ALLERGY

by MARIA GATT, B.Pharm.

Allergy is immunity gone wrong. Different people are allergic to a wide range of seemingly unrelated substances, but, the list of common allergens is curiously consistent. The pollen of ragweed is one of the first known allergens, while the connection between intestinal distress and one food, milk, was recognised more than 2 centuries ago. Most drugs are too small (mol.wt less than 1,000), to be able to stimulate an allergic reaction, but they can act as incomplete antigens or 'haptens' which become complete antigens in combination with a body protein. The penicillins and the sulphonamides are two classes of drugs which frequently cause an allergic reaction. Cross allergy within a chemical group is usual, while allergy between two chemicals of similar structures such as penicilins and cephalosporins is also usual. The most common manifestations are rhinitis, asthma, and skin rash, depending on the site of contact with the allergen. Allergy to food is less common than allergy to airborne materials but its true incidence is unknown because food induced symptoms are often less well defined than the hay-fever and asthma induced by airborne allergens, while cases of contact dermatitis caused by modern chemicals are on the increase.

Mechanism

The mediators of hypersensitivity reactions are the β-lymphocytes. Clones of β-lymphocytes carry receptors on the surface, which are specific for the antibody which they are prepared to synthesise in quantity. When an antigen binds to such a receptor it triggers the transformation of the cell. The cell proliferates and differentiates to form a clone of plasma cells in which the protein synthesising structure called the endoplasmic reticulum is greatly enlarged. The plasma cells synthesise and secrete into the bloodstream millions of identical antibody molecules, thus generating a humoral immune response. The antibodies involved in hypersensitivity reactions belong to the IgE class of immunoglobulins. When specific antibodies are synthesised in response to the binding of an allergen they move through the blood stream to mast cells in connective tissue and become firmly fixed to the receptors on the surface of the mast cells. As yet, however, there is no allergy reaction, that comes only when the individual next encounters the same antigen.

On second contact, the antigen need not go through the process of triggering β cells to transform. It goes straight to the IgE fixed to mast cells and binds to the antibody. As a result, the mast cell degranulates, the granules moving to the surface of the cell and releasing their content to the surrounding tissue. Calcium ions are needed for this degranulation to take place. It is the binding of the antigen with the antibody, which makes the cell membrane more permeable to calcium ions. The degranulation which results, leads to the release of histamine, serotonin, and chemical factors that activate blood platelets and attract the white blood cells called eosinophils, and also phagocytic cells.

Two other important groups of potent biological mediators are:— the prostaglandins and the leukotrienes, which are not only synthesised in mast cells, but also in several kinds of leukocytes. The prostaglandins and the leukotrienes are important factors in many nonallergic

conditions too. In allergy they join with the mediators liberated from the mast cell granules to give rise to the contraction of smooth muscle in the airways or the intestine, the dilatation of small blood vessels and an increase in their permeability to water and plasma proteins, the secretion of thick, sticky mucus, and (in the skin), the stimulation of nerve endings which results in itching or pain.

First Encounter With Allergen

Antigen + receptor on β lymphocyte

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β cell transforms to plasma cells

↓

Secretion of IgE antibody

↓

IgE binds to mast cell receptors

Second Encounter With Allergen — Allergic Reaction

Antigen + antibody on mast cell degranulation

↓

Release of Histamine/Serotonin/ Prostaglandins/Leukotrienes

↓

Hypersensitivity reaction

Treatment

Knowing the mechanism of allergy and identifying the allergen is important medically if patients are to be relieved of their symptoms and if possible advised on ways of preventing the allergy. Lack of previous exposure is not the same as lack of history of previous exposure. In the case of medicines, exposure is not necessarily medical. For example, the penicillins occur in dairy products following treatment of cattle, and penicillin antibodies are commonly present in those who deny having received the drug. The fact that antibodies are produced however, does not mean a patient will necessarily respond to re-exposure with clinical manifestations.

The old maxim that prevention is better than cure is the best advice to follow. If a patient says he is allergic to some drug, then that drugs should **not** be given without careful testing. However, in the case of other allergens, it is not always possible to avoid contact. Using hypoallergenic cosmetics is easy, but it is hardly possible to escape from the abundant pollen in spring time.

Desensitisation is possible, but it is not easy to prepare desensitisation vaccines in a sufficiently pure state and with standardised potency on a commercial scale. Also, the injections can generate severe local or systemic allergic reactions, which, in rare instances can be fatal.

Aspirin has been found to be useful in some cases of intestinal food allergy. It has been shown that such allergies are prostaglandin mediated. For this reason some patients who have been regularly treated for ulcerative colitis by sulphasalazine, a combination of sulphapyridine and 5-amino-salicylic acid, an aspirin analogue have found that taking aspirin before eating and drinking the irritant foods prevented the development of symptoms. However, not all allergies are mediated by prostaglandins. Indeed, aspirin or its analogues may actually provoke asthma in susceptible individuals.

Histamines appear to play an important role in skin rashes hence the very extensive use of **antihistamines** both orally and systemically in such condi-

tions. Antihistamines also provide relief in hayfever where the symptoms of itching of the eyes, sneezing and the secretion of water (tears and runny nose) are largely histamine mediated. In asthma, however, antihistamines have no effect and, as already mentioned, though some prostaglandins have a constrictive effect on the larger bronchi, aspirin, either has no effect or makes the asthma worse. It is the leukotrienes, which have been shown to have a constricting effect of a hundred to a thousand times that of histamine or prostaglandins in constricting the airways of the bronchial tree, that are now thought likely to be the most importan mediaors in asthma. So far, no antileukotriene drug is available.

Sodium cromoglycate is often prescribed for the treatment of hay fever and allergic asthma. It is thought to work by preventing the entrance of calcium ions into mast cells, hence forestalling the chain of events leading to degranulation. For this reason, the drug must be given in the very early stages before degranulation has had time to take place. Once the chain of events has started, treatment to counteract the mediator's actions is used. This may take the form of bronchodilators, like isoprenaline, mucolytics and expectorants which will help to clear the bronchi of the mucus which accumulates in them. In severe cases of allergy, as in severe cases of allergic asthma, or severe contact dermatitis accompanied with weeping skin conditions, corticosteroids may sometimes have to be used.

Inheritance

The exact mechanism of inheritance is not known. The genetics is complicated by the fact that allergy exhibits incomplete penetrance or variable genetic expression. For example, 2 people may

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RESEARCH

ANTI-LEUKOTRIENES — NEW TREATMENT FOR ASTHMA?

In the late 1930's, a substance was found in the extracellular fluid of the lungs which caused a slow, long lasting, and profound constrictions of the airways in experimental animals.

In the past three years, the substance, SRSA (slow reacting substance of anaphylaxis), has been shown to consist of a mixture of three substances with an unusual Chemistry. They are thioethers: fatty acids linked by one or more amino-acids. Their structure has been worked out by Bengt Samuelson of the Karolinska Institute in Stockholm, who called them leukotrienes because they are made by leukocytes and have three conjugated double bonds in their parent molecule. The chain of reactions by which leukotrienes are synthesised is initiated by lipoxygenase. Several leukotrienes have been isolated, A^4, B^4, C^4, and D^4. The mixture of leukotrienes C^4, D^4, and E^4, constitutes SRS —A.

The leukotrienes are from 100 to 1000 times as potent as histamine or the Prostaglandins in constricting the smallest airways of the bronchial tree. So far no antileukotriene drug is available. However, now that the structure of these mediators is known, intensive efforts are under way to find agents that can block their synthesis or their activity. The discovery of such a drug would be a major advance in the treatment of asthma.

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have the gene or genes specific for the allergic state and their environment may be similar, yet, only one of them may show chemical evidence of allergy.

Breastfeeding

An important factor which seems to effect the degree of penetrance is the mode of infant feeding, breast or bottle feeding. Under normal circumstances, in mature individuals, very little ingested protein gets through the intestinal wall into the bloodstream, where it can encounter cells and elicit an immune response. Most food protein is broken down into peptides and individual amino acids in the stomach and small intestine; it is these breakdown products that enter the bloodstream, and they are not antigenic. What little protein ordinarily gets through is apparently tolerated by the immune system. If too much protein passes through the epithelial lining of the intestine, however, the immune system can be sensitised and an allergic response can ensue. In the case of the newborn baby, the intestinal wall is probably hyperpermeable to food proteins, as it is known to be in the many newborn animals. Because of this, neonatal exposure to foreign (cow's milk) proteins may be allergenic, whereas exposure to the mother's milk proteins may not be. It is likely too that there are factors in mother's milk that help to seal the intestinal epithilium, making it impermeable to foreign proteins. For lack of those sealing factors, a bottle fed infant may be exposed even later in life to proteins it would not otherwise encounter. Such effects may be all the more important in an individual genetically predisposed to allergy. Whatever the connections between bottle feeding and allergy may be, many paediatricians have come to believe that a newborn infant, and in particular one with parents or siblings who are clinically allergic, should receive absolutely no milk other than mother's milk for the first 3 to 6 months of life; it is likely that the most vulnerable period is the first three to seven days.

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References: Scientific American, Aug. 1982, Vol. 247, No. 2.

Clinical Pharmacology by D.R. Lawrence.

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sease. In many leading medical countries such as England, low dose heparin prophylactic technique is done regularly. This should encourage us to expand this treatment in our hospitals.

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