Papers and Originals

Immunopathology*

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I have chosen immunopathology as the subject of this lecture as it is the common ground between immunology and pathology. Immunopathology is not simply a hybrid between the two sciences, as only a portion of each science is contributed to this common ground. Much of pathology has nothing in common with immunology, and, likewise, much in immunology has little to do with pathology. Immunopathology is the intersection of the two spheres of knowledge and practice (Fig. 1). Similarly, common ground or intersection with other sciences gives immunochemistry, immunobiology, immunogenetics, and immunohaematology.

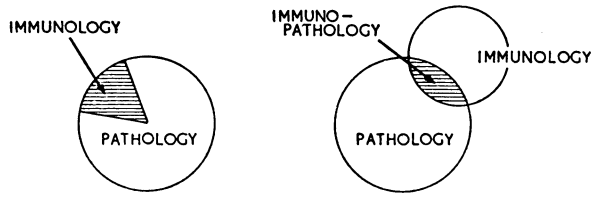

FIG. 1.—Immunology is not a subsection of pathology as shown on the left, but a distinct science with a common intersection which may be called immunopathology.

To appreciate this orientation we must inquire into the definitions and nature of both immunology and pathology, whose relationship in medical research, teaching, and practice over the years has been determined by considerations more pragmatic than scientific.

Pathology has many different connotations (W.H.O., 1969), but in the *Shorter Oxford Dictionary* (third edition) it is defined as the "study of disease" or "which treats of the causes and nature of disease." This seems to me an admirable definition, but it implies a science delineated entirely by a subject matter though not characterized by any central body of propositions, unique discipline, or types of reaction.

Immunology, I fear, it to be found only in the Appendix, and there it is defined as "the branch of medicine dealing with immunity from disease, immunization, and the methods used for this." Today this is totally inadequate—as is really the baptismal name—immunology—given to the science itself. The science certainly developed from the study of immunity, but today the frontiers are far extended over areas only remotely connected with immunity. One distinguished medical school in America begins its teaching course on immunology with an exhortation to students to forget any association they might think immunology has with immunity. This is of course quite outrageous, but it illustrates the point I am trying to make.

However, it is unlikely that immunology as the name of the science will ever be changed, but this is of little concern so long as people fully realize that there is much more to immunology than the study of immunity.

My purpose in this lecture is to give an outline and perspective for the scientific content of immunology which will bring into focus the areas likely to form common ground with pathology. Before attempting such an exposition I must remind you of the real confusion which has long bedevilled immunology because of its illogical terminology.

Terminology

The words "immune" and "immunization" are constantly used in two different senses—in one of which anything but immunity in the clinical sense is implied. Likewise the words "allergy" and "allergic" are used ambiguously—in the original and proper sense intended by von Pirquet and also, in complete antithesis, to describe clinically harmful "immune" reactions.

The common acceptance of this illogical terminology has made clear exposition and thinking very difficult, and so I am going to use a terminology which I and other like-minded persons have adopted because of its rationality. The terminology is a simple extension of that proposed by von Pirquet as long ago as 1906.

Antigen or allergen stimulates an allergic *response* which establishes the allergic *state*—the state of specific altered reactivity. This biological state of altered *reactivity* is uncommitted to being either beneficial to the host, as in the development of immunity, or harmful to the host in that it produces disease. The consequences of the *reaction* depend entirely on local circumstances.

Where the allergic reactions afford protection from disease these may be said to be "reactions of immunity" or "immune reactions" in *sensu strictu*. Allergic reactions against grafted tissue and tumour cells may, in a special sense, be regarded as reactions of immunity if they afford protection to the host. On the other hand, allergic reactions which are themselves responsible for disease are the reactions of clinical hypersensitivity. "Immunity" and "hypersensitivity," as suggested by von Pirquet, should be used as descriptive clinical terms, while "allergy" and "allergic" should be descriptive of the underlying molecular and cellular events (Fig. 2).

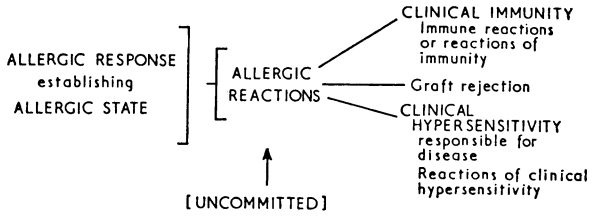

FIG. 2.—The allergic state and the reactions of immunity and clinical hypersensitivity.

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Outline Sketch of Immunology

To my way of thinking there are three main aspects to immunology. These are, firstly, the allergic response and all the consequences of this for the host. These are overtly seen in the expressions of immunity, in clinical hypersensitivity, and in special phenomena such as graft rejection. Secondly, immunology must take into account the numerous non-allergic factors concerned with immunity or protection from disease. Thirdly, immunology is concerned with antigen-antibody interactions, and, looking more to the future, with the interactions of antigen with the allergized cell. Because of the exquisite specificity and sensitivity of these reactions they have been sophisticated and developed as quite unparalleled investigative methods for the analysis of antigenic macromolecules and for the characterization of cells and tissues of all descriptions. This third aspect of immunology makes it relevant to many other sciences.

Allergic Response

There is very little in immunology that is not dependent on or derived from the allergic response. Essentially, the response consists of the establishment of a population of cells with a specific reactivity and ability to manufacture specific antibody. The phenomenon is being investigated today from every angle by literally hundreds of scientists equipped with the latest knowledge, methods, and techniques of modern molecular biology. Because of this it can only be treated either at great length and depth or very briefly and superficially. I have no choice in this lecture but to adopt the second course, but in doing so I must stress again that this response is the very core of immunology.

It appears that there is in the body a multitude of antigen-sensitive lymphocytes bearing individually one type of this vast array of recognition units. Interaction of antigen, which probably has to be processed in some way by a macrophage, with such a recognition unit stimulates cell division to produce more receptive or primed lymphocytes of this specificity, and sets in motion the synthesis of immunoglobulin according to the cell's innate genetic code. Primed small lymphocytes—actively allergized cells—encountering antigen, even unprocessed by macrophages, undergo transformation into blast forms and possibly division again. Receptor sites can be shown on small lymphocytes and blast-type cells. Whether these reactive allergized lymphocytes at some stage secrete antibody or do so only after full maturation into plasma cells is uncertain. There is some evidence also that actively allergized lymphocytes may be able to transform into macrophage-like cells.

Antibody globulin is now called immunoglobulin, and structurally a great deal is known about it. It is a symmetrical unit of two pairs of disulphide-linked polypeptide chains much of which has already been sequenced. In man there are five classes of immunoglobulin, some certainly with subclasses. Differences in class structure coincide with differences in biological behaviour of the antibodies.

Any analysis of the allergic response has to take into account the phenomenon of *actively acquired tolerance* which is the de novo specific inhibition of antibody synthesis—the very antithesis of antibody production. Relevant factors here may be the dosage and physical state of the administered antigen and the lack of participation of macrophages. This phenomenon has great significance for medicine, as also has the observation that certain classes of antibody may suppress a primary antibody response. This has relevance to primary Rh-sensitization in haemolytic disease and to the question of early prophylactic immunization in infants while maternal antibody is still present.

A moment's reflection reminds us of the much clearer and more functional definition coming to the cells of the lymphoreticular system as the result of studies on the allergic response. The same may be said about studies on the subsequent allergic reactions, which are discussed later and which have revealed much of a fundamental nature on macrophages, mast cells, basophils, and eosinophils.

Before leaving the allergic response I would mention that I always find it very helpful to differentiate clearly in my mind the stimulation and mounting of the allergic *response* and the state itself with its potential reactivity from the subsequent allergic *reactions* which occur in the tissues when antibody and reacting cells are again presented with antigen.

Allergic Reactions and Immunity

At the cellular and molecular level immunity is established by two classes of mechanisms: (1) those non-specific in the immunological sense, and (2) those specific or allergic. The state of enhanced protection in acquired immunity is mostly dependent on allergic mechanisms.

In considering any infection one must realize that most macromolecular substances of the micro-organism and its products (not simply toxins and virulence factors) are antigenic and produce their own individual specific allergic responses, and many of these reacting systems may play no part at all in immunity, and may even, as I shall mention later, promote the disease. Hence my plea that the cellular and antibody reactions occurring in any particular disease should not be designated immune reactions until shown to be concerned in immunity—the uncommitted term "allergic" is much better and presupposes nothing as to their role or significance. The antigenic substances stimulating antibodies or allergized cells

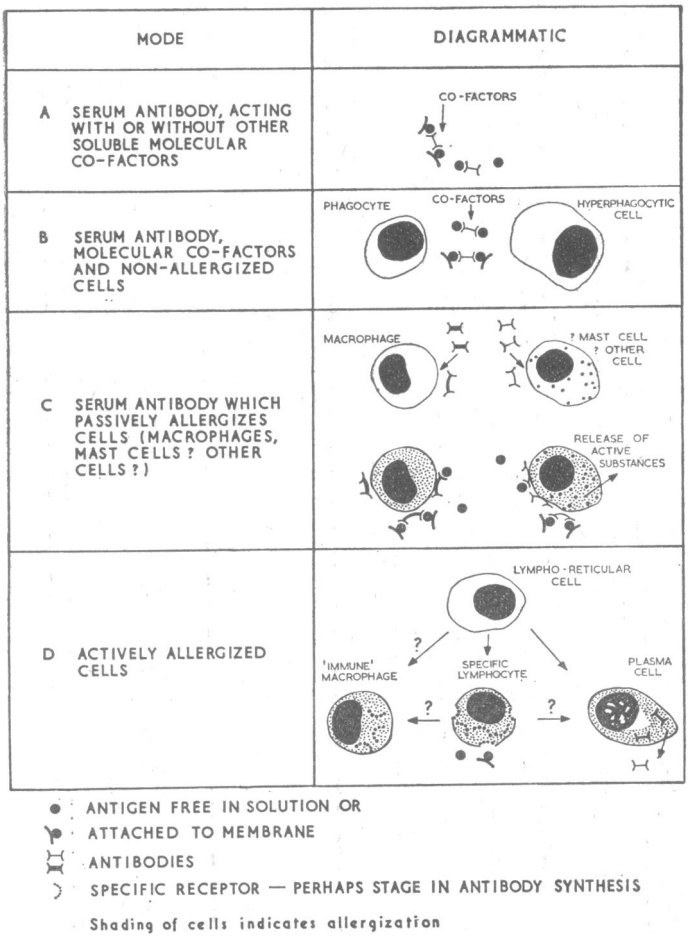

FIG. 3.—Grouping of allergic reactions into ways or modes of reactivity in which they are able to assist in establishing immunity. (Taken from Coombs and Smith, 1968.)

that, in reference to a particular case, are protective have been called "immunogens" (with the property of immunogenicity), and this has been a convenient usage; but here again this word is being used today for any antigen stimulating an antibody response, irrespective of any immunity it may produce, and this is far from helpful.

Microbiologists have made considerable progress in recent years in elucidating mechanisms of virulence and pathogenesis, but in many infective diseases these mechanisms are still little understood. Likewise, there is often still great uncertainty regarding the precise mechanism of immunity where empirically an acquired protection can be shown.

Despite the great complexity of reactivity in different diseases it is, I think, helpful to realize that the repertory of ways in which the allergic reactions can function in the build-up of immunity is limited. Professor Smith and I have recently set forth a scheme which reduces the complexity of immune reactivity to simply four modes of reaction (Coombs and Smith, 1968).

In any infection each mode of reaction may act alone or in concert. If, as we think, this set of four modes of reactivity reflects the full extent of our present knowledge, then it should be helpful to the specialist and non-specialist alike as a conceptual aid in analysing the immunity mechanisms in different diseases. Fig. 3 epitomizes the four modes of reactivity.

Mode A

Mode A (serum antibody acting with or without other molecular co-factors) is the simplest form of reaction and is illustrated where antibody acts as an antitoxin or acts by inhibiting virus adsorption on to cells. Antibody alone could possibly block a membrane enzyme system vital to a parasite and thus embarrass development, or it could activate complement to lyse a cell and kill the parasite. Also, reacting with antigen in the tissues, it could create a local milieu unfavourable to continued growth of the micro-organism. This may occur in tuberculous infection.

Mode B

Mode B (serum antibody, molecular co-factors, and non-allergized cells) is exemplified by phagocytosis. Phagocytosis may proceed in the absence of antibody and co-factors, but each stage of the process can be powerfully influenced by the molecular interactions of the allergic response; even the chemotactic gradient for polymorphonuclear leucocytes is fabricated from complement activated by the antigen–antibody interaction. This promotion of the phagocytic system is one of the main acquired defence mechanisms of the body. Incidentally, a great deal of attention is now being given to intracellular events following phagocytosis, and especially whether these also are influenced by allergic factors.

As is well known, some micro-organisms—for instance, the tubercle bacillus and *Brucella abortus*—may not be killed inside macrophages and may even gain a haven there, protected from the more destructive reactions of serum. This focuses attention on one of the major problems of immunity: what further mechanisms (allergic or otherwise) can be brought into play in such circumstances? There is evidence after endotoxin stimulation for a specially induced hyperphagocytic cell which is more competent in digesting bacteria. This hyperphagocytic cell is not thought to be an allergized cell, but may be regarded more as a cell brought up to "Olympic standards" in its functional prowess. The need for slight pedantry here is because there is the possibility also for an *actively allergized macrophage*, and we certainly have definite evidence for *passively allergized macrophages*.

Mode C

Mode C concerns such passively allergized cells. The guinea-pig has a cytophilic antibody which passively allergizes macrophages only. One has no certain knowledge of the functional role of this type of antibody, which has now been found in many species, but a macrophage so passively allergized might well have specifically enhanced phagocytic activities on serous surfaces where the full range of opsonic factors in serum are not present. Rowley, Turner, and Jenkin (1964) consider that the "cell-mediated immunity" to *Salmonella typhimurium* in mice is explained by macrophages passively allergized with a cytophilic antibody.

Reagin-like antibodies passively allergizing mast cells, basophils, and possibly other cells, and usually associated only with clinical hypersensitivity reactions, may also play a part in immunity. Reaction with antigenic material from micro-organisms would result in the release of pharmacological mediators which increase vascular permeability. At the site of primary lodgement of an infection this would allow access to the area of large-molecular-weight antibody and all components of complement. Salivary antigens of helminths attached to the gut mucosa can initiate this reaction-mechanism, and this seems to be one of the factors causing their disengagement and shedding of the worm load in immunity reactions.

Mode D

Lastly there is mode D—involving actively allergized cells. There is plenty of evidence from in-vitro experiments that certain actively allergized cells react to contact with antigen. Experimental transformation into blast forms, mitosis, hormone or mediator liberation, and a process referred to as allogeneic inhibition have been shown to follow interaction with antigen. Actively allergized cells are thought to play an important part in graft rejection, but whether they can act in a protective way against living micro-organisms and other parasites is still a matter of pure speculation, but it would seem likely. There is some evidence, as I have already mentioned, that such cells after contact with antigen may acquire macrophage-like properties, and here again this could be a very functional cell. Again, an allergized cell which has matured into a plasma cell will, of course, liberate locally a high concentration of antibody.

Any significance this scheme has rests on the supposition that it embraces all the known reaction-mechanisms of immunity, and should, for this reason, be helpful in analysing the mechanisms of immunity in different diseases. One can consider, for instance, how effective each mode of reaction would be against a toxic factor, against virus in the extracellular fluids, and, once inside the cell, against a Protozoa constantly changing its membrane-antigen structure, against facultative intracellular pathogens, or against a lumbering metazoan helminth migrating through the tissues.

Now, are these matters the concern of immunopathology? If the immunity mechanisms were totally successful then disease would not follow infection and the host would be in a healthy state of complete protection. However, unless the individual has been prophylactically immunized the response of the allergic apparatus may come too late to prevent the disease, though it may well affect its course. In this situation immunology overlaps into pathology and we have a focus again on immunopathology. The importance of the allergic reactions in the everyday maintenance of health is vividly illustrated with the infections being encountered in grafted patients who are under immunosuppression.

Immunoprophylaxis

Having just mentioned prophylactic immunization, I cannot refrain from drawing attention to the great significance today

of immunoprophylaxis, which, considering the countless lives saved annually, must undoubtedly be one of the most important branches of medicine. In view of this, I feel great concern at what seems to me to be a dangerously widening gulf between academic immunology on the one hand and commercial vaccine production, public health teaching and administration, and clinical practice on the other hand. This gap would be even wider were it not for the expert committees and reports of the World Health Organization. With the increasing awareness of the great complexity of antibody types and allergic reactivity I feel it is absolutely essential to achieve greater liaison.

Allergic Reactions as Responsible for Disease

We must now turn to consider the circumstances under which the allergic response and these same reactions may themselves be totally responsible for disease or, in a more minor way, play a discernible part in the pathogenesis of disease. In any way of thinking this clearly comes within the subject matter of immunopathology.

The apparatus for allergization responds not only to antigens of parasitic micro-organisms but to any macromolecule "foreign" to its immediate environment. And there is no shortage, in everyday life, of candidate-allergens or antigens: material from inhaled dust, moulds, or pollen, ingested material absorbed from the gut, especially in the young (for instance, cow's milk, on which we feed our infants quite unnaturally), chemicals absorbed via the skin, drugs, blood or vaccines injected by physicians, absorbed allo-antigens from foetal or grafted tissue, and the multitude of one's own body constituents which can become autoantigenic.

Once the individual is allergized or sensitized, serious reactions may follow on further contact with the allergen. Hay-fever, allergic asthma, anaphylaxis, and contact dermatitis—the commonly recognized clinical hypersensitivity diseases—are examples ; but there are many other conditions which I can mention only briefly and which hitherto have not been dealt with in so-called "allergy clinics." Nor, I suspect, would the persons running such clinics be educated or trained to deal with these other conditions.

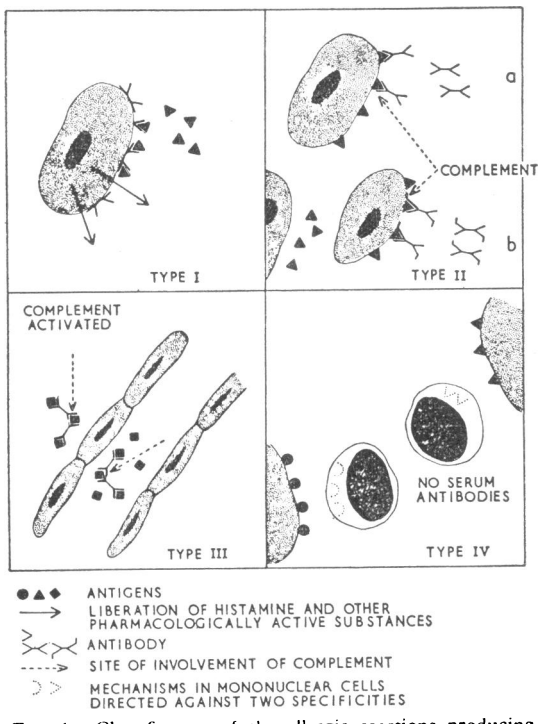

FIG. 4—Classification of the allergic reactions producing tissue damage and disease. (Taken from Coombs and Gell, 1963.)

The allergic reactions underlying these clinical states or diseases have also been put into a simple scheme (or classification), but this time by Professor Gell and myself (Fig. 4). There is one thing I must emphasize. This is not a classification of the allergic response or of the allergic reactions in toto but simply of the ways in which the allergic *reactions* can produce tissue damage and disease (Coombs and Gell, 1963).

Type I

Type I reaction ("anaphylactic," "reagin-dependent") initiated by allergen reacting with tissue cells—for example, basophils and mast cells—passively allergized by antibody, produced elsewhere, leading to the release of pharmacologically active substances. It is the activity of these pharmacological mediators (for example, in increasing vascular permeability and producing contraction of smooth muscle) that produces the tissue changes and clinical picture—for example, the oedema and irritation of the mucous membranes in hay-fever, the oedema of skin wealing and generalized urticaria, the bronchial constriction in asthma, and the profound fall in blood pressure in generalized anaphylaxis.

Type II

Type II reaction (cytotoxic) is initiated by antibody reacting either with an antigenic component of a cell membrane or basement membrane or with an antigen or hapten which has become intimately associated with these. Complement is usually, but not always, necessary to effect the cellular damage.

Examples from clinical medicine include blood transfusion reactions, haemolytic disease of the newborn, nephrotoxic activity in certain forms of glomerulonephritis, cytotoxic reactions consequent on impairment of the basement membrane, and drug reactions such as that seen in Sedormid purpura. The main comment I wish to make is that, although the examples cited may seem extremely diverse, the underlying allergic reactions responsible are similar.

A recent development in this category concerns a stimulating rather than a cytotoxic activity produced by complement and antibody to cell membrane antigens. Though the reaction itself is not cytotoxic or lethal to the cells the consequences are none the less damaging to the tissue and could well underlie certain disease processes. In these studies by Fell and Dingle, of the Strangeways Research Laboratory, and ourselves on chick bone rudiments in organ culture, this type of allergic reaction leaves the cells fully viable but with excessively stimulated metabolic activity. Also the lysosomal system is activated and the enzymes released from the cells completely degrade the cartilage matrix (Fell, Coombs, and Dingle, 1966 ; Dingle, Fell, and Coombs, 1967).

This is of course a model system, but it interests us greatly in that the pathology is not such as would at first sight be recognized as being allergic in origin. I may add that we are at present experimenting on the concept that the increased thyroxine secretion is thyrotoxicosis, where a membrane auto-antibody has already been described, may also be explained on this basis.

Type III

Type III reaction (Arthus type—damage by antigen-antibody complexes) is initiated by antigen reacting in the tissue spaces with antibody forming microprecipitates in and around small vessels, causing damage to cells and tissues secondarily by a variety of means. This is the situation of the Arthus reaction.

In another situation antigen in excess may react with antibody in the blood stream, forming soluble circulating

complexes which come to be deposited in the blood-vessel walls or in basement membranes, and these cause local inflammation. This is the situation in classical serum sickness (today another misnomer!).

Besides the Arthus reaction and serum sickness, type III reactions are involved in allergic pulmonary interstitial alveolitis, allergic vasculitis, polyarteritis, certain other forms of glomerulonephritis, and in the formation of the tissue lesions in systemic lupus erythematosus and other connective-tissue diseases. Obviously the precise histological site where the complexes come to lodge determines the overall pathology and clinical picture.

An anaphylactic syndrome can also be produced by this type of reaction after activation of complement by antigen-antibody complexes and the subsequent production of anaphylotoxin—now after all these years, a real entity which can be isolated.

Type IV

Finally, type IV reactions—reactions mediated by actively allergized cells (as those described under mode D reactions of immunity) infiltrating to the site where antigen is located—embrace the so-called delayed allergic reactions, taking one to two days to develop fully. We will obviously know a great deal more about these reactions when we know more of the properties and characteristics of actively allergized cells and what follows the interaction of these cells with antigen.

Clinically, type IV reactions manifest themselves in contact dermatitis and in delayed skin reactions. They are thought to play an important part in rejection of allogeneic grafted tissue, and pathologically we see their involvement in allergic granulomatous conditions and as a dominant feature in many auto-allergic diseases.

Microbial Pathogenesis

This brings me to a very important consideration—namely, the significant part that the allergic reactions may play in microbial pathogenesis. The concept is that many infecting micro-organisms would show very little pathogenicity on their own account or in an animal whose allergic responses were completely suppressed. The pathogenicity, in fact, is due to the antigenicity of the organisms and their products and consequent tissue-damaging allergic reactions wherever the surviving organisms or their products happen to be.

To develop this thesis is a lecture in itself, and here one or two examples only must suffice. Matsumura (1962) finds that *Shigella flexneri* is not pathogenic to normal rabbits but will infect, with a typical dysenteric syndrome, a rabbit previously allergized with a cross-reacting antigen. He feels this also has relevance to human bacillary dysentery. Buxton and his colleagues (Buxton and Allan, 1963 ; Buxton and Davies, 1963), struck by the similarity of clinical signs in acute fowl typhoid and in anaphylactic shock in birds, have accumulated impressive data implicating allergic reactions as the important factors in pathogenesis. Likewise, an anaphylactic reaction rather than toxaemia may explain the oedema disease and gastroenteritis of young pigs associated with *Escherichia coli* infection. The allergic reactions may also play an important part in the pathogenesis of lobar pneumonia in man. Examples can be quoted from protozoal diseases, and Webb and Gordon Smith (1966) have put forward evidence that the tissue lesions and neurological manifestations in virus encephalitis in man are due more to antibody reactions to viral antigen in the tissues than to any lesion produced by the virus *per se*.

Before leaving this section on the allergic reactions as responsible for disease and the simple scheme we have presented let me say here again that any significance it has rests on the presumption that all the tissue-damaging allergic reactions are accounted for by reactions types I–IV acting alone or, as is more usual, in concert. It holds equally for auto-allergic reactions and the drug-hypersensitivity reactions. Reactions in concert, though confusing, are only to be expected, for the allergic response usually acts as a co-ordinated system.

Finally—and of significance for the pathologist—in model systems which have been set up there are definite morbid histological characteristics—a hallmark, as it were, for each reaction type, and these hallmarks can be most helpful in interpreting the pathology of lesions of uncertain aetiology.

Immunological Methods as Investigative Tools

Today there are many immunologists whose work is in no way concerned with problems of immunity or clinical hypersensitivity. They specialize purely on the antigen-antibody interactions and their applications as analytical or diagnostic procedures which today are finding increasing relevance to nearly all the biological and medical sciences.

Choosing from the existing store of available methods requires the discernment of the specialist. Derived from simple precipitation, we have the methods of immunodiffusion, immunoelectrophoresis, and the various radio-immuno-assay methods that are now routinely used for hormone assay. Shortly all protein hormones will be assayed by such methods with a sensitivity down to the order of 10^{-15} moles. Various immunofluorescent tests give precise histological localization of antigenic components in tissues following reaction with fluorescein-tagged antibody. Simple agglutination tests are now sophisticated by antiglobulin reactions and various forms of passive agglutination where soluble antigen is previously fixed to a carrier cell or particle. Disaggregated tissue cells can now be characterized by various mixed agglutination techniques and complement-mediated reactions such as immune-lysis or immune-adherence.

The study of the macromolecular composition of body fluids and structural components of cells and tissues by these methods has recently had attention focused on it, and has been called seromorphology. As regards immunopathology these antigen-antibody reactions have been used to great advantage in investigations on auto-allergic diseases, and in the analysis and characterization of abnormal serum proteins in, for instance, myelomatosis and in immunological deficiency states. Experimentally the composition of fibrinoid, amyloid, and Russell bodies can be investigated. At present Drs. Sell, Mori, Rack and myself are bent on attempting an immuno-cyto-diagnostic test to identify the tissue of origin of malignant cells in ascitic fluid, using as reagents organ-specific antisera and the mixed antiglobulin reaction: experiments are not unpromising and we hope to be able to identify the tissue from which the tumours have originated.

Academic Standing and Teaching of Immunology and the Significance of this for Immunopathology

Finally, I want to make a few remarks on the teaching of immunology and, related to this, the question of the establishment of immunology within the university faculty structure and the significance of this for immunopathology.

The World Health Organization recently set up an expert committee to consider the teaching of immunology in the medical curriculum (W.H.O., 1967). Paradoxically, their concern did not arise primarily because of the situation in the so-called developing countries, but because of the state of affairs in many of the most renowned medical schools and universities throughout the world.

Fully conscious of the overloaded medical curriculum, the committee recommended a *minimal* basic course of 10 lectures with accompanying practical classes to be held towards the end

of the preclinical studies. They stressed the importance of extending this teaching into the clinical years. Also regarded as essential was the more advanced teaching of immunology as a science in its own right in elective undergraduate courses and in postgraduate courses to serve as an introduction to research.

It was recommended that this teaching should be the responsibility of a group of immunologists constituting a distinct designated unit or subdepartment with established posts of senior academic standing up to and including professorial ranking. The immunology division could be associated with departments of biology, biochemistry, physiology, microbiology, pathology, or medicine. It would be beneficial, in fact, if the associations varied from university to university, for immunology has large intersections with all these subjects. Obviously immunopathology as such would be best promoted by close association with departments of pathology. In this respect I would prefer to see departments of "pathological and related studies" of somewhat elastic structure but with established professorial divisions or subdepartments of morbid anatomy, chemical pathology, experimental pathology, haematology, microbiology (bacteriology, virology, or parasitology), and immunology. This, I think, would accord well with the ideas of Payling Wright (1963) when he discussed the future of university pathology.

One of the main aims of the College of Pathologists is, I believe, that of ensuring the standards and professional status of what is essentially clinical pathology. This is to be done to a large extent, I gather, by prescribing professional training and by a system of examinations.

I am a little worried lest, while achieving this aim, many young persons may be deflected from following a more academic career in the sciences having these large intersections with pathology as generally defined. My more personal concern is, of course, for young medical, veterinary, or science graduates coming into immunology. If they are subsequently to bring seminal ideas from the immunological side into immunopathology and to be able to lead and direct research in this field, then a more esoteric form of postgraduate training within immunology is most desirable. This may be done as B.Sc. or M.Sc. courses or by undertaking research under supervision for the Ph.D. degree, or, indeed, by simply doing good work within the field, and it seems to me this should not leave the pathologist, for such he may call himself, unaccredited in professional standing.

I am sure, however, that the College is very conscious of this very problem and will succeed, as is its avowed intention, in promoting not only the practice of pathology—and here the emphasis is on clinical pathology—but also the various contributing sciences which together establish so much of that body of knowledge we call pathology.

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Rapid Diagnosis of Respiratory Syncytial Virus Infection by Immunofluorescent Antibody Techniques

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Immunofluorescent antibody techniques have been advocated as the most promising means of rapid diagnosis of virus infection. To be successful any technique devised must be easily adapted as a routine test by virus laboratories and the results be so precise that there is no danger of an incorrect diagnosis. A test which gives equivocal results or readings which vary with different observers is useless as a routine procedure. One of the first to achieve success was Liu (1956), who examined direct smears of nasal mucosa from patients with influenza; the results by fluorescent antibody technique compared favourably with isolation methods. Biegeleisen *et al.* (1959) used scrapings from vesicles for the rapid diagnosis of herpes simplex. In both these conditions success might be expected, as the material is taken direct from a site where the virus is present in great concentration.

The fluorescent antibody technique has also been used for the diagnosis of rabies in tissues by Goldwasser *et al.* (1959) and by Hatch *et al.* (1961) for typing polioviruses grown in monkey kidney tissue culture.

If a fluorescent antibody technique is applied to the rapid diagnosis of virus respiratory infections in children two methods are possible. The first, which would be the more rapid, is the examination of direct smears or exudates from the throat and nasopharynx of patients. The second is the examination, at an early stage, of tissue culture cells inoculated with the specimen under investigation in order to detect the presence of virus antigen in the cells before the cytopathic effect, by which the virus is normally recognized, becomes obvious.

The main problem of investigating childhood respiratory disease is the wide range of causal or associated virus pathogens (Elderkin *et al.*, 1965), and a large number of highly specific antisera are required to examine such material. It is clear, however, from investigations over the last few years that respiratory syncytial virus is the most important cause of respiratory illness and respiratory death in childhood (Chanock *et al.*, 1961; Holzel *et al.*, 1963; Elderkin *et al.*, 1965; Gardner

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