Wellcome Film Project

Diseases Of The Chest: Allergic Bronchial Reactions – Asthma

Uptodate

From The Cardiothoracic Institute, London.

Presented by Professor Jack Pepys.

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Produced by Peter Bowen and David Sharp.

Black-and-white
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<Opening titles>

<Pepys to camera>

Asthma caused by extrinsic agents provides us with examples for the immunological analysis of allergic reactions in the bronchi. There are two main types of allergic reaction to be considered at the present time, although this does not, of course, exclude the possible participation of the other types of allergy as well.

There's a great deal to be learnt about these allergic reactions but by correlating the history, skin, serological and provocation tests, it's possible to identify an immediate type of asthmatic reaction mediated, it seems, by the reaginic antibody, IgE, and a slowly-developing, late asthmatic reaction, mediated by other classes of antibody – the precipitating antibodies with the precipitation of complement.

<Pepys to camera, seated behind lectern>

If we now start with type I immediate allergy in which reaginic Ig antibody is involved, skin testing is an important part of the investigation. The method of testing, however, is of considerable importance, since it is quite easy by using inappropriate methods to obtain false positive reactions. What I want now to do is to show the most accurate and precise method of skin testing for this type of allergic reaction.

<Pepys stands up and walks towards a patient seated in a chair with back to camera. The patient's right arm is flexed and resting on a table>

The method that is best employed for this purpose is to do the ordinary prick test <*Pepys marks patient's skin with a scalloped line*> in which a drop of extract is placed on the skin, and a superficial prick is made into the epidermis using a separate needle for each extract, in which the point of the needle is introduced only into the superficial layers with a gentle lifting motion. This test introduces into the skin one three millionth of an ml of allergen and this minute amount encounters in the tissues equally minute amounts of reaginic antibody IgE attached to the surface of the basophil cells.

When the allergen and reaginic antibody combine, the contents of the basophil, or mast cells in the case of the tissues, are liberated, and the histamine and other tissue mediators then proceed to produce their wealing effects. This is the nature of the immediate reaction produced by this type of allergy. And we will now have a look some 15 minutes later at a battery of such tests carried out on the skin of an atopic person, the sort of person who produces Ig antibody readily against common antigens encountered in daily life.

<Pepsy narrates over series of slides, interspersed with talk to camera>

As you will see here on the upper aspect of the forearm, there are small weals to the second test down to the mould *Alternaria*, a second small reaction further down to another mould, *Cladosporium*. On the middle line of tests – reactions at the top to

grass, flower and tree pollens; and at the bottom, a large wealing reaction to *Dermatophagoides*, the house dust allergy mite. In the lower set of tests, there are reactions to cat, dog and horse allergen, and again to a house dust extract.

Now the important point about these wealing reactions produced by the prick test <*to camera*> is that it has been shown that these weals correspond closely with the presence in the serum of specific IgE antibody against the relevant allergen, and that both of these findings correlate closely with the clinical history and with deliberate provocation tests, so that by using this very sensitive and highly precise prick test method, <*narrates over previous slide*> it's possible to get a good and reliable insight into the presence of reaginic IgE antibody in the patient's serum, and certainly with certain common allergens to the clinical relevance of these allergens.

<*To camera*> The next method of demonstrating convincingly the aetiological relationship of allergens to the patient's symptoms is to carry out bronchial provocation tests. These carefully carried-out tests are a valuable further method of study. One of the ways of doing this <*Pepys holds ups nebulising equipment*> is to nebulise or aerosolise the allergen from a Wright nebuliser through a rebreathing bag, and the patient then breathes in the allergen from the rebreathing bag under carefully controlled conditions. In such patients, the sorts of reactions that can be elicited can be seen on the following chart.

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<*Next slide*> As you can see, the forced expiratory volume runs down the vertical axis and there is a rapid fall in forced expiratory volume, reaching its maximum within about 10 minutes with resolution of the reaction in about 2 hours. The speed of appearance of this reaction and its duration are analogous to those of the type I IgE mediated reaction in the skin. Now if we take such a patient and give the patient an inhalation of disodium cromoglycate beforehand and then repeat the challenge, as you can see, the reaction is completely inhibited. This is attributed to an effect of the disodium cromoglycate on the surface of the mast cell where it permits allergen and

reaginic antibody to combine but it inhibits the liberation of the tissue mediators from the cell.

<*To camera*> A point of considerable interest here is that neither the immediate skin test reaction nor the immediate bronchial reaction are modified by corticosteroids. And this particular manifestation raises a variety of problems which we shall talk about further when we talk about the type III, the precipitin-mediated type of allergic reaction. I want now to show you how to elicit this sort of reaction.

<Pepys stands up and walks towards a new patient seated in the chair with back to camera>

As a rule, one needs to use intracutaneous methods of testing, although it can be elicited with prick tests in highly sensitive subjects. But the intracutaneous test is carried out for this purpose by introducing a tiny amount, 0.1 to 0.2 of allergen into the epidermis. <*Pepys carries out this procedure on the patient's right arm*> Almost invariably in type III reactions, there is first of all an immediate reaction which in the atopic subject is attributed to IgE antibody, whereas in the non-atopic subject, we are not at all sure as to what sort of antibody is responsible.

<Pepys to camera, seated>

It may perhaps be the IgG short-term homocytotropic antibody described by Parish, but this remains to be established. However, whatever the mechanism for this immediate reaction, this occurs first, coming up within minutes and resolving within about 1 ½ to 2 hours. Some hours later, 3 to 4 hours after the test, a second reaction appears, and this develops as a large, ill-defined oedematous reaction which you can see in the following illustrations.

<Pepys narrates over series of slides, interspersed with talk to camera>

This reaction is maximal at about 7 to 8 hours and resolves within a day to a day and a half.

<*To camera*> It is effectively inhibited by corticosteroid drugs. The type III reaction, which we are now examining, results from the combination of antigen in moderate excess with precipitating antibody to form toxic soluble complexes which fix and activate components of complement. The activated aggregates attack neutrophil cells which ingest the aggregates and are destroyed by them. In the process, the cells liberate into the tissues their own enzymes, the lysosomes, which then proceed to digest the extracellular tissues. Corticosteroids are said to preserve the integrity of the membranes of the lysosomes and it may be that this is why they are so effective in inhibiting reactions of this type.

Now we can pass on to examine what sort of bronchial reaction is attributed to immunological mechanisms of this sort. And the next chart shows the results of the inhalation test in a non-atopic subject with a <*next slide*> pigeon serum preparation against which the patient has precipitating antibodies. And you will see that there is no bronchial reaction until about 4 to 5 hours after the challenge. The reaction is maximal at about 8 to 10 hours and resolves in a day or so. And once again, we see in the bronchus, a speed of appearance and duration of reaction strictly analogous to that of the late skin test reaction.

If, as you can see in the following chart, the patient is given disodium cromoglycate to inhale beforehand, the late reaction is completely inhibited. The mechanism of this inhibition is not clear. It may be that the Intal is blocking an immediate reaction which is not itself capable of inducing an asthmatic reaction, and that the Intal is thereby preventing the late reaction from occurring. But the point here <*to camera*> is that Intal blocks the immediate reaction and appears also to block the late reaction, whereas corticosteroids have no effect on the immediate reaction but effectively inhibit the late reaction.

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Now we can see in the following chart the reactions of a patient who has both IgE reaginic antibody and precipitating antibody <*next diagram*>, in this case against

extracts of *Aspergillus fumigatus.* And as you will see the inhalation test produces a paroxysmal, rapid fall in expiratory volume which resolves in about 2 hours consistent with a type I IgE mediated reaction. Then after a short period of normality, a second slowly progressive, prolonged asthmatic reaction appears which corresponds with the late type of reaction attributed to a precipitating antibody complex and complement fixing reactions. Now if such a patient is given corticosteroid drugs, the immediate reaction is quite unmodified, the late reaction is inhibited.

<To camera> The example given here may seem perhaps a bit unusual, but similar reactions have been elicited with quite common allergens like those of house dust and the house dust allergy mite *Dermatophagoides.* And the next chart shows just such an investigation <*next slide*> carried out by Professor Urio[?] Freungen[?] in which you'll see that the inhalation of the house dust extract causes an immediate paroxysmal asthmatic reaction, which resolves in a little more than an hour, and is then followed by a second prolonged asthmatic reaction.

<*To camera*> If such a patient is given corticosteroid drugs for several days and the challenge is then repeated, <*next slide*> you see that the immediate asthmatic reaction is quite unmodified, but the late reaction is completely inhibited. <*Next slide*> When further tests are carried out and Intal or disodium cromoglycate is given beforehand, as you can see from the following chart, both reactions are completely inhibited.

<*To camera*> The allergens about which we have been speaking up to now have been common allergens: animal dander, pollen, house dust mites and so on, but it is of interest to appreciate that one can get identical patterns of immediate and late asthmatic reactions occurring either separately or together in response to inhaled chemical dust, vapours and fumes, and I want, very briefly, to show how we test for these.

Now here you see a patient being tested to the salts of platinum, very potent allergens which are really rather hazardous to test if one does not take care. <*Next*

slide> The patient is tilting from one receiver to another, a mixture of the platinum salt with lactose in a previously worked out proportion, and the patient inhales the dust that comes off from this manoeuvre over controlled periods of time. The reactions produced in the bronchus by such exposure are exactly of the types that I have been describing.

<*Next slide*> The next agent which can be tested in a similar sort of way are the fumes derived from the soldering of aluminium solder. This contains aminoethylethanolamine. And here you see the patient placing a hot soldering iron into the solder and taking two or three inhalations of this material. After such exposure, sensitised subjects give immediate, late or dual reactions.

<*Next slide*> And the last example I want to show in this context is a patient being tested to the fumes of toluene diisocyanate. Once again, an extremely potent sensitiser employed in the rubber and plastics industry and also used as a combination for certain polyurethane paints and varnishes. The way we test with this material is to get the patient to paint with the varnish itself on one day as a control, and then the following day to paint with the varnish plus the toluene diisocyanate added to it. And by such tests, we are able to elicit immediate, late and dual reactions just as we have in the other common allergens.

Now this method of occupational-type exposure opens up quite a large area of investigations of agents which have previously not been entirely easy to deal with in this sort of situation.

<*To camera*> I want now to try and summarise the material which we have just been through. This provides models of immediate and late asthmatic reactions attributed to type I and type III forms of allergy. But it is important to realise that the other forms of allergy may indeed be present and co-exist, and in the case of types I and III allergy, there is evidence that they may even be interdependent, so that whatever has been said up to now is open to further clarifications as we come to understand the immunological mechanisms better.

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But what about the clinical significance of these findings? I think there is a good deal to be learnt from these. The fact that a patient can, in response to a challenge with a particular allergen, have two entirely different forms of asthmatic reaction – a paroxysmal, immediate one of short duration and a slowly progressive, late onset one of prolonged duration – may explain why some of our patients tell us that they have asthma in the morning which then clears and that it then recurs at night. And indeed, even the way this responds to the ordinary palliatives, may find its explanation in the mechanisms which underlie the different reactions. For example, the immediate reaction is reasonably resolved by bronchodilators, the inhalation of isoprenaline, for example. And what I think is happening here, is that all the isoprenaline has to do is to antagonise the mediators liberated from the mast cells. And this is not too difficult, whereas with the late reaction, there is an ongoing immune-complex complement-dependent reaction which does not respond so readily to bronchodilators. So here we may have an explanation of why a simple palliative treatment will work well at one time of the day and yet work very poorly at another. If we then add to this, the fact corticosteroids only block the late reaction and have no effect on the immediate one, we once again clarify certain problems, but also reveal that there are others which remain to be answered. Under these circumstances, when the late reaction is blocked, what has happened to the immediate component of the reaction? Something that has yet to be established and yet to be clarified.

In the case of industry, we get good evidence of the association of, I think, these two types of reaction. In the industries where people are exposed to organic dust and become sensitised to these, the non-atopic people tend to give a history of asthma coming on on the way home from work or late at night, and then at a later date they claim that their sensitivity was greatly increased and that at these times the asthma could be produced immediately on coming into contact with the relevant agent. And what I think we are seeing here is the development, first of all, of a late asthmatic reaction, followed by the development of enough IgE reaginic antibody to give an immediate reaction.

Now all of these sorts of findings are pointers as to how we must try to analyse and examine the role of immunological mechanisms in asthma. There's clearly a great deal more to be done; with regard to the chemical agents for example, antibodies have been shown in some instances but not altogether convincingly, and yet have to be demonstrated in others. All in all, the whole field, it seems to me, is now open for a much more intensive immunological attack than has been the case in the past.

<End credits>