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1. *Allergy*

1. *Introduction*

The term allergy is used to describe an inappropriate damaging immune response which occurs in only a proportion of the population on encounter with what is usually a non-harmful substance such as pollen or food. Broadly-speaking, hypersensitivity reactions can either be antibody- or cell-mediated. According to Gell and Coombs, such reactions can be classified as ***Type I - IV***, which tends to follow known clinical disease patterns.

Type I depends on an interaction between antigen and IgE antibody attached to mast cells. Eosinophils and a subset of T-cells (Th2 cells) are also involved. Antigens which stimulate this type of response are often termed as allergens. Clinical examples of a type I reaction include allergic rhinitis (hay fever), allergic asthma and some food reactions such as peanut hypersensitivity.

Type II is a cytotoxic reaction between tissue- or cell-bound antigen and IgM or IgG antibody and clinical situations where this occurs include immune cytopaenias such as autoimmune haemolytic anaemia and immune thrombocytopaenia as well as in transfusion reactions.

Type III is an immune-complex reaction between circulating antigen and IgG antibody with subsequent deposition in the walls of blood vessels, joints, kidneys and skin manifesting as serum sickness or, in the case of some inhaled antigens, extrinsic allergic alveolitis.

Type IV is a cellular immune response mediated by sensitised lymphocytes. Such a reaction causes the local response that occurs on intradermal tuberculin testing in TB-sensitised individuals and for the skin manifestations of contact hypersensitivity.

These reactions can also be distinguished on the basis of their timing after antigen challenge with type I occurring within minutes, type II and III developing only after antibody is produced and persisting for as long as the antigen remains and type IV developing only a few days after antigen challenge and persisting until the antigen challenge is removed.

Considering the highly complex nature of the immune system, this classification of hypersensitivity reactions is oversimplified and generally, different immune mechanisms act in concert with eachother. This chapter considers type I and IV hypersensitivity.

Most allergy is IgE-mediated and it is now widely accepted that the use of the term allergy is restricted to those reactions and diseases where this mechanism underlies the pathologic process.

Allergic diseases are common and epidemiological studies conducted in several different countries show an increase in the prevalence in asthma and related disorders. It is estimated that up to a quarter of the population in the UK has or is predisposed to the development of an allergic condition and the cost to the NHS is significant with £750m a year spent on asthma care alone.

2. *Cells and Molecules in type I hypersensitivity*

Allergens. Antigens that elicit an IgE-mediated type I allergic reaction are called allergens. They are usually non-harmful substances except in those individuals predisposed to generating an IgE response to them. In general, allergens are low molecular weight proteins or glycoproteins with no distinguishing physical characteristics when compared with other antigens. Thus allergens are functionally characterised antigens. The mechanism by which allergens promote the generation of allergic responses is not fully understood but is related to the capacity to penetrate mucosal tissues due to their small size and solubility, their presence in very low concentrations which preferentially promotes a Th2-type response, exposure in early life when this type of response is more likely to occur and host predisposition to the generation of allergic responses according to pattern of antigen presentation, T-cell activation and cytokine responsiveness. Common allergens include house dust mite, pollens, moulds, and foods including eggs, nuts, fish and dairy produce.

IgE. IgE-producing plasma cells are distributed primarily in the mucosal lymphoid tissues adjacent to the respiratory and gastrointestinal tracts; antibody is synthesised on allergen exposure and subsequently distributed throughout the body where it promptly binds to its high affinity receptor FcεR which is densely expressed on the surface of mast cells. IgE is normally present in the blood at a very low concentration (0.0003g/l) or less than 0.001% of circulating immunoglobulin as most is bound to FcεR and is retained there until degranulation or death of the mast cell. The familial predisposition to allergic diseases suggests that genetic factors regulate IgE biosynthesis with some loci controlling the total level of IgE and others the immune recognition of specific allergens and the subsequent formation of specific IgE. A familial tendency to make high levels of IgE is associated with an increased incidence of diseases including bronchial asthma, allergic rhinitis and eczema. These diseases are classified as atopic and such individuals are said to manifest atopy. The genes involved have yet to be identified but may include MHC genes as well as a cluster of cytokine receptor genes (IL-4R cluster) which regulate antigen presentation and cytokine responsiveness respectively. IL-4 activity is important in allergy as it induces B-lymphocytes to switch to IgE production. Mast cells are putative early producers of IL-4 after antigen encounter. In addition, a subset of T-cells, Th2 cells which are preferentially activated in the allergic setting secrete IL-4 among other cytokines which up-regulate this population while suppressing activity of another subset of T-cells, Th1 cells, which secrete IFN-γ the actions of which include inhibition of IgE switching in B-cells. Sensitive immunoassays are used in the clinical laboratory to measure total levels of IgE. While this value is not absolutely required to make any diagnosis, it does reflect the degree of atopy in patients with eczema and it reflects the severity and number of allergies and recent allergen exposure in asthma and rhinitis. IgE measurement is useless in patients with chronic urticaria or a history of anaphylaxis. In addition to atopy, IgE levels may be raised in patients with parasitic infections and in a number of rare immunodeficiency conditions where T-cell regulation is abnormal (Hyper-IgE syndrome, Job's syndrome, Wiskott-Aldrich syndrome). Specific IgE levels can be assessed either by *in-vivo* skin prick testing or by *in-vitro* immunoassay. The clinical use of such tests vary depending on the clinical situation and the degree of atopy in the patient studied. They cannot substitute for thorough history-taking and examination. *In-vivo* testing is limited by the age of the patient, whether or not anti-histamine medications are being used and clinical sensitivity of the individual. *In-vitro* tests on the other hand are expensive and cannot give immediate information. Positive IgE antibodies do not necessarily correlate with the clinical situation as unlike *in-vivo* tests, they measure only IgE and not release of histamine from mast cells. Skin tests to a variety of allergens are positive in up to 30% of the population reflecting an underlying atopic tendency in this group. The predictive value of a positive test varies depending on the allergen. In general, positive tests to aeroallergens accurately predict either already existing clinical sensitivity or a potential to become sensitised with exposure. Food tests are more difficult to interpret but positive tests in the context of a supportive history can be valuable with particular foods including nuts, fish and eggs. In the right hands, these tests are useful provided their limitations and the potential for both false positive and negative results are appreciated and interpreted in the context of the clinical presentation.

Mast cells. Mast cells are found in most tissues, commonly close to blood and lymphatic vessels. They are found in especially large numbers subjacent to mucosal surfaces of the respiratory and gastrointestinal tracts and in the dermis of the skin. They are about twice the size of a red cell and are distinguished by cytoplasmic granules which stain purple (metachromatic) in haematoxylin stained tissue sections. Mast cells are derived from haemopoietic stem cells in the bone marrow but in the tissues they live for many months and retain proliferative capacity. Although derived from a common precursor the exact phenotype of mature mast cells varies according to their local microenvironment. This is reflected in minor variations in the mediators they release and response to stimuli. Appropriate stimuli cause mast cells to degranulate and release (exocytose) preformed inflammatory mediators into the tissues. Mast cell activation occurs when the FcεR-bound IgE is crosslinked by binding to multivalent antigen. Signalling in this way stimulates release of both pre-formed mediators and the production of new inflammatory mediators. Non-IgE-mediated stimuli of mast cell degranulation include components of the activated complement cascade (anaphylotoxins - C5a and C3a), some drugs (e.g. aspirin, opiates, some muscle relaxants), some foods (tartrazine and salicylate-containing foods such as commercially processed foods and tomatoes and other fruits respectively) and some low molecular weight substances such as some contrast media used in radiology. The most important of these preformed mediators release by the degranulating mast cell is a vasoactive amine called histamine. Histamine acts on a variety of different cells by binding to it's receptors (two main types - H1receptors present in skin, submucosal tissues and brain and H2-receptors in the gastrointestinal tract); it induces increased blood flow and increased vascular permeability with contraction of extravascular smooth muscle and stimulation of nerves which causes itching sensations. In the skin this reaction induces a typical wheal and flare response whilst in deeper tissues swelling (oedema) is more apparent. Other preformed mediators are heparin (an anti-coagulant proteoglycan), neutral proteases including tryptase and chymase, platelet activating factor which activates platelet release of serotonin as well as causing histamine-like effects and

kallikrein which contributes to inflammation by the formation of bradykinin. The action of most of these preformed mediators is immediate and short-lived. Mast cells can also be stimulated to produce new (not preformed) molecules which mediate a sustained inflammatory response long after the effects of histamine has worn off. This production occurs through activation of the two main arachidonic acid metabolic pathways. On mast cell activation, phospholipase is activated to generate arachidonic acid from membrane phospholipid The first pathway involves metabolism of arachidonic acid by cyclooxygenase and generates prostaglandins, mainly PGD2, which mediates increased blood flow and vascular permeability as well as being a chemoattractant for neutrophils. The second pathway involves metabolism of arachidonic acid by lipoxygenase and generates leukotrienes. Leukotrienes also mediate a sustained increase in blood flow, vascular permeability and extravascular smooth muscle contraction; additionally they attract and activate leukocytes including eosinophils.

Measurement of mast cell tryptase can be undertaken in specialised clinical laboratories. Elevated levels reflect recent (within hours) degranulation of mast cells and can be useful where the diagnosis of anaphylaxis is uncertain. Tryptase rather than histamine is measured as it is more stable and has a somewhat longer half-life than the biologically active histamine molecule.

Eosinophils. The eosinophil leukocyte is produced in the bone marrow from myeloid progenitors under the influence of IL-3, IL-5 and GM-CSF. It is a pro-inflammatory cell which can be identified by its bi-lobed nucleus and cytoplasmic granules which stain bright red with eosin, hence the name. The cell is characterised by its content of cytotoxic proteins including eosinophil cationic protein, eosinophil peroxidase and major basic protein. In germ-free animals eosinophils are barely detectable whilst in normal people the blood eosinophil count is <0.55 x 109/L. In people infected by helminthic parasitic worms the eosinophil count is elevated and these cells play an important role in elimination of parasite infections including *Schistosoma mansoni, Trichinella spiralis* and *Trypanosoma cruzi*. In allergy-predisposed individuals, eosinophils migrate and accumulate at sites of antigen challenge. This process is not fully understood but is related to the pattern of adhesion molecule upregulation and activation and chemokine release on antigen challenge. The toxic contents of the eosinophil granules which help control parasite infection are responsible for many of the damaging features seen in tissues affected by allergic processes. Measurement of eosinophil numbers may support the diagnosis of allergic diseases such as asthma and eczema but is not absolutely required to make a diagnosis. Serial rises in asthma may indicate worsening disease and steroid control of inflammation may be mirrored by falls in the eosinophil count. The measurement of levels of eosinophil mediators as indicators of allergic inflammation is under review but is not yet widely practised.

3. *Clinical disorders associated with allergy*

1. *Anaphylaxis and anaphylactoid reactions*

Anaphylaxis is a medical emergency caused by the rapid widespread degranulation of mast cells and basophils which can result in airway obstruction, cardiovascular collapse and sometimes death. All allergens have the potential to cause anaphylaxis but systemically administered agents such as drugs (penicillin-based antibiotics, anaesthetics) and insect venoms are most likely to cause this type of reaction. Foods also are important triggers of anaphylaxis outside the hospital setting. Peanuts, other nuts, dairy produce and shellfish are especially common culprits. IgE-mediated systemic reactions are termed anaphylaxis. Atopics are no more susceptible to anaphylaxis than non-atopic individuals but more severe reactions with a poorer outlook are commoner in asthmatics. When no triggering factor can be identified, it is termed idiopathic anaphylaxis. Some drugs such as X-ray contrast media, opiates, aspirin and NSAIDs and ACE inhibitors, some foods including tomatoes and strawberries and physical stimuli including cold and pressure can in some people cause mast cell degranulation by direct pharmacological action on mast cells (not via IgE), thus giving a picture identical to anaphylaxis but termed an anaphylactoid reaction.

The clinical features of either in roughly increasing severity are flushing, widespread urticaria, angioedema, abdominal pain, vomiting, wheezing, intraoral and laryngeal oedema, cyanosis, hypotension, cardiac arrhythmias, cardiac or respiratory arrest. Satisfactory treatment depends on early recognition and the prompt institution of therapy. Adrenaline is the most important drug in the treatment of anaphylaxis. As soon as anaphylaxis is recognized, it should be administered intramuscularly in doses of 0.3 - 0.5mg (0.3 - 0.5 mls of 1/1000 preparation) or 0.01mg/kg of body weight in children. Attention to the maintenance of the airway, breathing and circulation is vital. Regardless of the response to adrenaline, emergency medical assistance must be sought once the

initial treatment been attended to as late reactions can occur and may require monitoring and further therapy. Adrenaline has a short half life and can be repeated every 10 - 15 minutes, if indicated. In the event of cardiovascular collapse, judicious use of adrenaline by the intravenous route may be indicated but should only be given in the hospital setting and by experienced personnel because of the risks of serious arrhythmias. Once the acute event has been dealt with, anti-histamines and corticosteroids may be administered to prevent secondary relapse caused by newly-formed mast cell mediators but they are not substitutes for the adrenaline, particularly the steroids, which do not have a role in the early management of anaphylaxis. Patients who have experienced an anaphylactic attack must be assessed by an experienced doctor who can identify the likely triggering factor, advise on satisfactory avoidance strategies and instruct the patient and carers on early recognition and management of future attacks including the use of self-injectable forms of adrenaline, if required. In the event of anaphylaxis caused by allergy to bee or wasp venoms, desensitisation therapy whereby gradually increasing doses of the causative venom are administered intradermally can be undertaken. This is a prolonged procedure (satisfactory desensitisation can take up to three years of therapy administered over gradually lengthening intervals) not without risk and may not be entirely protective from adverse effects on subsequent exposure to the causative venom. Even where it is effective, the mechanism of action is not fully understood but is thought to be related to a reduction in levels of venom-specific IgE with an increase in anti-venom IgG which may act as blocking antibody.

2. *Urticaria / Angioedema.*

Urticaria (hives / nettle rash) is an eruption of migrating itchy wheals which occur as a result of histamine activity in the upper dermis. Angioedema is the deeper equivalent of urticaria and the two features often occur together. While attacks may be prolonged for a number of days, individual lesions rarely persist for more than 24 hours and are characterised by their rapidly evolving pattern. While itching can be severe, excoriation is not a feature of this condition and if present should cause other diagnoses to be considered. Urticaria is common affecting up to 20% of the population at some time in their lives. The majority of cases present as isolated acute attacks and the triggering agent, usually a food or drug is easily recognised and further attacks prevented by avoidance. Such reactions may be IgE-mediated or due to direct mast cell triggering. Less commonly, urticaria /angioedema occurs repeatedly and, when it persists for more than 4 - 6 weeks is termed chronic. A number of causes have been identified in relapsing urticaria / angioedema. Physical stimuli including trauma, pressure, cold, heat and sunlight are all associated with relapsing symptoms. Dermographism, the appearance of a wheal at the site of skin stroking with a blunt instrument, is often a feature in such patients. Careful history-taking with appropriate physical challenge testing allows this condition to be diagnosed. Allergic hypersensitivity is rarely a cause of chronic urticaria but should be ruled out by careful questioning to eliminate any possible sources of allergen exposure, especially in food and drugs. Likewise, details of diet and drugs should be taken to reveal any direct mast cell activators which may be chronically ingested. Inhaled allergens rarely cause urticarial eruptions. A proportion of patients with autoimmune thyroid disease detected either by the presence of antibodies to thyroid components with or without evidence of biochemical dysfunction manifest features of chronic urticaria. This may reflect an underlying tendency to form tissue specific autoantibodies as there is evidence that some patients have autoantibodies to mast cell antigens. These patients develop a wheal-and-flare reaction on skin prick testing with autologous serum.

The occurrence of underlying infections especially parasitic and viral should be considered in urticarial patients and rarely malignancy, especially lymphoma is co-existent. In occasional cases, especially those where the clinical features are slightly unusual with persistence of and inflammation in the lesions, autoimmune conditions such as S.L.E. and other vasculitides may underlie the urticaria. Biopsy and microscopic assessment of an urticarial lesion as well as serological screening is helpful where this is suspected. Despite this list of possible underlying causes of chronic urticaria, no trigger is identified in the majority (75%) of cases and so are termed idiopathic. This phenomenon is most common in middle-aged women and can be prolonged with episodes occurring for many years in up to 25% of cases although remittance is the rule with 50% recovered within one year and a further 25% in remittance at one year but experiencing periods of relapse beyond this time . Assessment to rule out fore-mentioned causes is important.

Treatment of urticaria consists of avoidance of triggers where these are identified and management of any co-existent condition which predisposes to the development of urticarial eruptions. Symptoms can be suppressed satisfactorily in 80 - 90% of patients using fast-acting, non-sedating anti-

histamines although much variation has been identified in individual responses to specific drugs and trials of a number may be required before a satisfactory treatment is found. Other groups of drugs may be useful in controlling difficult symptoms. In general, steroids should not be used but can sometimes be beneficial in breaking the cycle of rapidly relapsing urticaria. The benefits of other drug families including H2-blockers, calcium channel blockers and tricyclic antidepressants with strong anti-histamine blockade effects are variable and best reserved for use by doctors experienced in the area. Some practitioners advocate the use of diets in which dyes such as tartrazine and preservatives such as sulphites and benzoate are excluded but evidence of their efficacy is not convincing. Aspirin containing compounds can decrease the threshold for mast cell degranulation and should be avoided.

3. *Food allergy and intolerance*

Adverse reactions to food consist of food allergy and food intolerance (no immunological aetiology). Microbiological or toxic contamination of foods as well as naturally occurring pharmacologically active ingredients are by far the commoner cause of adverse food reactions. Reactions truly mediated by allergen-specific IgE can occur immediately after exposure to the foodstuff, and frequently involve tingling or swelling of the lips and tongue/throat, urticaria, angioedema and even anaphylaxis. The commonest offending foods are cows' milk (in infants), peanuts, eggs, wheat, fish and shellfish and citrus fruits. Some patients don't have an immediate reaction but have abdominal symptoms (nausea, bloating, wind, diarrhoea, pain) up to 24 hr after the ingestion of the offending food. Symptoms remote from the GI tract may also occur such as rhinitis, asthma, urticaria, angioedema, or eczema. Food allergy is diagnosed by careful clinical history, thorough examination to exclude other causes of symptoms, and it is confirmed by testing for allergen-specific IgE. Skin or RAST tests are positive in about 75% of patients who have immediate reactions to foods such as nuts, egg, or fish. The unreliability of testing, especially when symptoms are delayed or remote from the GIT, may in part be due to relevant epitopes being destroyed or unreliably created by cooking. Food elimination diets and double-blind placebo-controlled food challenge tests can be helpful but are very laborious to perform, and it is in general expedient simply to recommend avoidance of the suspected food. It is important to monitor food exclusion carefully to ensure complete avoidance of the culprit food, assess clinical response to exclusion and, in children in particular, to avoid malnutrition which is a real risk with the more extreme exclusion diets.

4. *Drug reactions*

Adverse reactions to drugs are common. As with food reactions, numerous mechanisms underlie drug reactions and immunologically mediated ones are responsible for only a proportion of cases. Reactions may result from complement activation, direct action of the drugs on mast cells, or follow binding of antibodies. Many organs may be involved and every one of the Types I-IV reaction referred to above have been described as forming the underlying basis of reaction to different drugs. Drug molecules are in general too small to act as complete antigens, and either polymerise or act as haptens (*i.e.* combine, usually covalently, with a larger serum or cell-surface molecule so as to form a new epitope against which an immune response develops). The active drug molecule may not be the culprit - it may well be the degradation products, derivatives or polymers of the drug (which may be present in tiny amounts) or various other constituents of drug formulations. Following administration of the drug formulation, these various components may be metabolised. The large number of potential antigens in drugs thus makes investigation of adverse reactions extremely difficult. The list of drugs capable of generating immune-mediated adverse reactions is exhaustive and would not contribute much to this discussion. Important examples however include penicillins, anaesthetic agents and blood products including immunoglobulin products.

Penicillin can give rise to anaphylaxis via the formation of specific IgE antibodies and mast cell degranulation on re-exposure in a sensitised individual; haemolytic anaemia (by a Type II mechanism - the molecule binds covalently to the rbc surface forming a new epitope against which IgG antibodies are produced); interstitial nephritis, delayed onset of a vasculitic-type skin rash, joint swelling and respiratory distress (by a Type III mechanism giving rise to immune complexes which are deposited in blood vessel walls and in highly vascular tissues as mentioned) and delayed contact dermatitis by a Type IV mechanism. The penicillin molecule has a molecular weight of 334 daltons and can form several *haptens in vivo* and *in vitro*. The penicilloyl hapten is called the major determinant as it causes the majority of the reactions seen. Many other haptens have been defined

which are referred to as the minor determinants as they cause the minority of reactions. The many penicillin drugs available differ at their side chains but not at the penicillin business-part of the molecules, so that sensitivity to any one of them results in sensitivity to all the others. Desensitisation along the lines of venom desensitisation is not usually an option with penicillin hypersensitivity. A history of penicillin allergy is not uncommon but IgE-mediated hypersensitivity is only manifested in a proportion. The other mechanisms of hypersensitivity, normal unpleasant effects of the drug especially on the gastrointestinal tract or indeed co-existent symptoms of the infection for which antibiotics have been used in the first instance may be mistaken for true allergy. In the event of penicillin being absolutely necessary, skin testing with the allergenic components may be cautiously undertaken and, if hypersensitivity is confirmed, a rapid desensitisation programme can be undertaken with gradually increasing intradermal and subsequently oral doses of the drug being used over a number of hours. This procedure is not without risk however and its effect may only be short-term limiting its use in desensitising healthy individuals with penicillin allergy.

A variety of drugs used in anaesthetics have the potential to cause adverse reactions by a number of mechanisms. The first problem for the anaesthetist is when to recognise an adverse anaesthetic event as being due to the drugs administered. All potential events require that the investigators have access to a full list of administered drugs including fluids and blood products as the latter group are associated with direct mast cell degranulation and complement activation respectively. True IgE-mediated allergy can be caused by suxamethonium and skin testing or RAST tests may confirm this. Muscle relaxants and opiate analgesics can cause direct mast cell release and although they do not mediate their adverse actions via IgE may be associated with positive skin test results. Because of the potential complexity of anaesthetic reactions, it is highly advisable that the assistance of a clinical immunologist or other specialist with an interest in the area be involved early after such a reaction to provide guidance on the likely cause and advise on investigations required to confirm the mechanism.

5. *Asthma, hay fever and eczema - the atopic triad*

Asthma, hay-fever and eczema are all associated with activation of the Th2 subset of T-cells and the expression of IL-3, 4, 5, 13 and GM-CSF in response to exposure to allergens. Eosinophil inflammation with varying degrees of mast cell activation are the characteristics of the pathological lesion. More chronic disease is associated with destruction of the normal structure of the tissue with subsequent repair mechanisms occurring. Which organ is predominantly involved may reflect the site of initial sensitisation to allergen, the site of continuing exposure, which organs the relevant T cells home towards and the committed response of cells already resident at these sites.

Asthma is a widespread reversible narrowing of small airways caused by inflammatory infiltration of eosinophils and T-cells and the constriction of smooth muscle in bronchial walls. The spectrum of illness ranges from mild episodic wheezing with breathlessness or nocturnal cough to life-threatening obstructive ventilatory disease. It is the commonest of chronic diseases in childhood affecting 5 - 10% of the population. Allergic or **extrinsic asthma** is responsible for 90% of childhood asthma and 30% of adult asthma. It is triggered by certain allergens, and there is often a personal or family history of allergic disease. Perennial (year-round) symptoms often result from allergy to House Dust Mite (HDM, Dermatophagoides Pteronyssimus) or animals (e.g. cats) and seasonal symptoms often from allergy to pollens (tree in March-May, grass in June-July, weeds in July-Aug). Hay-fever and allergic conjunctivitis are triggered by similar allergens at these times. Non-allergic or **intrinsic** asthma is associated with the same pathological changes in the airway but allergic triggers are not involved in the aetiology. A proportion of patients are sensitive to the actions of aspirin although this is not IgE-mediated. This group of patients can experience severe airway obstruction on exposure to aspirin and related drugs and rhinitis with associated nasal polyp formation is particularly common in this syndrome. A characteristic feature in all asthma disease is the hyperesponsiveness of the inflamed airway to non-allergic stimuli including viral infection, cold air, dusty and polluted environments.

The diagnosis is usually made on the basis of the history, supported by examination (e.g. when wheezing is present) and confirmed by showing a reduction in the peak flow rate of air on forced expiration which is increased following the administration of bronchodilator drugs. The allergens responsible may be identified by performing skin prick tests or alternatively by assay of total serum IgE and allergen-specific IgE concentrations. Extrinsic asthma has a biphasic response. The

immediate first phase occurs within 30 min of exposure to the allergen and is caused by the release of histamine and other pre-formed mediators from mast cells in the respiratory mucosa. The delayed second phase occurs 6-8 hr later due to infiltration of lymphocytes and granulocytes and the release of further mediators of inflammation. Bronchial hyperesponsiveness contributes to the prolongation of symptoms which can persist for many days or weeks after allergen exposure and is the hallmark of the symptomatic phase in intrinsic asthma. Anti - inflammatory therapy in the form of inhaled steroids have become the mainstay of treatment in asthma. Other treatments including bronchodilator inhalations and, in more severe disease, systemic anti-inflammatory drugs are also important. Desensitisation therapy is not useful in most cases of asthma and has in the past proved fatal in some subjects.

Hay fever or **allergic rhinitis** is perennial or seasonal and affects about 10 - 20% of the population. The symptoms are of nasal itching, sneezing, congestion and rhinorrhoea, and it may be accompanied by **allergic conjunctivitis** (itchy, lacrimating eyes). Mast cell degranulation resulting in inflammation and oedema can be so severe as to block the sinus ostia and Eustachian tubes with resulting secondary bacterial infection. Nasal polyps may occur (mucosal sacs containing inflammatory fluid and cells). Allergen avoidance is often difficult and treatment relies upon regular non-sedating selective H_1 receptor antagonists (e.g. terfenadine, loratidine, cetirizine) and topical corticosteroids (e.g. beclomethasone) for allergic rhinitis, or topical Sodium Cromoglycate drops for allergic conjunctivitis. Desensitisation is not widely practised but may be useful in intractable disease where a single allergen is responsible for symptoms. The potential benefits of immunisation with peptide epitopes of the allergen are currently being assessed. They work by altering the reactivity of Th-2 clones involved in the generation of the allergic response. The epitopes for cat fur and house dust mite are currently known and under investigation. This therapy is not yet widely practised.

Eczema or atopic dermatitis is a chronic inflammatory skin disease in patients who often have a personal or family history of asthma or hay fever. It is developed in about 80% of patients before the age of five. About 80% of patients with eczema also develop hay fever or asthma. Many of these outgrow their skin disease as they develop respiratory allergy, consistent with a change in the organ in which the disease is compartmentalised. Serum IgE levels are raised in about 80% of cases, and 80% of cases also have positive skin prick tests or RAST tests to various food and inhaled allergens. In some patients exposure to the relevant foods or inhaled allergens can result in worsening of the eczema, but this is the exception and patients frequently do not have positive challenge tests to those allergens against which they have skin or RAST reactivity.

Secondary skin infection is more common, with *Herpes simplex*, molluscum contagiosum, warts, *papilloma virus*, *vaccinia* and fungal infections. *Staphylococcus aureus* superinfection is present in up to 90% of cases and those with severe disease may show dramatic improvement after anti-staphylococcal treatment. It is possible that *S. aureus* may exacerbate inflammation by secreting superantigen toxins. Patients who have eczema produce IgE antibodies to these superantigens (indicating sensitisation and an unfavourable class switch), which might result in superantigen-triggered IgE mediated histamine release at the skin surface and thus scratch. Eczema is managed by strict attention to maintaining the moisture of the skin with bland emollients. Care must be taken to avoid unwittingly sensitising sufferers with peanut oil which up to recently has been a common constituent of these products. Topical steroid preparations are useful in suppressing inflammation in eczematous skin but must be used judiciously as chronic high doses can be associated with skin damage, particularly to the sensitive skin of the face. More powerful immunotherapies are sometimes recommended in intractable eczema. Dietary exclusion is rarely helpful.

6. *Delayed hypersensitivity*

Delayed hypersensitivity refers to the cell-mediated hypersensitivity classified by Gell and Coombs as type IV. This type of immune response occurs 36 - 48 hours after antigen exposure and differs pathologically from the first three types of hypersensitivity which are all antibody-mediated. Many clinical entities have their basis in this pattern of immune activation including the granulomatous lesion of T.B, tuberculin reactivity, sarcoidosis many forms of autoimmune inflammation and the further discussed contact dermatitis and coeliac disease.

Contact dermatitis is a cell-mediated inflammatory condition which superficially resembles atopic

eczema but which is very different immunologically; eczema beingTh-2-driven (where the T cells direct the development of a humoral response with production of IgE antibodies) and DTH being Th1 driven (where the T cells direct the development of a cellular immune response with stimulation of macrophage activity). A variety of substances can cause this dermatological reaction with nickel being the commonest described trigger. Latex in hospital and other health care workers is an increasingly well-recognised cause of contact dermatitis and can in a proportion also be associated with the development of IgE-mediated sensitivity with the risks of asthma and anaphylaxis. The sequence of events is that the applied haptens combine with proteins in the epidermis to form neo-epitopes. These are presented by relevant APCs (the Langerhans cell in the skin migrates to the regional lymph node) to CD4 T cells. Those of relevant TCR specificity undergo clonal proliferation and their progeny subsequently migrate out of the circulation into the skin by the usual mechanisms of lymphocyte recirculation. They accumulate selectively at the site of the neo-epitopes where they set up a cellular inflammatory response by directing macrophages at that site to mount a vigorous cell-mediated attack against those structures expressing the neo-epitopes. The thin skin of the hands and face which is in regular contact with environmental agents is most predisposed to contact dermatitis. Atopic eczema sufferers are also more prone to the effects of irritant contacts. Diagnosis of contact sensitivity can be confirmed by patch testing where, unlike the situation with skin prick tests where allergens are inserted into the dermis and reactivity occurs within minutes as result of mast cell histamine release, potential triggers of contact dermatitis are applied directly to the surface of the skin and positive tests are indicated by inflammation occurring only after 36 - 48 hours. Avoidance of irritants and topical steroid applications are the mainstays of therapy in this disorder.

Coeliac disease or gluten enteropathy refers to a state of intolerance to gliadin, the alcohol-soluble subunit of the cereal protein gluten with inflammatory infiltration of gliadin- specific T-lymphocytes and plasma cells in the mucosal surface of the small intestine most severe at the proximal end of the jejunum.. Local and systemic production of antibodies to gliadin and antibodies to endomysium are seen in most untreated patients. Patients with IgA deficiency have an increased susceptibility to Coeliac disease and can give false negative results if IgA gliadin and endomysial antibodies are measured alone without measuring serum IgA. Recently antibodies to an intracellular enzyme, transglutaminase, have been found in untreated coeliac patients. The protein gluten is rich in glutamine, and can act as a substrate for this enzyme and form a protein complex. A mechanism as outlined in section 6.7 may operate here, where T cell sensitivity to gluten may provide linked help to cells which recognise epitopes from the self protein transglutaminase, causing tissue damage to self. Antibodies to endomysium crossreact stongly with antibodies to transglutaminase.

The inflammatory infiltrate ultimately leads to destruction of the normal villous architecture and malabsorption develops. It is now recognised that a spectrum of disease severity can occur and diagnosis at any age is possible. There is a familial predisposition to coeliac disease and certain HLA types are overrepresented in sufferers, namely HLA-DQ2 and DQ8. A number of autoimmune conditions including rheumatoid arthritis and autoimmune thyroid disease also coexist with increased frequency indicating immune dysregulation. Sufferers usually respond well to dietary exclusion with symptom relief and reduction in the inflammatory gut lesion. Histological findings with a history of improvement of the lesion and symptoms on a gluten free diet are still the gold standards in diagnosing this condition but presence of antibodies as mentioned can be useful indicators for diagnosis and monitoring. Poor compliance with diet can in some patients predispose to development of small bowel lymphoma.

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