Occasional Review

Allergy and its mechanisms

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Scientific approaches to allergy have followed a kind of Popper's progress—a series of imaginative leaps that are regarded as flashes of genius if they prove right but dangerous nonsense if they are shown to be wrong. This was perhaps justified as long as we were dealing with untestable hypotheses, but things have changed in recent years. We can now detect and measure both the immunological and non-immunological events that are triggered by an allergic reaction and also measure the release of inflammatory mediators. There is sufficient basic knowledge to allow the development of pharmacological agents that will provoke or antagonise the allergic sequence and sufficient clinical skill to allow new products to be evaluated objectively.

Historical background

When a Manchester general practitioner called Charles Blackley went into an unused room in the middle of winter and moved a vase of dried grasses he gave himself an unseasonal attack of hay fever.¹ When he followed this up by looking down a microscope and identifying pollen grains this gave him the opportunity to study the effect more precisely. He scratched pollen into his arm and raised a 3/4 inch swelling. He also developed a mechanical spore trap that was carried up into the air by a series of kites, and he showed that pollen grains could be captured at a height of 1000 feet. At this point science ended and speculation began. As the pollen was so easily blown about in the wind he advised his well to do clients to spend the summer months on a peninsula or in a yacht. Then, having calculated that a small quantity of pollen could produce symptoms, he turned to homoeopathy, which he practised for the rest of his life.

It is not clear whether Blackley appreciated the difference between the initial response to contact with grass pollen and the exaggerated response that may occur later on. It was left to the Austrian paediatrician, von Pirquet,² to analyse the altered reactivity, which is so evident in conditions like serum sickness, and give it the name of "allergy." After 1906 the word came to be used for a less wide range of reactions, and since that time their immunological basis has slowly been unravelled.

Clinical trial method

One approach to this unravelling has been the clinical trial method. Noon showed that, by injecting increasing amounts of pollen extract, he could induce a refractory state among sufferers from hay fever, so that increasing quantities of pollen were required to induce a reaction in the conjunctival sac.³ Another line of inquiry was more basic. Henry Dale made the fundamental discovery, in 1913, that the anaphylactic contraction of plain muscle was begun by antibodies fixed on cells—a conception that was totally foreign to the scientists of the time. Fortune favoured the mind that was prepared. Some of the strips of muscle from guinea pigs that Dale used turned out to be exquisitely sensitive to horse serum. He then made inquiries and found that the animal that provided the strips had been injected with horse serum to assay antitoxins.⁴ It was, therefore, the horse serum injection that had caused sensitisation, and he subsequently found that these effects could be transferred by antibody from the sensitised animal. Once sensitisation had been transferred to a tissue no amount of washing would reverse it.

Dale showed that this kind of reaction released histamine, heparin, and other substances that remained to be identified. He made several other contributions, but their full impact was not appreciated for many years. Allergists were still ridiculed when they talked of "reaginic" antibody that stuck to the tissues and sensitised the skin and mucous membrane.

It is true that at this time many allergists paid lip service to scientific ideas while injecting their patients with a huge range of uncharacterised materials. They may have deserved all the ridicule they got. The clinical approach to allergy, however, was not always so uncritical. A W Frankland⁵ used controlled trial methods to show the potential effectiveness of vaccines, and further work was carried out on both the sensitisation process itself and the events that led, in various different tissues, to the release of histamine and other inflammatory mediators. There was also a tremendous upsurge of interest in the pharmacological manipulation of the inflammatory response.

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Quite rightly physicians who were impressed with the pharmacological advances thought that the immunological aspects of allergic disease needed to be better understood before they could be satisfactorily treated.

Since then there have been several new discoveries—not enough to lead to a reliable form of immunotherapy, but enough to arouse a new interest in the basic immunological mechanisms as a first step on the therapeutic pathway. Kimi and Terry Ishizaka discovered IgE,⁶ which sensitised the skin and mucous membranes in exactly the way the older allergists had expected. Working with Bennich, Johansson of Sweden also isolated IgE and then helped develop a type of radioimmunoassay that could measure the minute amounts of IgE antibody present in blood.⁷ Immunological changes after using IgE clearly led to the sensitisation of cells and to other events in the tissues, and with the discovery of the prostaglandins by Vane and the structure of the leucotrienes by Samuelsson and Bergson, the release of inflammatory mediators became the focus of attention, together with the events that take place in the tissues themselves.

Mainly through applying these new aspects of knowledge and the techniques that go with them new light has been shed on some of these old problems. By referring to recent studies of allergy to bee stings this can be shown, and the study of mediator release has also given us further insight into several unresolved difficulties. The work of Michael Kemeny, Tak Lee, Lawrence Youlten, and Samir Asad has been greatly concerned with these developments, and in quoting them I hope to show the different approaches that currently provide further advances in this rapidly developing subject.

Allergy to bee stings

With every bee sting roughly 50 µg venom is deposited under the skin. From the point of view of scientific study this is a conveniently measurable arrangement—more so than when grains of pollen land on the nasal mucosa in unmeasured amounts and penetrate the mucosa slowly and in unknown quantities. In a sensitised subject the reaction to a bee sting may range from a mild or a severe local reaction to a more generalised response entailing urticaria, angioedema, asthma, or life threatening anaphylaxis. The life threatening nature of some of these reactions justifies the frankly experimental approach to their treatment.

There is a contrast between a sensitive person's reaction to a single sting and the tolerance to multiple stings that is seen in many bee keepers. Jarisch has shown that non-allergic volunteers produce either no response to bee venom injections or a transient IgE antibody response, which disappears within six months (personal communication). In contrast, after being stung by live bees atopic people with a tendency to allergy produce a much more vigorous and prolonged sensitising response, which can also be seen in some non-allergic subjects. Inevitably, this may be seen as supporting evidence for the view that allergy is a failure of the mechanism that normally suppresses IgE after the first sensitisation has passed but might still be goaded into action by repeated injections of antigen.

While the sensitising role of IgE antibody is currently accepted, the role of IgG antibody in allergy is still being investigated. Some evidence suggests that it has a protective "blocking" role as bee keepers who have a history of many stings but appear to be "protected" tend to have much higher total concentrations of IgG antibody. The relation is, however, not simple. Persisting IgE antibodies to bee venom are often found in non-allergic bee keepers as well as in allergic subjects, and even the ratio of IgG to IgE antibody does not reliably predict whether a person is protected or not.⁸

How the available measurements can help us to understand our unsolved problems may be important. When Lichtenstein considered the many unsubstantiated claims that have been made for vaccine treatment bee venom allergy seemed a good model for further study. A boy who had had an almost fatal reaction to a bee sting was given injections of the type of bee body extract that was in current use in the United States. The treatment clearly failed. There was little antibody response. After six months of treatment he was accidentally stung again and nearly died. Lichtenstein then injected bee venom instead and showed that there was a striking rise in IgG antibody concentration. The boy was then stung by a live bee without any side effects. Furthermore, studies of release of histamine on the boy's leucocytes showed that, as treatment progressed, these cells had a diminishing sensitivity to bee venom.⁹ The observed immunological changes seemed to offer an explanation of the fact that, at least in this case, vaccine treatment worked.

In further studies three groups of patients who were all allergic to bee or wasp stings were injected with venom, insect body extract, or placebo.¹⁰ Further deliberate stings produced systemic reactions in only one out of 19 patients who had received venom, but in 14 out of 23 patients in the two other groups. Furthermore, after switching the patients who had not responded to treatment and giving them venom injections all but one were evidently able to tolerate stings without side effects. This suggested that in developing allergy vaccines it may be important to use standardised material that is rich in the relevant antigen, thus providing a striking contrast with the

previously available (and officially approved) squashed bee and wasp extracts. It also suggested that it might be useful to measure IgG antibody as one of the indicators of the patient's response to treatment.

Passive protection

If IgG antibodies are indeed protective a globulin fraction of bee keeper's blood could be taken and used to confer passive protection on the allergic subject. With the help of the Lister Institute, we obtained a gammaglobulin fraction of bee keeper's plasma and injected it into five subjects allergic to bee venom in a collaborative study with Lichtenstein and Sobotka.¹¹ Bee keeper's globulin could indeed provide passive protection, but this protection was transient, and the injection of plasma seemed to offer no advantage over the stimulation of an active IgG response. Seven of our subjects allergic to bee venom were excluded from the main study because they did not have a reproducible anaphylactic reaction, but they nevertheless had a brisk IgG antibody response to the bee venom that they received during the assessment period. This was thought to support Lichtenstein's observations on the value of active immunisation but did not invalidate the main conclusion of this particular study—that is, that IgG antibody can indeed have a protective or "blocking" role.

There was one worrying feature about our observations on the transfer of passive immunity. One subject, who had the highest IgE concentration we had ever encountered, also had a high concentration of IgG antibody even before he was given bee keeper's globulin. A dose of bee keeper's globulin, which scarcely affected his own blood concentration, nevertheless seemed sufficient to protect him so that he was able to tolerate 100 µg bee venom—more than three times the amount that had previously caused severe asthma. Eighteen days later 100 µg bee venom again caused a severe asthmatic attack.

Reasons for failure of treatment

In this unique bee venom model we seemed to have an opportunity to learn much more about immunotherapy for allergic conditions, about the circumstances in which it succeeds and fails, and perhaps about the ways it can be modified both to boost the IgE reaction and to suppress IgE production and the cell sensitisation that goes with it. To do this we needed to concentrate not on those straightforward cases in which the treatment worked but on those in which it failed. To do this we had to measure the antibody response to each antigen within the bee venom mixture and categorise the antibody response in terms not only of IgE and IgG but also of subclasses of immunoglobulin: IgG₁, IgG₂, IgG₃, and IgG₄. This presented Kemeny with some technical problems.

Much of the work on IgE had depended on the radioallergosorbent test. After that the enzyme linked immunosorbent assay allowed plastic plates with multiple wells to be used in the automated reading of the colour changes. Like the radioallergosorbent test attempts to increase the sensitivity of the method led to non-specific reactions, and, with Urbanek, Kemeny showed that some of the problems were due to the loose binding of the test antigen to the plate. When a specific antibody is used as an "antigen presenter" it is more firmly attached and better able to react, and this simple step increases the sensitivity of the subsequent assay 10-20 times or more.¹² When antibody from a test serum is then allowed to bind it can be analysed accurately in terms of class and subclass as well as the quantity bound.¹³

This approach showed that, as Aalberse first showed by other methods, an initial IgG₁ response to bee venom switches to a more sustained IgG₄ response.¹⁴ The total IgG antibody concentration therefore offers a fairly crude guide, and, apart from differences in subclass, there is also a differential response to different venom components. In one subject anaphylactic reactions were originally associated with IgE antibody to phospholipase A₂, and these reactions ceased when IgG antibody to phospholipase A₂ rose after several exposures to bee venom. He subsequently had another anaphylactic reaction to a further sting. Kemeny was able to show that, after the initial treatment, IgG antibodies to the main bee venom, protein in phospholipase A₂, had risen and IgE antibodies had fallen. After this new anaphylactic episode there was no evidence that these changes had gone into reverse, but he had evidence of a new sensitisation—this time to another venom protein, hyaluronidase.⁸

Follow up studies of IgE antibodies to the different venom components showed a new feature: that immunotherapy can be followed by not only a rise in IgG antibodies but also a switching off of IgE antibodies, first to one venom component and then to another (D M Kemeny, personal communication). Each antibody appears to be regulated separately, and this switching off can also be seen in the natural course of an allergic disease. In a patient of Ross Barnetson who had a transient allergy to cows' milk, the patient's recovery was signalled by a decline in IgE antibody, firstly to lactalbumin and then to lactoglobulin and casein. Both in the natural course

of allergic disease and after immunotherapy we may therefore need to find better ways of stimulating a more selective IgG antibody response or a specific suppressive response for the relevant IgE antibody.

Mediator release

This analysis is admittedly an oversimplification. Much of the effect of IgE antibody depends on its ability to sensitise mast cells and basophils. When Miyachi repeated Lichtenstein's experiments and exposed the white cells of a sensitised subject to bee venom in different concentrations he showed that histamine was released and also that this release could be inhibited by using whole blood containing IgG antibody (personal communication). As Ullrich Wahn has since shown, different purified venom components can also stimulate histamine release,¹⁵ but there is no simple relation between histamine release and IgE concentration in the serum. It may, therefore, be worth considering what happens in intact man and whether the release of mediators into the bloodstream correlates with the final reaction of the tissues themselves—the spasm of smooth muscle, the increased capillary permeability, the attraction of other cells, and the amplifying mechanisms that lead to urticaria, asthma, angioedema, or anaphylaxis.

Lawrence Youlten showed that a bee sting in the hand of a sensitive subject led to the release of histamine and prostaglandin $F_{2\alpha}$ into the venous blood of the same arm (personal communication). Little of the released histamine and prostaglandin $F_{2\alpha}$ was detectable in the venous blood of the contralateral arm. These studies should be repeated and extended to the wide range of mediators that are measurable, but they raise the question of whether the flushing, nasal blockage, and bronchoconstriction that some of these patients suffer might be explained by local mediator release rather than the dissemination of venom. Indeed, the scale and type of local mediator release—whether provoked by immunological or non-immunological means—may well determine the clinical manifestations that are usually interpreted as allergic. We know that the final common pathways that affect mediators do not always entail an immunological trigger—for example, in aspirin induced urticaria and asthma, in which there is not always an association with atopy and the serum IgE concentration is often normal. In these subjects the resting blood prostaglandin $F_{2\alpha}$ concentration is usually raised, even before an aspirin challenge,¹⁶ returning to normal after aspirin is given at the time that symptoms develop. As Stephen Holgate and Samir Asad have shown the blood histamine concentration follows a similar pattern.¹⁷ In these people it seems, therefore, that some biochemical abnormality or enzyme deficiency is present whether or not they take aspirin. The powerful pharmacological effect of aspirin in suppressing synthesis of prostaglandin allows symptoms to develop for the first time and the question is why? Theoretically, this might be due to the unopposed action of leucotrienes, but there is no evidence of this point. What seems superficially to be indistinguishable from an allergic reaction seems to have a pharmacological basis.

Conclusion

We may therefore have to exercise some caution in analysing clinical syndromes that suggest allergy. For example, when people sensitive to tartrazine develop angioedema there is no evidence that that reaction is immunological, and the possibility of a non-immunological trigger has to be considered. If it is true, as it seems to be, that mast cells can be activated in different ways we shall need to study the profile of mediators that can be released from mast cells, basophils, and various other cells in the blood and tissues, in response to both immunological and non-immunological events.

The benefits we are beginning to see after the discoveries of Bergson, Samuelsson, and Vane offer some exciting possibilities. A knowledge of the structure of mediators and their biosynthetic pathways has already led to the development of precise assay methods and, in future, may also lead to the development of new drugs and novel ways of modulating the enzymatic cascades. An example is the use of different diets to modulate inflammation. When the legendary good health of the Eskimo was analysed in terms of a diet rich in fish oils this brought back memories of the cod liver oil supplements that were thought to be so healthy in the 1920s and 30s. Fish oils are rich in eicosapentaenoic acid and docosahexaenoic acid, which have now been shown to influence the types of mediator that are released from activated polymorphonuclear leucocytes. Tak Lee's finding that in people taking these oils as dietary supplements the generation of one of the inflammatory

products of leucocytes, leucotriene B_4 , is substantially suppressed and partly replaced by the less active leucotriene B_5 , has provided yet another twist to the story.¹⁸ We need to analyse not only immunological mechanisms but also mediator release and the ways in which the reaction pattern can be modified by vaccines, drugs, or diet.

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What sports are to be encouraged for short children (up to third percentile) who are active and healthy so that in later years, especially in adolescence, the child will be able to keep up adequately with his peers?

The difference in the rate at which children grow and mature means that care should be taken to ensure that a child is matched with a sport or activity that is safe, equitable, and consequently enjoyable. In general, selecting an appropriate sport (or sports) for any child depends on three related factors: (1) the risks in particular sports; (2) the conditions under which the competition and training routines take place; and (3) the maturational, behavioural, and motor characteristics of the child.¹

The needs of the short child are generally no different from those of any youngster. There is no empirical evidence to suggest that stature has an important effect on the acquisition of motor skill.² Consequently it is important that before puberty emphasis is placed on activities that develop coordination, balance, dexterity, and flexibility. Where the needs of the short child do differ is that care should be taken to avoid activities where the risk of collision or contact are high. In sports such as soccer or basketball their size would not only increase the risk of injury but also put them at a considerable disadvantage. It is important that the short child obtains feelings of competence and mastery from their own participation in sport as this may have considerable implications for the development of positive body image. The coach or teacher should not, therefore, try to overcompensate or overload the child in an effort to help him or her keep up with their peers. I would suggest the following sports, although the eventual choice must be made by the individual in direct contact with the child. It is they who must assess the child's suitability for any of the activities mentioned: 7-10 years swimming, baseball, softball, gymnastics and for those aged 10 and upwards tennis and running.—STEPHEN ROWLEY, research officer, training of young athletes study, London.

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