to be produced in the lymphoid system but is immediately combined with antigen as it enters the circulation; and secondly, when antibody is present in the blood and antigen is injected into the tissues in high local concentration – the first being the 'serum-sickness' situation, and second the 'Arthus-type' situation. Serum sickness will be considered in more detail in Chapter 16, and it will be sufficient to say here only that the site of the localization of complexes from the blood stream is naturally in the vessels themselves. In the Arthus-type situation, antigen deposited intra- or hypo-dermally will presumably diffuse from the site, and at some point in the diffusion zone it will meet and combine with blood-borne antibody at the concentration required to produce antigen-excess irritant complexes. After this the mechanism in the two sorts of Type III situation may be identical, although the initial events and exact histological site are different.

Complexes of the right sort once formed, (i) they will tend to produce both local histamine release, and also possibly the release of actively cytotoxic hormones; (ii) circulating leucocytes will be affected by them causing aggregation locally or elsewhere; (iii) activation of local vascular endothelium (Biozzi *et al* 1948) will also promote the lodgement of affected leucocytes, platelets and fibrin, with resultant thrombosis and haemorrhage. Thus according to the amount of complexes produced anything from transient polymorph infiltration and oedema to extensive vascular thrombosis and local necrosis may develop. The late development

of plasma cells suggests the occurrence of local antibody formation. Stetson (1951) has produced evidence that there may be generalized as well as local involvement of the leucocytes so that these cells become 'sticky' and may be deposited at inflamed sites remote from the original lesion.

We use advisedly the term 'Arthus-type'. The Arthus reaction as originally described (Arthus 1903) is probably more complicated since there is evidence that both a delayed (Type IV) (Tremayne & Jeter 1955) and possibly a Type I component are also involved. The simple model is the Passive Arthus, in which antibody is injected intravenously and antigen locally. The Reversed Passive Arthus, in which antibody is injected locally and antigen intravenously has presumably, *mutatis mutandis*, a similar mechanism. (It should be noted that the terms Passive and Reversed Passive are used in a contrary sense to that of Ovary's 'Passive Cutaneous Anaphylaxis' reaction, where antibody is injected intradermally, not intravenously.)

DIFFERENTIATION FROM TYPE I REACTIONS

Since it is a characteristic of a Type I reaction that the antibody is fixed to cells the use of a non-fixing type of antibody, e.g. horse antibody in the guinea-pig, should provide a model in which the anaphylactic type of passive sensitization of cells and histamine release is eliminated. However, histamine release is an element of any inflammatory reaction, particularly where complement is involved; and therefore although Arthus-type reactions are not inhibited by antihistaminics, it is not surprising that some elements in them, in particular the oedema, may be reduced. On the other hand the intensity of a Type III reaction is greatly reduced by eliminating the animal's circulating platelets or polymorphs (Humphrey 1955) or by heparin (Benacerraf & Biozzi 1953). Again the intensity of a Type III reaction is proportional to the level of circulating precipitating antibody, which is not the case in a Type I reaction. Finally in performing a passive reaction, no interval for fixation to the tissues is required in a Type III reaction, as it is in a Type I reaction.

The important consideration from the point of view of the classification we are presenting is that the initiating antigen-antibody interaction proceeds independently of cells or tissues. These become involved in the reaction and damaged only secondarily, owing either to the primary irritant action of complexes of a particular antigen-to-antibody ratio or to pharmacologically active agents released under the influence of these complexes.

SIGNIFICANCE OF TYPE III REACTIONS IN MEDICINE

(i) The full Arthus reaction used to be seen quite commonly in man following repeated administration of antitoxic or antibacterial sera derived from animals; for an illustration of a very severe reaction see Kohn, McCabe & Brem (1938). It may be seen today after several injections of horse tetanus antitoxin or as a rarity in persons receiving long-continued courses of materials such as insulin.

(ii) Similarly serum sickness proper is not so often seen today as in the days of extensive immunotherapy, at least in severe form. In typical 'delayed serum sickness' occurring in non-atopic individuals a Type III reaction involving circulating complexes probably plays the main role in the pathogenesis. So-called 'immediate serum sickness' is on the other hand an 'atopic' manifestation involving reagins, a typical Type I reaction (see Chapter 16).

(iii) There is reason to believe that many cases of drug sensitivity, in particular those involving penicillin and sulphonamides, are examples of a Type III serum-sickness-like mechanism (see Chapters 16 and 19).

(iv) Finally because the lesions and other findings in experimentally produced 'hyperimmunization serum sickness' in animals are suggestive of a similar mechanism being operative in nephritis, polyarteritis, rheumatoid arthritis, disseminated lupus erythematosus and other diseases, it is possible that when these diseases are more fully understood it will be found that a Type III reaction plays an important role.

Before concluding this section a word should perhaps be said on the significance of the source and supply of antigen in these Type III reactions. If the antigen is administered as a single dose, the lesions should regress and heal as in classical serum sickness. If on the other hand the antigen is given repeatedly, as during treatment with penicillin, or is endogenous, as is presumably the case with the desoxyribonucleoprotein-antigen of lupus, the lesions will recur in crops. Corticosteroids will be effective both as 'anti-inflammatory' agents and as damping-down antibody production.

TYPE IV REACTION OR RESPONSE

The Type IV response, usually referred to as delayed (cellular) hypersensitivity, bacterial or tuberculin-type allergy, is an allergic response whose importance in human disease is well recognized, but whose exact role is obscure. The reaction is inflammatory and involves a specifically directed infiltration of mononuclear cells into an area where antigen is localized. The reaction is called 'delayed' as it takes anything up

to 24-48 hours to become full blown. An essential characteristic is that the reaction is independent of serum antibodies.

The tuberculin reaction is the *locus classicus* of the Type IV reaction but as a prototype for analysis of the mechanism it has certain disadvantages, the chief of which are that the complex nature of the tubercle bacillus complicates the study of the conditions initiating sensitization and that the difficulty of a rigid purification and characterization of 'tuberculin' complicates the test. The violent response of the tuberculous animal to parenteral injection of tuberculin was first observed by Koch (1891) and it was not long before it was realized that the judicious intradermal injection of small amounts of tuberculin could be used as a diagnostic test for tuberculosis. The clear separation of this kind of reaction, which we are now calling the Type IV reaction, from the other allergic or 'anaphylactic' reactions has been a long and arduous process. It is agreed by most investigators nowadays that under appropriate experimental conditions (for a review of which see Gell & Benacerraf 1961) virtually any antigenic material (with the possible exception of the polysaccharides) can provoke a Type IV response whether or not the appearance of the reactions corresponds at all points with those of the tuberculin reaction itself.

DIFFERENTIATION FROM TYPE III REACTIONS

Theoretically Type IV reactions may be clearly differentiated from reactions of Types I, II and III by the time taken to mount the reaction after injection of antigen, say, into the skin and by the fact that it occurs in the absence of circulating antibody. From this it may be gathered that it is not possible to transfer the reaction passively by means of serum — although this is possible using cells. Again the reaction has a fairly characteristic though not diagnostic histology (Gell & Hinde 1951).

In practice, however, it may be exceedingly difficult to differentiate with absolute certainty a Type IV from a Type III reaction. Absence of circulating antibodies may be a pointer and the delay in appearance of the test reaction is certainly a useful guide, i.e. the observation that a reaction is not maximal within the first few hours; although an Arthus reaction in an animal with a rapidly rising antibody titre could show a somewhat similar appearance. The macroscopic appearance may be useful; in a strong Type IV skin reaction, the edges are well defined with a pallid or necrotic centre while a moderate reaction takes the form of a uniform indurated erythema: in contrast the pure Arthus (Type III) reaction usually has a haemorrhagic centre and ill-defined edges.

Histologically the test sites show infiltration with cells, particularly around the small blood vessels, and in a mild reaction without necrosis such cells are predominantly mononuclear, though even in the mildest a few polymorphs occur. Some of the swelling and induration may be put down to the packing of the tissues with such cells, though oedema and hyperaemia also play a part.

MECHANISM OF TYPE IV REACTIONS, AND RELATIONSHIP TO ANTIBODY PRODUCTION

The mechanism of delayed hypersensitivity is still very much in doubt. The assumption usually made is that on sensitization certain cells, probably in the lymphoid system but possibly throughout the mesenchyme, are specifically altered to contain something in the nature of an antibody. The term 'cell-fixed antibody' is often used and is convenient, but open to criticism in that there is as yet no evidence for anything of the sort. Type IV sensitivity in animals can be transferred with blood leucocytes or lymphoid cells; in man the extensive researches of Lawrence and co-workers (1959) have shown that even cell extracts may be effective in transfer, and that the transferring material, which they call 'transfer factor' certainly has not the properties of an ordinary antibody.

In spite of the close relationship between the two, it is simplest to regard delayed hypersensitivity and antibody production as independent immune mechanisms. There is evidence that 'delayed reactivity' and production of serum antibody to the same antigen can co-exist, although sometimes 'delayed reactivity' tends to wane and disappear, or at least becomes difficult to demonstrate when appreciable amounts of antibody are being produced (Leskowitz & Waksman 1960). In some cases at least this may be due to 'deviation' of antigen by the more rapidly occurring Arthus reaction. By various experimental techniques it is possible to prolong the stage of Type IV sensitivity in guinea-pigs and to reveal it for antigens to which it has not been demonstrated before (see Gell & Benacerraf 1961); but such methods cannot easily be generalized to give a rule for or explanation of its genesis, beyond the rather vague indication that 'poorly antigenic' materials, such as gelatin and altered homologous proteins, or very low doses of 'good' antigens, tend to favour its elicitation.

ROLE OF TYPE IV REACTIONS IN DISEASE

It is possible that a relatively mild delayed reaction may play a part in defence, perhaps by (specifically) stimulating non-specific defence mechanisms. A violent, and especially a 'chronic' reaction, can certainly cause

M*

evident damage to the host, in two ways: firstly by causing vascular blockage and necrosis, and secondly by replacing normal tissue with infiltrating mononuclear cells. There may well be further activities of the specifically modified 'sensitized' cells, which are still unknown to us.

In an intense reaction necrosis may occur, as in an Arthus reaction, and histologically this is often associated with obvious vascular damage and thrombosis; nevertheless fairly strong delayed reactions can occur in the absence of microscopic evidence for any events of this sort. Thus although there well may be a truly inflammatory and even 'hormonal' element in the reaction it seems most likely that the main chronic damage is produced by the infiltration, disorganization and replacement of the tissue by mononuclear cells.

In many 'auto-allergic' diseases, the demonstration of circulating antibodies has been taken as an indication that the antibodies cause the disease. This is unjustified, for two reasons: firstly because stimulation of the immune mechanisms may be the effect of specific tissue changes with a non-allergic pathogenesis: secondly because the presence of antibodies may be evidence of a pre-existent or concurrent state of delayed sensitivity, and it may be that this rather than any antigen-antibody reaction, is at least the initial cause of the lesions.

In concluding this chapter we would apologize for, at times, appearing to be somewhat dogmatic. This follows from trying to keep within our limits of space and from our attempt to emphasize the simplicity and yet comprehensiveness of this classification of the allergic reactions. We would stress again that this is essentially an immunological classification being based on the mechanism of the initiating antigen-antibody reaction: however, in reflecting the basic immunological mechanism it should prove helpful to the clinician.

There are two final points we would like to make. Firstly, drug reactions are so called simply because the antigen or hapten involved is a drug, but the mechanism underlying the reactions may be any of the reaction-Types I-IV. Likewise auto-allergic diseases are so called and grouped together simply because the responsible antigen is an auto-antigen: the responses or reactions set up may again follow any or all of the paths of Type I-IV reactions.

REFERENCES

ARTHUS M. (1903) Injections repetées de sérum de cheval chez le lapin. *C.R. Soc. Biol. (Paris)* **55,** 817
BENACERRAF B. & BIOZZI G. (1953) Proc. IV. International Congress of Microbiology

BIOZZI G., HALPERN B. N. & BINAGHI R. (1959) The competitive effect of normal serum proteins on antibody fixation in passive cutaneous anaphylaxis in the guinea-pig. *J. Immunol.* **82,** 215

BIOZZI G., MENE G. & OVARY Z. (1948) *Rev. Immunol. (Paris)* **12,** 320

COCA A. F. & GROVE E. (1925) Studies in hypersensitiveness. *J. Immunol.* **10,** 445

FREEDMAN A. L., BARR P. S. & BRODY E. A. (1956) Haemolytic anaemia due to quinidine; discussion of its mechanism. *Amer. J. Med.* **20,** 806

GELL P. G. H. & BENACERRAF B. (1961) Delayed hypersensitivity to simple protein antigens (review). In *Advances in Immunology*, vol. I. New York and London: Academic Press

GELL P. G. H. & HINDE J. T. (1951) The histology of the tuberculin reaction and its modification by cortisone. *Brit. J. exp. Path.* **32,** 576

GOLDBERG B. & GREEN H. (1959) The cytotoxic action of immune gamma globulin and complement on Krebs ascites tumor cells. *J. exp. Med.* **109,** 505

HUMPHREY J. H. (1955) Reversed passive Arthus reactions in rabbits. *Brit. J. exp. Path.* **36,** 268

IRVINE W. J. (1960) The cytotoxic factor in thyroid disease. *Scot. med. J.* **5,** 511

KOCH R. (1891) Fortsetzung des Mitteilungen über ein Heilmittel gegen Tuberkulose. *Dtsch. med. Wschr.* **17,** 101

KOHN J. L., McCABE E. J. & BREM J. (1938) Anaphylactic gangrene following administration of horse serum. *Amer. J. Dis. Child.* **55,** 1018

LAWRENCE H. S. (1959) The transfer of hypersensitivity of the delayed type in man. In *Cellular and Humoral Aspects of the Hypersensitive States*, ed. LAWRENCE H. S. New York: Hoeber-Harper

LISKOWITZ H. S. & WAKSMAN B. (1960) Studies in immunization. I. The effect of route of injection of bovine serum albumin in Freund adjuvant on the production of circulating antibody and delayed hypersensitivity. *J. Immunol.* **84,** 58

MOESCHLIN S. (1958) Agranulocytosis due to sensitization to drugs. In *Sensitivity Reactions to Drugs*, pp. 77-88, ed. ROSENHEIM M. L. & MOULTON L. Oxford: Blackwell Scientific Publications

MUIRHEAD E. E., HALDEN E. R. & GROVES M. T. (1958) Drug-dependent anti-globulin (Coombs) test and anaemia: observations on quinine and acetophenetidid (phenacetin). *Arch. intern. Med.* **20,** 806

OVARY Z. (1958) Immediate reactions in the skin of experimental animals provoked by antibody-antigen interaction. *Progr. Allergy* **5,** 459

PARISH W. E., BARRETT A. M., COOMBS R. R. A., GUNTHER M. & CAMPS F. E. (1960) Hypersensitivity to milk and sudden death in infancy. *Lancet* **ii,** 1106

REDFERN W. W. (1926) A study of the primary toxicity of heterophile immune rabbit serum for guinea-pigs, and its apparent relation to the phenomenon of anaphylaxis. *Amer. J. Hyg.* **6,** 276

ROBERTS G. F. (1957) *Comparative Aspects of Haemolytic Disease of the Newborn.* London: Heinemann

SCHILD H. O., HAWKINS D. F., MONGAR J. L. & HERXHEIMER H. (1951) Reactions of isolated human asthmatic lung and bronchial tissue to a specific antigen. *Lancet* **ii,** 376

STETSON C. A. (1951) Similarities in the mechanisms determining the Arthus and Shwartzman phenomena. *J. exp. Med.* **94,** 347

TREMAYNE M. & JETER W. S. (1955) Passive cellular transfer of hypersensitivity to serum antigens in rabbits. *J. Immunol.* **74,** 96

WEIGLE W. O. (1961) Fate and biological action of antigen-antibody complexes. In *Advances in Immunology*, vol. I, p. 283. New York and London: Academic Press

WITEBSKY E. & NETER E. (1935) Primary serum toxicity as demonstrated by the chicken embryo. *J. exp. Med.* **61,** 489

WRIGHT G. P, (1957) The current concept of hypersensitivity. *Practitioner* **178,** 651