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Review

Clinical Immunology

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Clinical immunology has developed very significantly as a speciality over the last twenty years, as has the understanding of the immunological basis of many diseases and the development of immunological therapies. Indeed it is difficult to think of a speciality that has not developed an "immunological dimension" in this time.

The purpose of this mini-review is to update the non-specialist reader on the basic immunological mechanisms which underlie an effective immune response and the clinical disorders which results when the processes are deficient or disordered. The basic science description is, of necessity limited in scope and detail. Further explanation of the basic cellular and molecular mechanisms involved in immune defence can be found in recent textbooks[1,2].

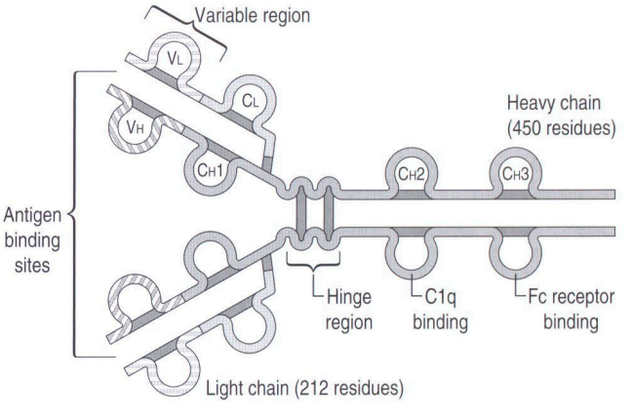

Fig 1. The basic structure of IgG1. The n terminal end of the heavy and light chains is the variable region responsible for antigen binding (Fab). The Fc region is responsible for complement (C1q) activation and binding to cell surfaces via Fc receptors.

Innate and adaptive immunity

Innate immune defences are the body's constant, unchanging defence against infection. These are non-specific and include physical components such as skin, mucous membranes, gastric acid, nasal cilia etc as well as phagocytic cells and proteins of the complement system. In contrast, the **adaptive** immune system includes lymphocytes and immunoglobulin (antibody) molecules which share characteristics of **specificity** and **memory**. The components of the adaptive system recognise and are stimulated by specific fragments of microorganisms termed **antigens** (from *Anti*body *Gen*erating). When antigens are appropriately presented to lymphocytes by specialist **antigen presenting cells** (APC: see below), they generate antigen specific T cells and B cells that develop to produce antibody molecules.

There are five isotypes of immunoglobulin, or antibody, molecules: IgG, IgM, IgA, IgD and IgE. All five share a basic "Y- shaped" structure (Figure 1) although IgM and IgA tend to exist in pentameric or dimeric forms. IgG is the major isotype present in serum, IgA has a crucial role at mucous membranes and IgM is the isotype that dominates the primary antibody response to first encountering a foreign antigen. IgD molecules function as cell surface receptors and IgE, whilst important in protection from parasitic infection is most notable in western societies for its role in allergic or type 1 hypersensitivity disease.

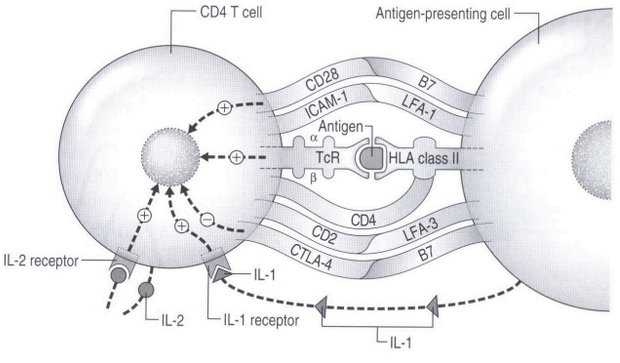

Fig 2. Activation of CD4+ T cells. In addition to antigen recognition via the T cell receptor(TCR), a range of cell surface molecules and soluble cytokines deliver additional positive (+) or negative (-) signals. Interleukin 2 (IL-2) secretion activates both the secreting T cell (autocrine) and it's near neighbours (paracrine)

The normal peripheral blood lymphocyte population comprises 70-90% T cells; 5-10% B cells and 1-10% natural killer (NK) cells. These are all derived from lymphoid stem cells in the bone marrow. Lymphocyte subsets are defined by their expression of surface markers termed CD antigens (CD: cluster of differentiation). T cells are classified by their cell surface markers as CD3+, with the helper subset (Th) defined as CD3+CD4+ and the cytotoxic subset (Tctx) as CD3+CD8+. There are also a number of regulatory T cell subsets which are described below. B cells are CD19+ and

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NK cells CD16+CD56+.

Immature T cells emerge from the bone marrow and undergo maturation during their passage through the infant's thymus gland. During that maturation, T cells with specificity for "self antigens" are deleted and only those with appropriate reactivity to foreign antigens complete their passage to the peripheral circulation. This is one of the "central" mechanisms of inducing "self-tolerance" and preventing autoreactivity against self antigens.

The process of developing specific immunological responses to microorganisms involves elements of both the innate and adaptive immune systems. Innate cells with phagocytic function recognise and engulf (phagocytose) invading microorganisms. Once phagocytosed, the microorganisms are broken down into short amino acid sequences which ultimately stimulate an immune response through a process of **antigen presentation** to lymphocytes (Figure 2).

Mature T cells recognise antigenic fragments/ peptides, only when they are *presented* to them bound to one of the **major histocompatibility complex (MHC)** molecules (MHC Class 1 or 2). MHC molecules are coded for by a discrete area on the short arm of chromosome 6 and have central roles in enabling the body to distinguish the recognition of self from non-self molecules. **MHC Class 1** molecules are expressed on all nucleated cells, whereas **MHC Class 2** are only expressed on specialist **antigen presenting cells (APC).** Each type of MHC molecule binds antigen fragments and presents these to their respective T cell subset. **CD4+ Th** cells only recognise antigen presented in the context of **MHC Class 2** molecules whilst **CD8+ Tctx** cells only recognise antigen fragments in the context of **MHC Class 1** molecules. The specific binding of the T cell receptor to antigen presented in the peptide binding groove of the MHC molecules leads to cellular activation. There are a also a number of non-specific co-stimulatory cell surface molecules that serve to enhance the binding and influence the nature of the cellular activation (Figure 2). The fact that T cells only respond effectively when antigen is appropriately presented is termed **MHC restriction**, and it is important to understand as it relates to the major functions of the two main cellular subpopulations. **CD4+Th** cells are central co-ordinators of the immune response, only being activated by specialist APC cells. **CD8+Tctx** cells are effectors, and therefore must be capable of recognising infection or malignant transformation of any nucleated cell in the body.

CD4+ Th cells stimulate B cells both by direct cell surface interaction but also by the secretion of cytokines. Cytokines are low molecular weight polypeptides that act to provide inter cellular signals. Most are known as **interleukins** (meaning that they effect communication between white blood cells) and are numbered in the order in which they were discovered. So, **interleukin 2 (IL-2)** is an important activator of T cells and was discovered before **interleukin 8 (IL-8)** which has an important role in recruiting neutrophils. Cytokines may affect the cell that produced them (autocrine effect) or other cells in their immediate vicinity (paracrine effect) but generally have little influence on cells at distant locations (endocrine effect).

The interaction of **APC, CD4+ T cells and B cells** is central to the adaptive response to pathogens resulting in primary and secondary antibody responses (Figure 3). The first or primary exposure to a microorganism is characterised chiefly by production of antigen specific IgM , however on secondary exposure, memory B cells are stimulated and high levels of protective IgG are produced. It is that highly specific, high titre IgG that provides long term protection.

Table 1:

UK Immunisation Schedule (www.immunisation.co.uk)

2 months:

- Diphtheria, tetanus, pertussis (whooping cough), polio and Haemophilus influenzae type b given as a 5-in-1 single jab known as DTaP/IPV/Hib
- Pneumococcal infection

3 months:

- 5-in-1, second dose (DTaP/IPV/Hib)
- Meningitis C

4 months:

- 5-in-1, third dose (DTaP/IPV/Hib)
- Pneumococcal infection, second dose
- Meningitis C, second dose

Around 12 months:

- Meningitis C, third dose
- Hib, fourth dose (Hib/MenC given as a single jab)

Around 13 months:

- MMR (measles, mumps and rubella), given as a single jab
- Pneumococcal infection, third dose

3 years and 4 months, or soon after:

- MMR second jab
- Diphtheria, tetanus, pertussis and polio (DtaP/IPV), given as a 4-in-1 pre-school booster

Around 12-13 years:

- Cervical cancer (HPV) vaccine (girls only): three jabs given within six months

Around 13-18 years:

- Diphtheria, tetanus and polio booster (Td/IPV), given as a single jab

65 and over:

- Flu (every year)
- Pneumococcal

T cell regulation

It is important that once an immune response is initiated, there are mechanisms to control and/or limit reactivity to prevent

uncontrolled or inappropriate immunological activation and potentially harmful inflammatory reactions. In terms of responses to microorganisms, the destruction and eradication of the microorganism itself is an important mechanism for "switching off" an immune response.

Within the population of **CD4+ Th** cells there is further differentiation into different functional subpopulations which have various regulatory functions. **T helper 0, 1 and 2 (Th0, Th1 and Th2)** subdivisions are defined by their preferential patterns of cytokine secretion and their differing influences on ultimate nature of the immune response to a pathogen. **Th0** differentiate into either **Th1** or **Th2**. The **Th1** cytokines are IL-2, IL-12 and IFN-γ favouring a cellular immune response whilst the **Th2** cytokines, favouring an antibody response, are IL-4, IL-5, IL-6 and IL-10. There is mutual suppression between these two dominant patterns of cytokine secretion such that, once a response has become committed in either direction, this pattern will tend to be maintained (Fig 4). The secretion of IL-4 and IL-5 tends to promote eosinophilia and IgE production and therefore Th2 responses are associated with type 1 hypersensitivity reactions and allergy. Other clinical examples of the consequences of **Th1/Th2** response include the response to protozoal and mycobacterial infection. In lepromatous leprosy, there is a dominant **Th2** response to the mycobacterium, which results in poor cytotoxic killing, high microbiological load and poor granuloma formation. In contrast, in granulomatous disease, there is a dominant **Th1** response, potent cytotoxic response with localisation of microorganisms within an inflammatory granuloma and a consequently low mycobacterial count. There are other direct clinical consequences of this understanding of T cell functions. In some specific primary immunodeficiency states, there is an inability to mount effective **Th1** type responses because of deficiency in either interferon γ or IL-12 secretion or responses. In such patients, replacement or supplementary treatment with interferon can be life saving. In other clinical situations e.g. multidrug resistant tuberculosis or eradication of non-tuberculous mycobacteria from the bronchiectatic lung, adjunctive interferon γ therapy can be similarly effective through boosting of the **Th1** response.

The concept of "central tolerance" has already been mentioned, however "peripheral tolerance" also occurs as a means of maintaining control of potentially autoreactive lymphocytes[3]. The population of **CD4+CD25+** (CD25 is the IL-2 receptor and is a marker of "activated" T cells) regulatory cells are also important in controlling self reactive responses and abnormalities in this population may predispose to autoreactivity and autoimmunity[4,5].

The **Th17** population is relatively recently described cell subset also thought to be involved in development of autoimmunity, particularly multiple sclerosis, diabetes, psoriasis and Rheumatoid arthritis[6]. **Th17** are probably developmentally distinct from **Th1** and **Th2** cells and they preferentially produce cytokines IL-17, IL-21 and IL-22. Their pro-inflammatory functions may indicate an important role in protective immunity at mucosal sites and they are thought to be down regulated by both **Th1** and **Th2** subsets[7,8].

Immunology of the newborn

The newborn infant is immunologically immature and depends on its innate immune defences and passively acquired maternal immunoglobulin G (IgG). Newborn infants, particularly those born prematurely, who have not had adequate transfer of maternal immunoglobulin in the last trimester of pregnancy, are therefore vulnerable to developing infection.

Maternally acquired IgG binds specifically to the wide range of microorganisms already encountered by the mother and is a form of **passive immunity**. It provides immediate wide-ranging protection until the natural process of antigen exposure has stimulated the production of endogenous antibody by primary and secondary responses. The half life of IgG is approximately 3 weeks *in vivo* and typically, maternally derived immunoglobulin levels will wane and fall so that the newborn reaches an ***immunological nadir*** of serum immunoglobulin levels between 3 to 6 months of age. At this stage the infant is most vulnerable to infection. If the production of immunoglobulin is abnormally delayed, the infant can develop ***transient hypogammaglobulinaemia of infancy (THI)***, which may require treatment with immunoglobulin replacement therapy should significant infection occur. It is crucial that **THI** is differentiated from one of the potentially life threatening **Primary Immunodeficiency Disorders** (PID: see below) that typically present in the first year of life. **THI** is therefore a diagnosis of exclusion.

Infant Immunisation

The UK immunisation schedule (Table 1) has been developed to protect the population from common infectious disease with potential for significant morbidity and mortality. The schedule is under regular review and is updated as new vaccines are developed. For most infectious agents, a series of vaccine doses is required, given at intervals, to generate a high level of protective antibodies. Underlying this is the concept of the primary and secondary antibody response of the adaptive immune system (Figure 3). Individual vaccines vary in their immunogenicity and the dosing and booster schedules are therefore individually determined to maintain appropriately high protective antibody levels.

Immune deficiency

Development failure of immune system components, or breakdown in its control can lead to the development of a wide range of ***primary immune deficiencies (PID)***. Figure 5 indicates how immune deficiencies arise as a result of failure of development or depletion of T cells at different stages of development (ontogeny). Whilst many PID present in childhood, they can present at any age in life and can affect individual components of the immune system e.g. immunoglobulin molecules[9], complement components[10], neutrophils[11] or lymphocytes or they can be combined deficiencies affecting both lymphocyte and immunoglobulin numbers and levels[12].

The most common PID are those characterised by deficiency of immunoglobulins (IgG, IgA or IgM). The most common type of antibody deficiency is ***common variable immune deficiency (CVID)***. CVID usually presents in children or young adults with a prolonged history of recurrent upper and lower respiratory tract infections, although it may also

present with autoimmune disorders affecting the GI tract, haematological or endocrine systems. An important aim for CVID patients is to establish the diagnosis and commence treatment before recognised complications of the disorder e.g. bronchiectasis have developed. A UK wide audit in 1996 suggested that the average diagnostic delay for such patients was of the order of 7 years, however anecdotally we know the delay can be much longer for individual patients[13,14]. Commencement of immunoglobulin replacement therapy by either the intravenous (IvIg) or subcutaneous (ScIg) routes is highly efficacious in reducing the number of infections and therefore preventing the development of complications[15]. IvIg and ScIg are usually lifelong treatments and may both be self administered at home after appropriate patient training. In Northern Ireland we currently have data on 218 patients with PID. 151 of these receive immunoglobulin replacement, around 80 of whom are treated at home (Table 2).

TABLE 2

Patients on treatment for Primary immunodeficiency & auto inflammatory syndromes in Northern Ireland, 2010

Common variable Immune deficiency (CVID)	93
C1-inhibitor deficiency	27
X-linked agammaglobulinaemia (XLA)	22
Other hypogammaglobulinaemia	14
Specific antibody deficiency	11
IgG subclass deficiency/IgA deficiency	9
Wiskott-Aldrich syndrome	4
Autoimmune polyendocrinopathy and chronic ectodermal dysplasia (APECED)	4
Severe combined immune deficiency (SCID)	4
Ataxia Telangectasia	4
Good's syndrome	3
Interferon gamma receptor deficiencies (IFNgR1 def)	3
X-linked Hyper IgM (XHIGM)	3
Hyper IgD syndrome	3
Autoimmune lymphoproliferative syndrome (ALPS)	3
Chronic mucocutaneous candidiasis (CMC)	2
Chronic granulomatous disease	2
Complement deficiencies	2
Idiopathic CD4 cytopaenia	2
Schnitzler syndrome	1
Immune dysfunction, Polyendocrinopathy, Enteropathy, X-linked (IPEX)	1
X-linked lymphoproliferative disease (XLP)	1

One of the few "immunological emergencies" and the most serious PID is ***severe combined immune deficiency (SCID)***. SCID usually presents during the first months of life. Affected infants are characterised by failure to thrive, recurrent bacterial, viral and/or fungal infections and there may be additional features including diarrhoea, rashes and liver dysfunction caused by **graft versus host disease** as well as morphological abnormalities. Graft versus host disease occurs in this context when functioning maternal lymphocytes transfer to the newborn at birth. The infant's immune system is unable to eradicate these and instead these maternal lymphocytes go on to proliferate and attack skin, liver and gut, resulting in a syndrome very similar to that seen after bone marrow transplantation. The acronym SCID

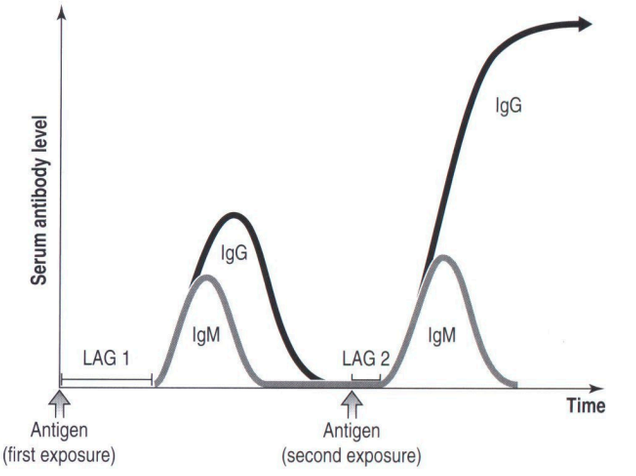

Fig 3. Primary and secondary antibody responses typify the adaptive immune response to antigen. Memory cells generated from the primary response become rapidly activated upon re-exposure to the same antigen.

can erroneously suggest a clinical presentation so severe and so rare, that an average paediatrician is unlikely to encounter the condition. This is however not the case and whilst SCID is rare, as is the case for other PID, it is almost certainly under diagnosed. There may be several factors contributing to the under diagnosis of SCID. Affected infants may initially appear relatively well, with perhaps frequent attendances related only to symptoms of relatively mild viral infection, diarrhoea or oral/perineal thrush. Identification of infants at high risk of SCID is therefore difficult, but one should have a higher index of suspicion if the parents are from a cultural background in which first cousin marriage is common (e.g. the Indian subcontinent). It should be emphasised that children with SCID do not typically have *absent* lymphocytes and/or immunoglobulins. Rather, their lymphocyte and

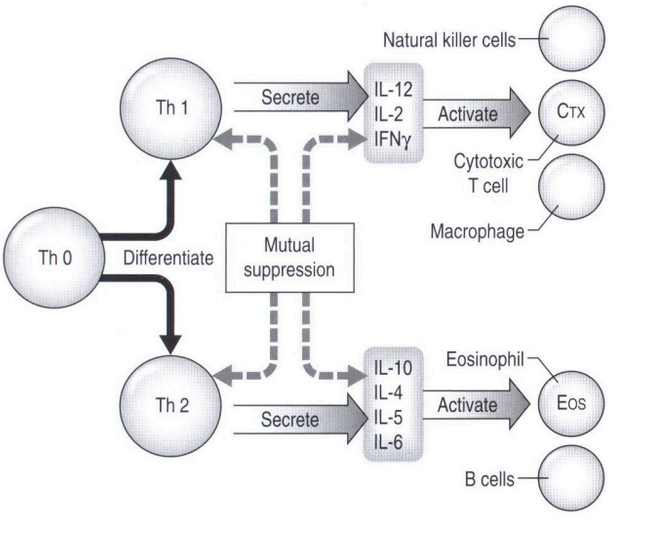

Fig 4. T cells differentiate along two major axes depending on their pattern of cytokine secretion. To give T helper 1(Th1) cells, which tend to promote cellular responses, and T helper 2 (Th2) cells whch tend to promote antibody production and IgE mediated responses. Th1 and Th2 cells are mutually suppressive. The distinction between these two subpopulations is not absolute in humans.

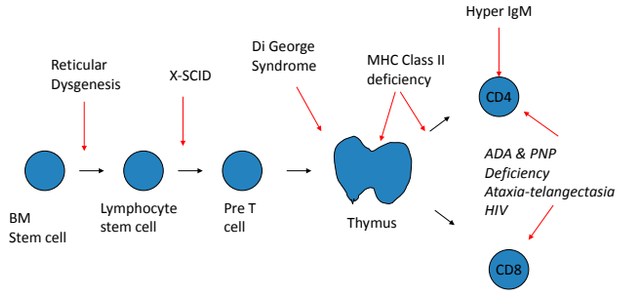

Fig 5. T cell development and Immunodeficiency

immunoglobulin levels are well below normal age-related reference ranges. A useful guide is that any child with a total lymphocyte count of <2.8 x10^9/L should be investigated for SCID, although a normal lymphocyte count does not exclude the diagnosis. We assess children for SCID on a regular basis and probably make the diagnosis at least once every year. If diagnosed early and managed appropriately, including early bone marrow transplant, long term survival from the disorder is currently of the order of > 85%.

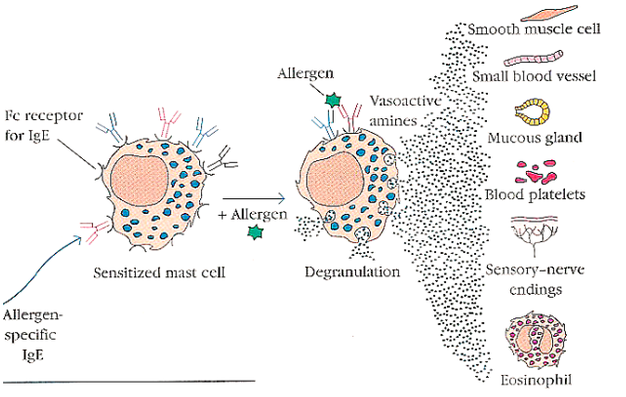

Fig 6. Antigen cross links specific IgE molecules on the surface of Mast cells causing degranulation and release of multiple mediators including histamine, heparin, platelet activating factor and leukotrienes. These mediators cause different symptoms depending on the anatomical site of release.

Under diagnosis is a major problem for patients with PID. There is also significant geographical variation in perceived prevalence across the UK which is probably at least partly explained by the patchy provision of immunology services. In Northern Ireland there were approx 25 patients diagnosed with PID in 1996, and this has risen to over 200 patients in 2010. This relentless annual rise in the number of diagnosed cases shows no signs of abating.

Whilst the most severe conditions require bone marrow transplantation[16], others are managed with regular immunoglobulin replacement therapy, enzyme replacement therapy, cytokine treatments or prophylactic antibiotics. Many of these disorders are on the basis of single gene defects and PID have been the candidate conditions in which much of the success in clinical trials of somatic gene therapy has been achieved.

Understanding of the prevalence of PID across the UK is limited and this is currently being addressed through the establishment of a UK-PID registry under the auspices of the UK primary immunodeficiency network (www.ukpin.org.uk). Servers for this project went live in 2009 and already approx 1300 out of an estimated 5000 patients have been registered. Across Europe, the linked database of the European Society for Immune Deficiency (http://www.esid.org/statistics.php) established in 2004 has details of over 12,000 PID patients.

Allergy

Allergic disease is a much more common clinical problem than PID and a source of considerable workload in primary care, organ based specialities (eg ENT, dermatology & respiratory medicine) as well as clinical immunology services. The spectrum of allergic disease seen in specialist allergy clinics includes potentially life threatening anaphylaxis, drug and venom allergy and complex multisystem allergic disease. A particular problem is the patient with chronic urticaria and /or angioedema of uncertain aetiology and that will be specifically addressed below.

TABLE 3:

Gell & Coombs classification of hypersensitivity

Type of Reaction	Effector Mechanism	Clinical Disorder
I	IgE, Mast cells	Allergic rhinitis, urticaria, angioedema, anaphylaxis
II	IgG directed at cell surface bound antigen	Transfusion reactions, acute graft rejection, Graves disease, Myasthenia Gravis, goodpasture's syndrome
III	Immune complexes	Cryoglobulinaemia, post-streptococcal glomerulonephritis, systemic lupus erythematosus
IV	CD4+ lymphocytes	Delayed type hypersensitivity, contact eczema, granulomatous reactions

Is the rise in allergic disease real?

It is sometimes suggested that the apparent rise in allergic disease is due to greater awareness and hence increased rates of diagnosis. However there is a well documented rise in the prevalence of allergic disease in "westernised" societies, but not in most of the less industrialised regions including Africa, India and South East Asia. Why should this be the case? It is recognised that societies with a high prevalence of allergy tend to have smaller family sizes, lower rates of infectious disease in infancy, higher rates of immunisation and greater degrees of domestic cleanliness. The ***Hygiene Hypothesis*** suggests that all of these factors lead to a decreased rate of microbial turnover at the infant's mucosal sites and that this in turn promotes abnormal immunological responses to antigens encountered, be they inhaled (pollens, animal dander, house dust mite) or ingested (foods)[17,18]. Allergic disease is

therefore characterised by the presence of antigen specific IgE to (usually) innocuous antigen and is the end result of a disordered immune response.

What is the cellular basis for allergy?

As already stated, Th2 cytokines, in particular IL-4 & 5 tend to promote IgE mediated responses to antigens. Once produced, antigen (or allergen) specific IgE binds via specialised receptors to the surface of mast cells. When later exposure to the allergen occurs, the IgE molecules are cross linked causing mast cell degranulation and the release of histamine and other mediators (leukotrienes, heparin, platelet activating factor etc) into the local tissue (Figure 6). These mediators have a wide range of effects and depending on the site of allergen exposure and location of mast cells activated, the resulting symptoms may include eg: rhinitis, conjunctivitis, urticaria, angioedema, vomiting, diarrhoea or anaphylactic shock.

Clinical Allergy

The increasing prevalence of allergic disorders represents a great challenge to the health service. Most medical practitioners have little or no formal training in allergic disease, however they are aware of the potentially severe nature of some allergic reactions. Paediatricians have historically taken an interest in food allergy and in Northern Ireland there is now a network of paediatricians with an interest in allergy, with at least one consultant in most of our hospitals.

The spectrum of allergic disease is wide; however the underlying mechanisms are common to most. The term *allergy* is widely misused in the popular press to refer to any adverse reaction. However in this context, allergy means Type 1 hypersensitivity (from the Gell & Coombs classification: Table 3)

Urticaria

Urticaria is caused when mast cells are activated in the epidermis. It is commonly described as resembling "nettle stings" and is typically raised and intensely itchy (Figure 7). It may occur as part of an acute allergic reaction or be a chronic problem, occurring on an almost daily basis for at least 6 weeks (***chronic idiopathic urticaria / CIU***). In patients with CIU it is very rare to identify an allergen and extensive laboratory investigation of such patients is not usually recommended. Management is usually with prolonged courses of non-sedating oral antihistamines, often at 3-4 times the recommended dose, to obtain complete suppression of the rash. Several variants of CIU occur, including autoimmune urticaria, urticarial vasculitis and physical urticarias. Good guidance is available on their diagnosis and management[19].

Angioedema

Angioedema is a non-dependent, non-pitting swelling that can affect any part of the body but frequently affects the perioral and periorbital regions, tongue, genitalia and peripheries such as the hands and feet. It can also occur internally causing laryngeal oedema or acute intestinal obstruction. Mast cell activation in the deep dermis is the usual cause; however in addition to histamine release, increased generation or reduced degradation of bradykinin is thought to be a key causative factor. Angioedema and urticaria commonly occur in the same person either as part of an acute allergic reaction or in approximately 40% of people with CIU. Management of the latter group is the same as for CIU. Approx 10% of "CIU patients" have chronic angioedema but no urticaria. Two important variants exist which are distinct in terms of both aetiology and treatment. Angiotensin converting enzyme inhibitors (ACEi) can cause potentially life threatening angioedema and the history is not typical of an allergic mechanism. In such patients, angioedema usually occurs after prolonged ACEi treatment, the swelling is not related in time to taking the medication and in some people, swelling may persist for some time after withdrawal of the drug. Anyone presenting with angioedema whilst taking an ACEi, must have alternative anti hypertensive drugs prescribed. There is a smaller but well described risk of angioedema with the Angiotensin II receptor blocking drugs and therefore alternatives such as calcium channel blockers and Beta blockers are preferred if possible.

Table 4

Factors associated with fatal nut reactions

- **Being away from home**
- **Eating food from commercial sources**
- **Not carrying rescue medication**
- **Alcohol**
- **Age: Between 15-25**
- **No deaths < 13 years (one series)**
- **Asthma**
  - **Excessive reliance on β2 agonists for asthma control**
  - 12 of 13 cases of fatal and near fatal reactions
  - 24 of 25 fatalities had asthma

Partial deficiency of the complement control protein C1 esterase inhibitor (C1-inh) also leads to recurrent angioedema in genetically affected individuals. Although C1-inh deficiency causes a loss of control of the activation of the classical complement pathway, it is via its indirect effect on bradykinin metabolism that angioedema occurs.

These patients are at risk of sudden death due to laryngeal oedema after intubation or dental treatment. They also suffer regular peripheral swellings and are frequently treated with either the prophylactic androgens danazol or stanozolol or the antifibrinolytic tranexamic acid. Acute laryngeal oedema requires administration of intravenous C1-inh concentrate. The angioedema of C1-inh deficiency does not respond to anti-histamines, corticosteroids or epinephrine.

There are approx 27 patients with C1-inh deficiency in Northern Ireland and these families are well defined and have management plans that include the possession of C1-inhibitor concentrate at home for emergency use. However it

is important to note that in approx 33 % of new cases, there is no suggestive family history and the diagnosis rests on identifying typical angioedema, usually without urticaria and on testing, serum complement C4 levels are usually low as are levels of C1-inh enzyme. The diagnosis of C1-inhibitor deficiency is not uncommonly made late, in adulthood and therefore should be considered in any patient presenting with otherwise unexplained angioedema usually without urticaria.

Table 5

Management advice for nut allergy

(i) A nut free environment at home

(ii) *Oral antihistamine for:*

a. Inadvertent / presumed nut exposure
b. Minor reactions: skin rash, non-life threatening angiodema
c. pre-medication

(iii) *Injectable adrenaline for*

a. life threatening airway obstruction (includes severe asthmatic symptoms)
b. anaphylactic collapse

(iv) *Warning device/card*

(v) *Emergency contacts in mobile phone: ICE (In case of emergency) / SOS*

(vi) *Support information*

a. www.anaphylaxis.org.uk
b. www.allergyni.co.uk
c. www.epipen.co.uk

Anaphylaxis

The term **anaphylaxis** originally indicated a state of susceptibility to severe allergic reactions and it was derived from *ana* (against) and φύλαξις *phylaxis* (protection). *Anaphylactic reactions* are now defined as "severe, life-threatening, generalised or systemic hypersensitivity reaction". The usual defining clinical characteristics are significant airway obstruction or hypotension, but clinical features may include a sense of impending doom, urticaria, angioedema, abdominal pain, vomiting or diarrhoea. The route of exposure, dose and nature of the allergen as well as coexisting conditions such as asthma or infection and concomitant medications e.g. Beta blockers may all affect the dominant clinical features. It is crucial that medical practitioners recognise anaphylactic reactions and treat them promptly to ensure the best chance of survival[20]

The underlying pathophysiology is the systemic activation of mast cells throughout the body. In the clinical diagnosis of allergic reactions this may be confirmed by the measurement of serum mast cell tryptase levels at the time of reaction (and 2 and 24 hours later). Formal protocols exist both locally and nationally for the structured investigation of anaphylactic reactions e.g. during anaesthesia[21]

Food allergy

Food allergy is often misunderstood and its prevalence overestimated. There is often confusion between food allergy and intolerance. True food allergy is common in early infancy with cow's milk protein, egg white, wheat, shellfish, peanuts and tree nuts being common allergens. Diagnosis of food allergy in infancy rests on the typical clinical features, supported by specific IgE skin or blood testing. Most infants eventually outgrow their food allergies with the notable exception of peanut and tree nut allergy.

Peanut & tree nut allergy

Peanut and tree nut (e.g. brazil, cashew & hazel nuts, walnuts, almonds, pistachio etc) allergy came to the attention of the medical community in the UK in the late 1980's and early 1990s. Initially, it was thought to be a rare condition, but the prevalence of peanut allergy rose significantly in the 1990s such that now approx 1:75 pre-school children is said to be affected in the UK. There is great public awareness of the issue of peanut allergy both because of the precautions now taken e.g. in schools and commercial food suppliers and the small number of deaths that have occurred and received much media attention. Approximately 50% of peanut allergy sufferers will also report reactions to tree nuts. Some people are allergic to tree nuts but not peanuts, but the prevalence is not well defined and almost certainly varies between different tree nuts. Peanuts are in fact legumes and some peanut allergy sufferers will also react to cross reacting legumes including beans and peas.

What are the defining characteristics of peanut allergy?

Peanut allergy is often first noticed in infancy or early childhood, although onset can be at any age. It is usually a prolonged allergy, with sensitivity lasting into adulthood. Although there are published reports that up to 20% of affected children may outgrow this allergy this is not generally reflected in current clinical practice in the UK. For the most part we advise that one should assume peanut allergy is effectively a lifelong condition. It is recognised that there is a spectrum of severity of reactions with some individuals being exquisitely sensitive, reacting even to the smell of peanuts whilst others may be able to consume a small amount of peanut before reacting. The fact that severe reactions can be triggered by small amounts of nut antigen in some people causes great anxiety for patients and their families.

Allergic reactions to nuts are almost universally of very rapid onset. Typically the individual will spit out the offending food or vomit. Reactions often involve angioedema of the perioral region, tongue or larynx with resultant respiratory difficulty. People with asthma will often experience wheeze. Hypotension can be profound.

A popular misconception is that allergic reactions typically increase in severity over time and e.g. with peanut allergy that there is an inexorable increase in severity and that severe anaphylaxis will ultimately be unavoidable. This is not the case. In most people, if the circumstances and degree of exposure to allergen are similar, the reaction tends to be stereotypical. However there are a number of factors associated with increased risk of severe reactions and these are listed (Table 4). It is however important to emphasise that

the vast majority of patients with peanut and nut allergy, who have been properly assessed at a specialist clinic, practice careful nut avoidance and have an effective management plan in place which includes rescue medication, manage their condition very effectively[22]. A summary of our management advice for patients with peanut allergy is also provided (Table 5).

Although the potential severity of peanut allergy is widely recognised, deaths are fortunately rare. National audit data for the UK indicates that there are on average 2.6 deaths per year caused by peanut or tree nut allergy.[23,24]

Desensitisation

Desensitisation (or allergen immunotherapy) is a therapeutic strategy which is aimed at reducing the degree of allergic sensitisation of an individual patient. The basic approach is that the patient is exposed to minute amounts of the substance to which they are allergic on a regular basis, often over a prolonged period, typically three years. The result is that by regular, low dose exposure to allergen, the harmful IgE mediated allergic response is largely "switched" to an IgG (usually IgG4) protective response[25]. Allergen may be administered subcutaneously (SCIT), orally (OIT) or sublingually (SLIT). Pollen SCIT was widely practised in general practice the UK in the 1970s and 1980s however there were 17 deaths reported to the regulatory authorities and as a result, desensitisation is now highly regulated and restricted to specialist centres. In retrospect, it is felt that the deaths were at least in part due to inappropriate selection and monitoring of patients. It is worth noting that desensitisation has remained widely practiced in Europe and North America and is an effective therapeutic strategy[26,27]. Delivery of SCIT is however burdensome for both patients and doctors in terms of time commitment and precautions required. This is a major factor limiting its delivery in the UK. The advent, in 2007 of a licensed product for grass pollen SLIT (Grazax, ALK-Abello) has transformed delivery of grass pollen desensitisation. In our service, we have treated well over 100 patients in that time with good clinical effect on their hay fever symptoms and very few side effects. It is anticipated that OIT and SLIT will continue to be developed for a wider range of allergens. Recent trials from UK and North America provide encouragement that this may be an effective strategy for the management of nut allergy in the future[28,29].

Autoimmunity

Autoimmune reactions and diseases indicate that in certain circumstances, the normal immunological control mechanisms which are outlined above become defective. A number of mechanisms are thought to be responsible for this abnormal reactivity to "self-antigens". These include cross reactivity, molecular mimicry, provision of T cell epitopes, release of sequestered or cryptic antigens, failure of T cell regulation and anti-idiotype responses. The classical association between group A streptococcal infection and rheumatic heart disease is an example of "cross reactivity" in which the streptococci express antigens that are structurally similar to self antigens on cardiac muscle. Antibody and T cells specifically generated against the streptococcal antigen therefore cause damage to the structurally similar self proteins.

At a molecular level, the concept of "molecular mimicry" is also postulated. It is known that short molecular sequences (e.g. 5-amino-acid sequences) are commonly shared between microorganisms and self proteins. It is thought that both these mechanism may contribute to the development of autoreactivity. The potential linkage of foreign proteins (e.g. drugs or chemicals) to self proteins provides another mechanism for bypass of normal immunological control. B cells binding to the self-non-self complex have the potential to process and present the non-self component to T cells reactive to the foreign proteins. Thus it is possible for T cells to deliver inappropriate helper signals to B cells binding the self component, stimulating an autoimmune reaction. This is known as "provision of T cell epitopes". Furthermore, some self antigens are not normally exposed to cells of the immune system and are said to be "sequestered", e.g. lens proteins from the eye. Tissue damage can release such antigens and allow an immune response to occur e.g. after traumatic damage to one eye, the release of proteins can cause autoimmune damage to the other – **sympathetic ophthalmia**.

Cryptic antigens are those that are only released during the normal turnover of body proteins by antigen presenting cells. Because they are not normally expressed, tolerance does not develop and their release can allow the generation of autoimmune responses. It is likely that cryptic epitopes are normally only released in low concentrations; however coincidental factors such as infection or inflammation may be necessary to initiate the autoimmune response. T cell regulation has already been mentioned and a failure of T cell regulation (or suppression) has long been postulated as a mechanism for the generation of autoreactive responses. The balance of cytokines secreted in the microenvironment is important in influencing the nature of an immune response to a microorganism is therefore thought that the balance of T cell cytokine secretion in humans may be important in influencing autoimmune responses. Finally, the antigen binding sites of antibody molecules are known as **idiotypes** and it is possible that during a normal response to infection, a "second wave" of **anti-idiotype antibodies** is generated, directed not against the microorganism, but against these idiotypic sites, thereby generating auto antibodies

Two specific diseases highlight the importance of maintenance of central tolerance and effective regulatory T cell mechanisms[30,31]. In **Autoimmune PolyEndocrinopathy-Candidiasis-Ectodermal Dysplasia syndrome type 1 (**APECED Type 1) there are mutations in the autoimmune regulator gene (AIRE) on chromosome 21. These mutations lead to failure of apoptosis of autoreactive T cells and the consequent development of autoimmunity. Patients with **IPEX** (Immune dysfunction, Polyendocrinopathy, Enteropathy, X-linked) syndrome harbour mutations in the forkhead box P3 (FOXP3) gene in regulatory T cells, which leads to severe autoimmunity and immune deficiency.

In clinical terms, it is important to distinguish between those autoimmune reactions, (that may occur as a consequence of infection, surgical procedures, drug treatment or increasing age and are characterised by the detection of autoantibodies in blood) and autoimmune disease.

Autoreactivity may only be temporary; indicating that the immune system can regain control of autoreactive lymphocyte

clones after the "external insult" has been withdrawn. Autoimmune reactions are much more common than autoimmune disease. The detection of autoantibodies in blood, even in an unwell patient, does not therefore necessarily mean that the patient is suffering from an autoimmune disease, e.g 10% of the population over 70 years of age have detectable antinuclear antibodies in serum. Autoimmune disease is said to be present only when tissue damage and symptoms occur and autoreactive antibodies or T cells are detected.

Autoantibodies may be primary or secondary. Primary autoantibodies are rare in clinical practice and are defined as directly causing disease. Examples include the anti-TSH receptor antibody in Graves' disease, the anti-acetylcholine receptor antibody in Myasthenia gravis or the anti-voltage gated calcium channel blocking antibodies in Lambert Eaton Myasthenic syndrome. Secondary autoantibodies occur as part of an autoimmune process, may be associated with specific disease (and be diagnostically helpful), but do not directly cause disease. Examples of secondary autoantibodies include antinuclear antibodies in systemic lupus erythematosus and antimitochondrial antibodies in primary biliary cirrhosis.

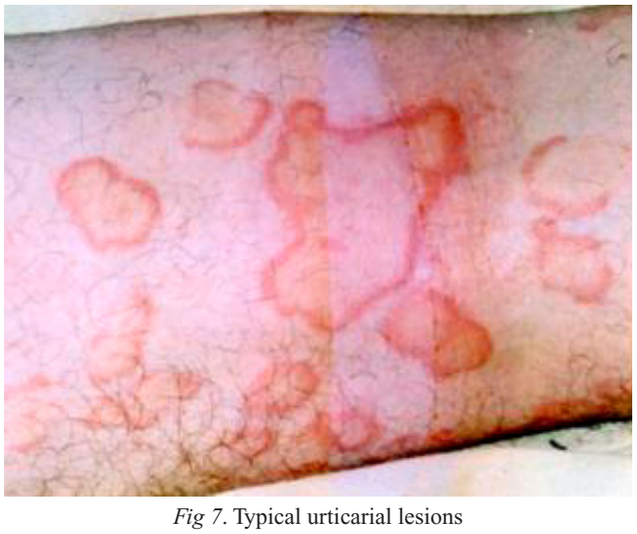

Fig 7. Typical urticarial lesions

Auto inflammatory disease

A further group of clinical conditions, characterised by disordered immunological responses, is gaining increasing attention. These conditions are typically characterised by regular fevers, lymphadenopathy, rashes, joint pain, mouth ulcers etc. They are often referred to as **Periodic Fevers,** and our understanding of their pathogenesis and treatment has increased rapidly over recent years[32]. Several have very specific genetic causes and respond exquisitely to therapeutic immunological intervention. **Familial Mediterranean Fever (FMF)** is one of the best known of these conditions and is characterised by recurrent fever, serositis (abdominal, chest or joint pain), typically beginning before the age of 18 years. It is caused by a mutation in the MEFV gene which encodes the protein pyrin, which normally acts to indirectly inhibit production of the inflammatory cytokine IL-1. Acute attacks are managed with analgesic and anti-inflammatory drugs and the long term administration of colchicines reduces the frequency and severity of attacks. **TNF Receptor Associated Periodic Syndrome (TRAPS),** previously known as **Familial Hibernian Fever (FHF)** (as affected patients seemed to share Irish ancestory,) is associated with mutations in the TNF Receptor gene (TNFRSF1A). It has similar clinical features to FMF, but patients respond very well to treatment with the decoy TNF receptor, etanercept. A number of other periodic fever syndromes exist; including hyper IgD syndrome (HIDS) and Muckle Wells/Familial Cold Urticaria syndrome (associated with mutations of MVK and NLRP3 genes respectively). In a number of these patients, specific immunological intervention with drugs such as the IL-1 antagonist Anakinra is proving particularly effective[33].

CONCLUSION

This mini-review has outlined the basic components of the immune system and how they work together to generate normal effective immune responses. I have also highlighted how the response may be defective through deficiency, over-reactivity (allergy) and dysregulation (autoimmune/ autoinflammatory diseases). Constraints of space dictate that each area has been touched on only superficially and therefore further suggested reading sources are listed for those who wish to explore these issues further.

The field of primary immune deficiency has been revolutionised by the identification of single gene disorders which have assisted in disease classification and led to specific success in gene therapy. Allergic disease is also increasingly well understood in terms of basic science and it seems likely that we are on the threshold of a series of new developments in the area or desensitisation which should bring enormous benefits to patients. The combination of increased understanding of basic immunological inflammatory mechanisms and the development of novel therapeutic agents continues to deliver new effective treatments for immunologically mediated conditions that were once thought to be untreatable.

For the clinician interested in the application of basic science to the investigation and treatment of a wide range of different diseases, affecting both paediatric and adult populations, it is difficult to think of a more exciting area of medicine.

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