Section of Pædiatrics

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Suppression of Immunopathological Disease

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Immunopathological Mechanisms and their Treatment

In planning any treatment, its effect on the disease process and on the patient generally must be weighed, and the disease must be considered in terms of three basic variables–causative agent, mechanism (or mechanisms), and host reaction. Recent rapid progress in immunology has permitted us to consider possible lines of treatment of immunopathological disease in terms of these variables. A further help has been the organization of the nomenclature of allergy by Coombs & Gell (1962). This classification, with some examples, is outlined in Table 1. Clearly the possible causative agents are numerous and each may be associated with reactions of more than one type, not only in different patients, but also in the same patient at the same time. In human serum sickness some aspects of Type 1 reaction occur as well as of Type 3 and in the fascinating group of patients with progressive pulmonary fibrosis following inhalation of various antigens, recently described by Pepys & Jenkins (1965), serum and skin tests seem to imply a combination of both these reactions in the disease mechanism. The different reaction types depend on the nature of the antigen, the mode of entry, and on the host's own reaction. The 'causative agent' may also apparently be self, in autoallergic disease, but two words of warning are needed here. First, there is an important distinction between autoallergic phenomena and autoallergic disease; complement fixing autoantibodies are probably present in all normal sera and many autoantibodies occur as a result of disease, and have no role in its course. Second, the principal experimental means of inducing autoallergic phenomena in experimental animals are outlined in Table 2. Superficially these appear to have little relevance to processes in human disease, but antigenic cross-reactivity between certain bacterial and certain human antigens occurs and the possibility that bacterial toxins present when tissue is disrupted by bacterial infection may have an adjuvant effect in induction of autoantibodies and possibly even autoallergic disease must be considered. So one should not exclude the possibility of extraneous causative agents in this group. There is good reason to believe that this group of diseases results in tissue damage through the same mechanisms as the other allergic disease, summarized in Table 1.

Possible lines of treatment and their applicability to each of the types of allergic reaction are given in Table 3. The dramatic effect of avoidance of allergen, in those cases of immediate type allergy, due to a single allergen which can be avoided, clearly demonstrates that this is the most effective line of treatment, when possible. Such

Table 2
Autoallergic phenomena following experimental immunization

Auto-antigens – Freund's adjuvant (or very large doses)
Cross-reacting hetero-antigens – smaller doses
Cross-reacting bacterial antigens – smaller doses
Tissue damage (bacterial, &c.) – ? release of sequestered antigens

Table 1
Types of allergic reaction

	Type	*Reacting mechanism*	*Transfer*	*Example*	*Some allergens*
1	Immediate	Reagin	Serum	Hay fever	Pollens
2	Cytotoxic	Antibody and complement	(Serum)	Autoallergic hæmolytic anæmia	Cell surface antigens
3	Toxic complex	Antibody and complement	(Serum)	Serum sickness, Arthus reaction, ? nephritis	Large amounts of soluble antigen
4	Delayed	Sensitized cells	Lymphocytes	Contact sensitivity	Tuberculin

Table 3
Possible lines of treatment of allergic disease

	Type of allergy
Antigen specific treatment	
Avoid antigen	1, 2, 3, 4
Administration of antigen	1, (?3), (?4)
Nonspecific suppression of reactivity	
Antibody synthesis	1, 2, 3
Lymphocytes	4
Complement	2, 3
Suppression of effects of reaction	
Antihistamines	1 (+3)
Corticosteroids	1 (and others)
Cytotoxic drugs	1, 2, 3, 4
Anti-inflammatory drugs	?
Anticoagulants (heparin)	?3, ? others

dramatic successes are not common and one must recall that even this line of treatment is occasionally harmful, in that children have sometimes been placed on grossly inadequate diets on very insecure grounds that certain foods may be inducing a doubtful allergic disease. No line of treatment is completely safe! Avoidance of antigen may also be possible in some examples of each of the other types of reaction.

It is in immediate type allergy that treatment by administration of antigen is most widely adopted. I cannot discuss here the full mechanism of hyposensitization treatment, but it has perhaps had less application in this country than it deserves. Conversely, rather extravagant and insecure claims have explained though not justified this excessive scepticism. The multiple allergens involved in so many patients and the many other factors in the symptomatology make dramatic success a rare event and so a simple statistical trial is hardly a valid approach to a treatment which could be effective only in a minority. This treatment is also not without its risks. Some success has been claimed in delayed hypersensitivity – I shall discuss later its possible role in soluble complex disease.

Both the other two groups of possible treatments – suppression of reactivity, and suppression of effects of reaction – are nonspecific. Suppression of humoral responses occurs with a group of drugs which have been called immunosuppressants, though perhaps they are best called cytotoxic. In the next paper Dr Berenbaum (p 1162) outlines the mechanisms of these treatments and their nonspecificity will be clear, in terms of their effects on all immune mechanisms, and on effects of the response, and on many other functions. Antilymphocyte serum is by no means the specific reagent it sounds to be, and therapeutic complement inhibition is not yet possible. Many fields of application of the other lines of treatment are well known. The role of clotting in the vascular damage of the toxic complex type of reactions particularly needs more study. Anticoagulants (also substances of very wide biological significance) prevent the damage in some forms of experimental nephritis (Vassalli & McCluskey 1964).

It is in the field of nephritis that I have tried to apply these measures to human disease. This field is attractive to study as the effects of the disease can be so accurately measured by a range of relevant tests. First came the necessity to recognize individual disease processes within the complex of glomerulonephritis so that mechanisms and possible lines of treatment could be studied for each. Patients presenting with the nephrotic syndrome provide a wide range of reasonably recent forms of glomerulonephritis, and their heterogeneity was clear from the varied response to treatment, and differential protein clearances (Soothill 1962) permitted objective correlation between a function test and the response to corticosteroid treatment (Blainey *et al.* 1960). Though rapid steroid response is the usual experience in childhood nephrotic syndrome, we all know of exceptions, which are the rule in adults. There is expanding recognition of the role of other nonspecific modes of treatment in such patients. In the course of a comparative trial of another 'anti-inflammatory' reagent – hydroxychloroquine – for which there is some anecdotal evidence of effect in glomerulonephritis (Soothill & Hardwicke 1964) and relatively little toxicity, as against a cytotoxic drug – cyclophosphamide – a group at Great Ormond Street have obtained impressive improvement in some patients receiving the latter, as others have shown. Dr White (p 1164) discusses such cytotoxic treatment in this situation in detail; my intention is simply to put it in its context, stressing its nonspecificity.

There is some reason to believe that antigen-specific lines of treatment can also be applied to

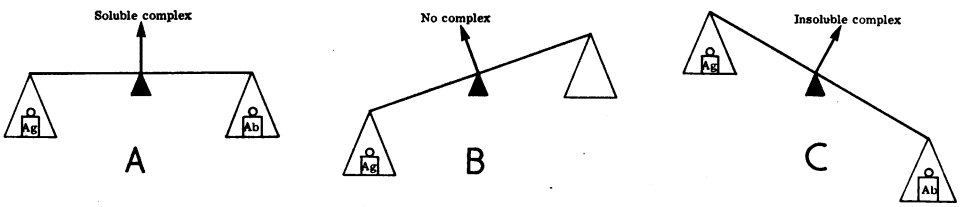

Fig 1 *Possible ways of preventing soluble complex formation.*
A, *postulated balance of antigen and antibody inducing soluble complex.* (*Antigen avoidance – no complex.*)
B, *immunosuppression.* C, *immunization* (*? with adjuvant*)

some forms of glomerulonephritis. We have recorded (Hardwicke *et al.* 1959) complete recovery following hyposensitization with grass pollens, in a man with nephrotic syndrome, with highly selective proteinuria and minimal glomerular abnormalities to light microscopy, in whom there was strong circumstantial evidence to suspect that the disease of his kidneys was of the immediate allergy type. Antigen avoidance is possible; elimination of a nephritogenic streptococcus from a community can certainly be thought of as antigen avoidance treatment or prevention. But it is far from clear what antigens are involved in most progressive glomerulonephritis, and what mechanisms are involved. There are now many methods of inducing glomerulonephritis in experimental animals, usually entailing some sort of immunological procedure, but most of them bear little resemblance to possible happenings in human disease. One possible exception is Dixon's experiment of administering bland inert antigens (human serum albumin, &c.) to rabbits daily for many months (Dixon *et al.* 1961). He bled the rabbits twenty-four hours after each injection, and tested the serum for antigen and antibody. With little dose dependence, the serum of some of the rabbits had free antigen, some had free antibody and some had neither. Those with free antigen never got nephritis, those with antibody sometimes got acute nephritis which was transient, but those with neither got a progressive chronic glomerulonephritis which persisted even when the injections were stopped. I would describe the histology of their kidneys as lobular proliferative glomerulonephritis, and human disease can certainly look very similar histologically. This is essentially a chronic serum sickness situation, and there is reason to believe that the reaction depends on an antigen excess soluble complex with complement being an essential step in the tissue damage (Type 3 reaction). For reasons which will become apparent later I am anxious to investigate the possible roles of such a mechanism in human nephritis, and one feels that one should be able to detect this material in serum if it is relevant. The group of human disease which most closely resembles this animal situation, to my mind, is the lobular proliferative glomerulonephritis associated with the nephrotic syndrome in Nigerian children thought to be associated with *Plasmodium malariæ* infection (Gilles & Hendrickse 1963). By a combination of immunological techniques we have been able to identify a remarkably homogeneous group of children in this population who seem to have an allergic complement-dependent disease. Using the complement antigen β_{1c} as a marker to detect macromolecular complexes separated by G-200 Sephadex gel filtration, we believe we have obtained evidence of presence of such complexes in the sera of these patients (Soothill & Hendrickse 1967). This technique should permit us to prepare and identify the antigen involved, and Fig 1 illustrates the possible therapeutic implications of this. If Dixon's findings are applicable in this disease, it seems likely that the nephritis arises during the acquisition of immunity to the enormous amount of parasite antigen released all the time; the trouble arises when antibody is being produced at just the rate at which it reacts with the available antigen to produce antigen-excess soluble complex. It should be possible to eliminate this nephritis by elimination of the malarial parasite, but this is not likely to be effected for a long period of time, so the possibility must be considered of curing these children by administering more antigen, perhaps in adjuvant, to make them rapidly better antibody producers so that they will behave like Dixon's good antibody-producing rabbits, getting an acute nephritis-like disease, which should be self-limiting.

I have ended with hypothesis because I think it illustrates the possibilities of application of modern immunological knowledge to the cure of immunopathological disease, as well as of infective disease. First, we must test it in the situation of the malarial nephrotic syndrome, and then try to establish what other forms of glomerulonephritis are soluble complex disease, and find the antigens responsible for each one of these in order to attempt a similar line of treatment. Next, we must study the role of this type of mechanism in other disease processes to see if they are also similarly treatable by antigen specific means. I suspect that the treatment of autoallergic disease will for a long time be confined to nonspecific immunosuppressive and anti-inflammatory measures, but, even here, antigen elimination has been attempted with some evidence of effect (Lachmann 1967). In planning nonspecific treatment let us always recall that much disease could conceivably be approached in an antigen-specific manner and this is much more likely to be both effective and safe.

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