An Introduction to Allergic Disease

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In Western countries, allergic diseases affect over 15 per cent of the population and impose a substantial physical and economic burden on the individual and on society. We are all endowed with the components needed to produce an allergic reaction, namely immunoglobulin E and other antibodies, mast cells, basophils, lymphocytes and pharmacological mediators. What is unclear is why some people never show an allergic response, why some have an occasional mild reaction, why some suffer lifelong debilitating allergic disease or, more rarely, why others react with severe and sometimes fatal anaphylactic shock.

In 1906, Von Pirquet defined allergy as ‘a specifically altered state following exposure to antigen’, a term that covered both untoward and beneficial immune responses. By common usage over the years, however, allergy has come to mean a disadvantageous immune response to extrinsic antigens. With the introduction of the Gell and Coombs classification of hypersensitivity reactions[1], the term allergy became almost synonymous with hypersensitivity of the immediate IgE type[2].

However, the clinician who regards allergic disease merely as an IgE response to a specific antigen will have to reconcile many anomalies. Not all allergic reactions are IgE-mediated; other types of antibody and delayed hypersensitivity responses are sometimes evident. Furthermore, non-sensitised individuals can develop severe, immediate, adverse reactions to drugs and chemicals without evidence of a specific immune reaction of any kind-pseudo-allergy.

Immediate Hypersensitivity Responses

Immediate hypersensitivity reactions usually occur following the interaction of antigen and specific IgE antibody.

Biological Properties of IgE

IgE has the Y-shaped structure common to all classes of immunoglobulin. The Fab fragments enclose the antigen-binding sites and the Fc portion contains those determinants that make IgE a unique class of immunoglobulin.

Certain aspects of IgE antibody synthesis are unusual compared with other immunoglobulin classes[3]. First, IgE antibodies are present only in minute amounts in the serum; this is true even in allergic individuals, although their circulating levels may be many thousand times higher than normal. Second, IgE is synthesised locally in the respiratory and gastrointestinal mucosa, suggesting an important role for such antibodies in protecting the host against agents likely to invade at these sites. Third, the antigens which readily stimulate IgE production differ in some ways from antigens stimulating responses of other immunoglobulin classes: for example, parasitic nematodes usually induce high titres of IgE antibodies whereas bacteria and viruses usually stimulate high titres of IgM and IgG antibodies but not of IgE.

The bulk of IgE in any individual is bound to the surface membranes of circulating basophils and tissue mast cells, via surface receptors recognising determinants in the Fc portion of the e-chain of IgE (FceR). The receptor is a glycoprotein of three sub-units: α, available to the extracellular environment; β, and a γ component believed to be linked to the β component, both of which are embedded in the plasma membrane and might protrude into the intracellular environment. Each mast cell possesses between 1 and 3 x 10^6 free binding sites[4].

The IgE bound to the target-cell surface is presumed to present its antigen-binding sites (Fab regions) to the micro-environment of the cell and is thus still able to react with specific antigen. The binding of IgE molecules by basophils and mast cells is very strong; this high affinity compensates for the low serum levels of IgE and its rapid catabolism (half-life of two days), allowing the biological activity of cell-bound IgE to persist much longer than in the free state.

The Mast Cell

Recent studies suggest that mast cells originate from pluripotential bone marrow cells under the influence of a specific thymus-dependent lymphocyte growth factor[5]. The mast cell is ovoid (length 10-30 µm) and contains many dense cytoplasmic granules. Evidence, based upon fixation characteristics, electron microscopic variations, staining responses, mediator content and response to pharmacological agents[6,7] indicates that mast cells are heterogeneous.

Mast cells are widely distributed but are noticeably present in connective tissue, particularly surrounding blood vessels and nerves. In the lung, for example, over 80 per cent of pulmonary mast cells are located in and around the airways, with the highest density being found in the peripheral airways. While most bronchial mast cells are located in the submucosa, it is those cells superficial to the basement membrane which assume particular importance in the pathogenesis of antigen-induced airways
constriction, since they are the cells that first become exposed to inhaled antigens[8].

**Triggering of Mediator Release**

It is generally accepted that the release of biologically active mediators is triggered when an antigen molecule interacts with two adjacent cell-bound IgE antibody molecules, so forming a bridge composed of IgE-antigen-IgE. This implies that the antigen must possess repeating antigenic sites per molecule, with a minimum of two sites. This interaction induces conformational changes in the cell surface membrane, activating intracellular enzyme systems and culminating in the release of the mediators of acute hypersensitivity. However, mediator release can also be induced by pre-formed IgE-antigen complexes, polymerised IgE without antigen, Fc fragments of IgE and by anti-IgE antibodies, suggesting that antigen is not always required for mediator release. More recently, it has been shown that the Fce receptors on the cell surface and their bound IgE molecules migrate as a complex on the cell membrane. Bridging of cell-bound IgE molecules will also bring these receptor sites into close proximity. Mediator release from mast cells can be triggered by antisera raised against the exposed regions of the IgE receptor sites[9] and by the (Fab')2 fragments of these antisera[9], but not by the Fab fragments, implying that it is the binding of a pair of receptor molecules which is primarily responsible for the activation of membrane-associated enzymes.

**Non-IgE Triggered Release of Mediators**

Non-IgE triggered release of mediators can cause clinically relevant disease: some known non-immune factors include naturally occurring endogenous substances (such as acetylcholine, α-adrenergic substances, prostaglandins and complement components) and exogenous chemicals and drugs which act by poorly understood mechanisms. These include some intravenous anaesthetic agents, radiocontrast media and plasma volume expanders. In most instances, prior exposure to the drug is not required and IgE antibodies are not involved. The most likely explanation is that such agents either directly activate the complement system, with release of the complement-derived anaphylatoxic fragments C3a and C5α[10], or directly trigger basophils and/or mast cells.

In most, if not all, allergic individuals, there is some degree of non-immune triggering in addition to the classical IgE-mediated release of chemical mediators.

**Effects of Mediators**

Mediators liberated from mast cells and basophils may be pre-formed (that is, present in cytoplasmic granules ready for release) or newly generated (that is, synthesised following the triggering stimulus and after the release of pre-formed mediators). Pre-formed mediators include histamine, lysosomal enzymes and proteases, neutrophil chemotactic factor, eosinophil chemotactic factors and heparin. Other mediators are newly generated from arachidonic acid via the cyclo-oxygenase and lipooxygenase pathways: these include prostaglandins (especially PGD2), thromboxanes, leukotrienes (LT) and platelet activating factor. The slow-reacting substance of anaphylaxis (SRS-A) is now known to be composed of a mixture of LTC4, LTD4 and LTE4, all of which have biological activity. These mediators all contribute to the variable clinical features of acute hypersensitivity.

**Late Phase Response**

It has long been known that a ‘delayed’ reaction can occur following mast cell degranulation. This late phase response begins 4–6 hours after the initial reaction, peaks around 12 hours and lasts 24 hours[11]. Such late responses are IgE-dependent and most frequently affect the lung and skin, which show a cellular infiltrate that includes eosinophils, basophils, mononuclear cells and neutrophils.

**Regulation of IgE Antibody Synthesis**

**Genetic Control**

Different strains of laboratory animals vary greatly in their capacity to produce IgE antibody after specific immunisation. Most strains require a large dose of antigen to produce an IgE response which, when it occurs, is transient and usually cannot be boosted by further antigenic exposure[12,13], a situation rather analogous to non-atopic humans. In contrast, certain strains develop unusually high levels of IgE antibody following immunisation with small doses of antigen and are capable of producing secondary responses as well[14], a situation similar to the atopic state in man.

In the mouse, the capacity to develop high titres of persistent IgE antibody to an antigen is genetically controlled and linked to the major histocompatibility complex (MHC) situated on chromosome 17[15,16]. Genes determining high responsiveness are dominant over those coding for low responsiveness to the same antigen. However, a strain which is a high responder to one antigen may be a low responder to a different, unrelated antigen. In humans, it has been postulated that analogous genes exist linked to the MHC (HLA) on chromosome 6. Evidence suggests that one such gene controls the immune response to ragweed antigen E[17]; thus, segregation analysis of two large families with atopic disease indicated autosomal dominant inheritance of seasonal ragweed allergy, the locus for this trait being HLA-linked.

**Regulation by T Lymphocytes**

Rats which normally produce high-titre IgE antibodies following immunisation with an appropriate antigen cannot do so if they are subjected to neonatal thymectomy before immunisation[18]. This defect can be overcome by giving normal thymocytes to the thymectomised animals, showing that thymus-derived lymphocytes are needed for the development of an IgE antibody response. Further-
more, co-operation between both T and B lymphocytes is essential for the synthesis of specific IgE antibodies[19-21]. While these studies illustrate the need for T lymphocyte participation in IgE antibody responses, the more intriguing question is what mechanisms normally prevent or minimise the development of excessive IgE antibody synthesis in strains of animals belonging to the low IgE responder phenotype. These strains do not have an innate incapacity to respond since experimental manipulations, such as appropriate doses of whole body irradiation[22], administration of some anti-T-cell antisera, or certain immunosuppressive drugs[23] can convert these animals from low to high IgE production. The enhanced IgE responder animals can be converted back to poor responders by the passive transfer of T cells from normal litter-mates[24] or by soluble factors derived from these cells[25]. The implication is that regulation of IgE antibody synthesis is dominated by a suppressor T cell regulatory or ‘damping’ mechanism which limits the extent of IgE antibody production following antigen sensitisation.

On the basis of this experimental evidence it has been argued that a defect of suppressor T cell function underlies the atopic diathesis in man. The evidence for this hypothesis rests on the observations that elevated IgE levels are found in a number of primary diseases with impaired thymus dependent immunity[26] and patients with certain diseases characterised by markedly raised IgE levels, such as the hyper-IgE syndrome or acute graft versus host disease, have reduced numbers of circulating suppressor T cells. However, no convincing reproducible differences have been demonstrated in suppressor T cell numbers and function in atopic subjects compared with controls[27], although in vitro IgE synthesis by lymphocytes from atopic subjects can be suppressed by the addition of T lymphocytes from non-atopic individuals[28,29].

Regulation of IgE Synthesis by T Cell Derived Soluble Factors

Numerous studies of rodent models have demonstrated specific T cell factors which selectively enhance or suppress the IgE response [see reviews 3,30,31]. In particular, Ishizaka and co-workers have shown that T cells bearing Fc receptors for IgE (FcERI+) produced these IgE-binding regulatory factors[32-34].

Recently, Marcelletti and Katz[35-38] have identified a new family of soluble mediators termed IgE-induced regulators (EIR), each of which participates in precise steps and on distinct cellular targets involved in regulating the IgE system. Exposure to IgE in vitro induces T and B lymphocytes to express FceRI and to secrete EIR that regulate FceRI expressed by other lymphoid cells. The remarkable feature of this complex regulatory network is the pivotal role played by the IgE molecule itself; it initiates the sequence of events and seems to control the eventual magnitude of its own production.

In man, only a very small proportion (<1 per cent) of circulating FcERI+ lymphocytes have been detected in non-atopic subjects, but the percentage is higher in allergic individuals[39,40]. It has recently been shown that activated human T lymphocytes also release IgE binding factors following incubation with IgE[41], although the functional roles of these factors are currently less well-defined than in the rodent model.

Pathogenesis of the Atopic Trait

An important insight into the aetiology of allergic disease was the observation that allergies tend to run in families. In 1923, Coca introduced the term ‘atopy’, best defined as a tendency, subject to hereditary influence, to spontaneously produce high levels of IgE antibodies to common environmental antigens.

Several theories attempt to explain why some individuals produce IgE antibodies to common environmental antigens while others do not. The increased incidence of IgA deficiency in atopic individuals and an increased incidence of atopy in IgA-deficient subjects have lead to the suggestion that a qualitative or quantitative deficiency of IgA at mucosal surfaces allows the absorption of excessive amounts of antigens capable of stimulating IgE synthesis.

However, it has been argued by Jarrett [42] that the stimulation of the immune system by antigen absorbed across mucous membranes, far from evoking deleterious IgE responses, normally maintains the IgE regulatory mechanism in an active state throughout life. An IgE response would occur only when the amount of antigen absorbed was below the threshold needed to stimulate IgE-suppressive mechanisms: this threshold would be very low in normal individuals but much higher in atopic subjects. Factors which influence the development of IgE suppressive immunocompetence include: first, factors inherent in the constitution of the individual—the genetic determination of maturity of the immune system with time and the eventual capacity to regulate IgE and other antibody responses; second, factors relating to antigen exposure—the form, dose, frequency and time of stimulation relative to the stage of immunological maturity; and third, the influence of the immune response of the mother.

It is an attractive idea that maternally transferred IgG may compensate for immaturity of the IgE regulatory system of the normal infant. Immunisation of female rats, for instance, induces a marked suppression of IgE responsiveness in their progeny, a state which persists for many weeks and well beyond the time that maternal antibody can be detected in the circulation[43]. It has therefore been suggested that one function of transferred maternal antibody is to suppress the IgE-responsiveness of the young animal to the potential antigens in its environment.

Administration of antigen to rats early in life, whether or not they have maternal antibody, also suppresses IgE responses[44]. As in the rat, IgE responses may be suppressed in both normal and atopic human infants fed with relatively large amounts of cow’s milk, whereas very small amounts stimulate rather than suppress the response[45,46].

Experimental work on animals has led Katz to propose a concept termed ‘allergic breakthrough’[3,30]. This
concept also considers that IgE production is normally kept at a low level following sensitisation by a damping mechanism which reflects the net balance of the suppressive versus enhancing factors involved. If, when some disturbance depresses the damping capacity beyond a critical level, the individual is simultaneously exposed to one or more appropriate antigens, the allergic breakthrough could result in excessive IgE antibody production specific to the relevant antigens, and the subsequent development of symptoms. In addition, the genetic predisposition of any individual must be considered as capable of response to the antigens concerned.

In children, onset or exacerbation of allergic disease often follows a viral respiratory infection. It is possible that upper respiratory tract infections are a common though transient cause of perturbation of the damping mechanism. In one prospective study, the onset of clinical and immunological evidence of allergy in children of allergic parents usually coincided with, or closely followed, upper respiratory tract infection, most commonly with para-influenza virus, respiratory syncytial virus or cytomegalovirus[47]. Certain endogenous events (e.g. marked shifts in steroid hormone production) can also contribute to changes in those regulatory mechanisms[48].

Delayed Hypersensitivity

It is now recognised that mast cells and basophils are also involved in delayed hypersensitivity responses. In mice, the expression of delayed-type hypersensitivity is critically dependent upon mast cells[49]; delayed hypersensitivity is preferentially elicited in sites rich in mast cells; mast-cell deficient strains of mice show poor delayed responses; and delayed responses are inhibited by drugs that either block mediator release by mast cells or deplete mediators.

It has been suggested[49] that activated T cells release an antigen-specific factor, quite distinct from IgE, that is transported via the blood to sensitise tissue mast cells. Upon meeting antigen, for instance at a site of contact antigen challenge, these mast cells release vasoactive amines which open gaps between adjacent endothelial cells and increase vascular permeability. Once this early response has occurred, other antigen-specific T cells enter the site, interact with antigen presented by Langerhans’ cells and induce the late response. This late response is independent of further mast cell mediator release but depends on the ability of these T cells to release chemotactrant lymphokines that recruit bone marrow-derived circulating leukocytes to infiltrate the reaction site. This early component of delayed-type hypersensitivity is optimal about two hours after antigen challenge. Many studies of delayed hypersensitivity have overlooked the early component and the biphasic nature of classical contact allergic dermatitis in experimental animals. Mast cell degranulation and the formation of endothelial gaps in delayed hypersensitivity reactions in man[49] suggest that an analogous process may well be involved in human contact dermatitis.

There appears to be an inverse relationship between the frequency of mast cells and basophils in various species. It has been suggested that both are supplementary cells with similar functions but the basophils, being quickly-mobilised, short-lived cells, represent an appropriate initial response in delayed reactions, while in the more chronic responses in man they give way to mast cells[50]. This certainly appears to occur in renal allograft rejection, allergic contact dermatitis and atopic dermatitis[51].

Diagnostic Tools in the Investigation of Allergic Disease

There is no substitute for a thorough history. A detailed history should suggest a provisional diagnosis and indicate the most suitable procedures needed to confirm this diagnosis. Two important questions are whether allergic symptoms are seasonal or perennial and whether they are worse indoors or outdoors.

Seasonal allergies in the UK are usually caused by pollens and, in general, trees pollinate first, followed by grasses and then weeds. Moulds sporulate during the grass and weed pollen season; this may cause diagnostic difficulty since moulds occur on both indoor and outdoor plants. Perennial allergies are most likely to be caused by house-dust mite, foods, animals and yeasts.

Although a family history of atopic disease will reinforce other evidence of an atopic trait, it will not provide any clue as to the specific sensitivities of the patient under investigation.

Laboratory Investigations

All laboratory tests can be graded according to their value in the care of patients. Some tests are essential for diagnostic or prognostic purposes, some are useful, while others are of interest only for research purposes. Some tests are absolutely useless if requested in inappropriate circumstances.

Total IgE Levels

A raised serum IgE level provides an objective measure of an atopic state but gives no pointer to the cause of the symptoms. IgE levels will, however, help to identify the patient at risk, whether or not he or she is symptomatic. While many variables other than IgE contribute to the clinical features of allergy in adults or older children, the serum IgE level alone may be a helpful diagnostic and predictive tool during the first two years of life[52]. At this early age, the distinction between atopic and non-atopic individuals is much clearer. In the atopic child the serum IgE level rises earlier and climbs higher than in normal children. Total serum IgE levels can therefore be of value in infants and neonates with a positive family history of atopic disease and in infants with troublesome symptoms of suspected allergic origin[53,54].

The diagnostic value of serum IgE determinations in adults and older children is less clear-cut. High serum IgE levels often accompany atopic disease, particularly asthma, seasonal allergic rhinitis and atopic eczema. The
levels seem, in general, to be related to antigen exposure; the longer the period of exposure and the more antigens the patient is sensitive to, the higher the IgE level.

Serum IgE levels show a wide variation. Some 'normal' individuals may have raised IgE levels, but a low serum IgE does not preclude an allergic aetiology. Occasional patients are sensitive to one antigen: as a result, total IgE may be normal while skin tests or radioallergosorbent tests are positive.

Nevertheless, approximately two-thirds of non-atopic subjects but only 2 per cent of atopic patients have IgE levels below 20 U/ml. In contrast, almost two-thirds of atopic patients have levels in excess of 100 U/ml[55].

Serum IgE concentrations are also raised in non-atopic conditions, particularly parasitic infestation, and quoted 'normal' ranges for Europeans may not apply to residents from zones where parasites are endemic.

Measurement of the total IgE level is not essential in any clinical condition; instead it should be considered a rough diagnostic tool, most useful when the clinical picture is ambiguous or other test results are difficult to evaluate. In clinically convincing cases of allergy, the test adds nothing.

Antigen-specific IgE Antibodies

The most widely used technique for detecting and measuring antigen-specific IgE antibodies is the radio-allergosorbent test (RAST: Pharmacia Diagnostics). The RAST procedure is simple. A paper disc labelled with antigen is incubated with a small amount of test serum. After washing the disc to remove free unbound IgE, radio-labelled anti-human IgE is added. After further washing to remove free, unbound, radioactive label, the level of radioactivity attached to the disc is measured, the amount of antigen-specific IgE being directly related to the counts obtained. The use of a specific antiserum to human IgE means that antibodies of other immunoglobulin classes are not recognised in this assay.

RAST results are interpreted by comparison with a reference sample run in parallel and classified as negative (class 0), borderline (1), positive (2), strongly positive (3), or very strongly positive (4).

The diagnostic value of RAST is often assessed by comparison with skin testing and nasal or bronchial provocation tests. While the overall agreement between RAST and such tests is about 75-85 per cent, agreement is higher in patients with moderate to severe hypersensitivity but considerably lower for milder hypersensitivity. The usual type of discordance is a positive RAST with a negative skin or provocation test. In most cases, the mild degree of hypersensitivity detected by RAST is of doubtful clinical importance. In some cases, however, a negative RAST is found in a patient with positive skin or provocation tests, highlighting the danger in assuming that serum IgE specificities necessarily reflect those of tissue-fixed IgE.

The interpretation of RAST results is hampered by a number of pitfalls. (a) The commonly used commercially available kit yields results related to a single reference serum. For this reason, comparison with other results is almost impossible. (b) RAST classes for different antigens are not comparable. (c) Most antigen preparations are impure or inadequately defined. (d) Antibodies of other immunoglobulin classes, particularly IgG, can interfere with IgE binding.

RAST assays are expensive and time-consuming. They are not essential in any clinical condition and have a limited role in the investigation of patients with putative allergy[56]. Skin testing is a cheaper and quicker way of identifying those antigens to which the patient can mount an IgE-mediated reaction. RAST testing need only be performed when skin testing is unreliable or contraindicated: for example, in very young children; in patients with severe and extensive eczema or dermographism; in those in whom symptomatic treatment may influence skin reactions; in patients with exceptionally high levels of sensitisation in whom even skin testing is potentially hazardous; and in some patients with 'food allergy' where skin testing may be unreliable. Properly used, RAST testing can reduce the frequency of provocation tests.

Skin Tests

Prick testing is a traditional and sensitive diagnostic tool in allergic disease. The assumption is made that skin responsiveness reflects and correlates with the reactivity of the mucous membranes of the bronchi, nose and other target organs. However, there is no clear evidence that this is so.

Many factors can affect prick test reactivity. Variability in the potency of antigen extracts may be considerable among batches from different suppliers or even in lots from the same source. Differences in the stability and purity of extracts also affect biological potency, and the preservatives used to improve stability and prevent contamination, for example phenol, can have non-specific irritant effects. The magnitude and reproducibility of the response is often influenced by the biological variability of the skin. In healthy individuals, skin reactivity is greatest at about the third decade and declines from the fifth decade onwards; skin reactivity may vary with circadian rhythms and menstrual cycles and, in the presence of dermographism, there will be positive skin tests to all antigens, including negative saline controls.

Despite these hazards, clinical studies have shown that prick tests provide good specificity (few false positives) and good sensitivity (few false negatives) in patients with moderate or high degrees of sensitisation.

Histamine Release Assays

Human basophils which have fixed IgE antibodies will degranulate on the addition of specific antigen; degranulation can be scored morphologically or by measuring histamine release. In practice, basophils from a normal (non-allergic) individual or animal cell preparations (rat mast cells, chopped monkey lung) are passively sensitised with serum from an allergic patient. Although the method is reliable when performed with appropriate controls by experienced investigators, present application of the method is limited by the need for large volumes of fresh
blood (or animal tissue) to provide sufficient numbers of functioning basophils.

**Provocation Tests**

Target organ challenge with a suspected antigen is, in theory, the best test of allergy because it most closely simulates the physiological effect of natural exposure. As routine clinical procedures, however, provocation tests are of limited value because they are time-consuming, affected by the medication being taken by the patient, and cannot be used in a symptomatic patient. In the case of bronchial provocation tests, a major source of misleading results is the tendency of some patients with hyper-reactive airways to respond to numerous non-immunological stimuli, such as impurities or preservatives in the antigen extracts.

Nasal challenge is useful in patients with a history suggestive of allergic rhinitis. Some patients have negative RAST or skin tests yet show positive reactions to nasal challenge, reflecting the ill-defined nature of these antigens and the varying potencies of available extracts. Specific IgE antibodies can sometimes be demonstrated in the nasal secretions. Major problems with nasal provocation tests include their lack of value if the nasal mucosa is already congested, or if the patient is taking medication, the subjective nature of the criteria required for a positive result and the need to limit testing to one antigen at a time.

Food allergy often presents a difficult diagnostic problem. A high index of clinical suspicion is required, since skin tests with dietary antigens, total IgE levels and RAST often fail to correlate with the clinical picture. A diagnosis of food allergy can be confirmed only by observation of symptomatic relief on dietary withdrawal of the offending food and the return of symptoms following food challenge.

**Unorthodox Tests**

There are a number of other tests which, in spite of numerous and sometimes extravagant claims, have never been shown to be of value[57,58]. These include pulse testing, sublingual food testing, leukocyte cytotoxicity, intradermal skin testing and bogus methods such as radionics, radiesthesia, radionic hair testing and hair trace metal analyses[58].

**Conclusion**

The appreciation of early and delayed aspects of IgE mediated allergic reactions and the involvement of mast cells and basophils in delayed-type responses suggest that conventional immunological dogma separating immediate and delayed hypersensitivity from one another by focusing on their time course and suggesting that they are unrelated may no longer be adequate to explain the manifestations of allergic diseases.

The identification of factors regulating IgE synthesis gives hope of a potential therapeutic handle for future manipulation of the IgE antibody system. The recent availability of long-term T cell lines and T cell hybridomas which secrete IgE binding factors should make it possible to characterise these factors and study their modes of action.

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The ‘Langdons’—Three Distinguished Fellows

Langdon recurs in the names of John Langdon Haydon Langdon-Down, Sir Walter Langdon Langdon-Brown and Sir Geoffrey Langdon Keynes. It is therefore of interest to enquire whether these three distinguished Fellows of the College were related.

John Langdon Haydon Langdon-Down (1828–96), remembered eponymously for his description of mongolism in 1866, was the son of a Cornish apothecary, in whose family tree the names Langdon and Haydon frequently appear. John Langdon-Down’s sister, Jane Elizabeth Down, married the Reverend David Edward Ford; their daughter, Ada Haydon Ford, married the Reverend John Brown, whose son, Walter Langdon Brown (1870–1946) became consulting physician to St Bartholomew’s Hospital and later Regius Professor of Physic at Cambridge. When he was knighted in 1935, he altered his name to the hyphenated version, Sir Walter Langdon-Brown. In his memory, his widow founded the Langdon-Brown Lecture at the Royal College of Physicians. Sir Walter Langdon-Brown was a great-nephew of John Langdon-Down. John Langdon-Down’s granddaughter, Stella Langdon Down, married another distinguished Fellow, Lord (Walter Russell) Brain, who was President of the College (1950–57).

Sir Walter Langdon-Brown’s sister, Florence Ada Brown, married John Neville Keynes, whose two sons were Lord (John Maynard) Keynes, the eminent economist, and Sir Geoffrey Langdon Keynes (1887–1983), famous as both surgeon and man of letters. Sir Geoffrey Keynes was a great-great-nephew of John Langdon-Down, a cousin of Sir Walter Langdon-Brown and a distant cousin of Lord Brain.

ALEX SAKULA

Fig. 1. Sir Walter Langdon-Brown.