Scientific Basis of Clinical Practice

Immunological Deficiency and Impaired Resistance to Infection

K. W. WALTON

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The preservation of an internal environment unaltered by external influences is an essential requirement for all living things. In man this is partly secured by the interplay and successive interaction of several processes designed to prevent the entry, or to secure the elimination, of extrinsic noxious agents (Table I). Integrity of the skin and mucous membranes, reinforced by non-specific bactericidal secretions (for example, lysozyme in tears), constitutes a first line of defence. Once "foreign" material gains access to the tissues a clearing mechanism comes into action. In primitive unicellular life-forms phagocytosis and digestion or re-excretion is the only form of protection. In more complicated multicellular organisms this process is reinforced by the more complex mechanism of inflammation and by immunological reactions.

TABLE I—*Factors in Resistance to Invasive Infection*

Non-specific:
Integrity of skin and mucous membranes
Non-specific bactericidal secretions (for example, lysozyme in tears, saliva, etc.)
Clearing mechanism (phagocytosis)
Reactive mechanism (inflammation)
Specific Immune Response:
Humoral—primary and secondary antibody responses (B-cells)
Cellular—delayed hypersensitivity reaction (T-cells)
Reinforcement by interaction of complement components

In recent years it has been recognized that innate (genetically-mediated) or acquired deficiencies may occur at different points in these inter-related processes to give rise to a broadly similar clinical picture of impaired resistance to infection.

Failure of Protective Mechanism

This may occur in two main forms. Firstly, failure of clearing mechanism, as is seen in rare cases of congenital aleukia; in agranulocytosis (idiopathic or secondary); and after massive whole body irradiation, though in the last other mechanisms are also affected. The second type is failure of inflammatory reaction, which is seen in a primary form as chronic granulomatous disease,[1] which may be inherited either as an X-linked recessive[2,3] or as an autosomal recessive[4] defect. The condition is manifested in infancy with skin sepsis and abscesses, suppurative lymphadenitis, and enlargement of the liver and spleen. Apparently paradoxically, the lesions are not caused by the common pathogens but by bacteria that are relatively avirulent in healthy children. The essential defect has been shown to reside in the phagocytic cells, which ingest the bacteria but lack certain essential intracellular enzymes to detoxicate the particular kinds of bacteria concerned (catalase-positive organisms) and digest them. Deficiencies of at least three separate enzymes—NADH oxidase,[5] glucose-6-phosphate dehydrogenase,[6] and glutathione peroxidase[4]—have been reported in different cases. In these patients true immunological reactivity (the capacity to make antibodies and to produce cell-mediated immunological reactions) is intact—in fact this is stimulated by persistence of antigen, so that hyperglobulinaemia, proliferation of lymphoid tissue, and (as the name implies) granuloma formation are prominent. In some patients with a similar clinical picture it has been suggested that the defect is not in the leucocytes but is deficiency of a serum factor necessary for leucotaxis.[7]

Even when the clearing mechanism is intact, some extrinsic materials resist digestion or rapid elimination. Such materials may serve as antigens, evoking the next stage of the defence process—the immune response.

Normal Immune Response

Immunological reactivity is mediated through humoral and cellular components. The humoral component is manifested by antibody production. Antibodies are found in a group of plasma proteins which are functionally and physicochemically heterogeneous but which share certain characteristics in common so that they are known collectively as immunoglobulins (Igs). At present, five classes of immunoglobulin are recognized (Table II).

In response to primary antigenic challenge antibody activity ordinarily first appears in association with IgM, a macroglobulin which is predominantly intravascularly distributed and which has a rapid turnover rate. As antigen is eliminated from the body the output of IgM antibody wanes. In the later stages of the

TABLE II—*Some Characteristics of Human Immunoglobulins*

Class	Sedimentation Constant in Ultracentrifuge	Molecular Weight	Concentration in Normal Serum (mg/100 ml)	Antibody Activity
IgG ..	7S	150,000	800–1500	Antibacterial Antiviral etc.
IgA				
Monomer	7S	150,000	100–400	Antibodies in bodily secretions and serum
Dimer	9–11S	400,000		
IgM ..	19S	900,000	50–200	Macroglobulin antibodies
IgD ..	7S	150,000	1– 40	? (Antibodies to insulin reported*)
IgE ..	8S	196,000	0·01–0·04	Reaginic antibodies

*See reference No. 8

Department of Experimental Pathology, The Medical School, Birmingham
K. W. WALTON, M.D., F.R.C.PATH., Professor of Experimental Pathology

primary response, and with subsequent exposure to the same antigen, antibody response occurs in association with other Igs, depending on the portal of entry of antigen into the body and the nature of the antigen. In most circumstances IgG antibody predominates quantitatively and appears to be the main instrument of immunological "memory". In extravascular secretions (tears, saliva, colostrum, and intestinal and pulmonary secretions) antibody activity is mainly expressed in IgA molecules. But in response to certain allergens (for example, pollen or horse-dander) the special kind of response known as reaginic activity is expressed in IgE molecules, which are therefore increased in concentration in the serum in allergic asthma, hayfever, and certain kinds of skin reactivity (for example, atopic eczema). Little is as yet known of the special function of IgD but antibodies to insulin have been shown to be of this class.[8]

Antibodies are produced by plasma cells present in lymph nodes, spleen, bone marrow, and other reticuloendothelial tissues. The production of each immunoglobulin class may be shown to be carried out by separate cells or groups of cells in the lymphoid tissue at these sites.

CELLULAR COMPONENT

The cellular component of the immune response is mediated through the small lymphocyte. These cells appear to be capable of migrating freely into tissue compartments and even over the surface of or within other cells (emperipolesis[9]). The work of Gowans and his associates[10] has shown that lymphocytes recirculate through lymph nodes, spleen, and other sites via the lymphatic channels and blood stream so that they have maximal opportunities for contact with antigen. At sites where insoluble or "indigestible" antigen persists, in conjunction with macrophages, they give rise to the tissue reaction described as a "granuloma." In some lymphocytes sensitized by antigen the "memory" of antigenic exposure appears to be retained for an indefinite period. Renewed exposure to antigen produces an accelerated and augmented response, even in vitro, with enlargement and proliferation. It is currently accepted[11] that certain forms of immune response (for example, "delayed" or "tuberculin-type" sensitivity, contact dermatitis, homograft reactions, and certain autoimmune responses) are mediated by a cellular and not a humoral response.

SPECIES DIFFERENCES

In some species (for example, in birds) the two components of the immune response are particularly clearly delineated and appear to be under the control of separate functional units—namely, the thymus controlling cellular immunity, and a lymphoid organ in the gut (the bursa of Fabricius) controlling the humoral component. In animals which have undergone thymectomy at birth the cortical areas of lymph nodes and the periarteriolar lymphoid sheaths in the spleen are denuded of lymphocytes. The depleted areas are thus known as "thymus-dependent" areas and the cells normally populating them as "thymus-derived" cells (T-cells). Germinal centres and the medullary regions of lymph nodes and spleen are much less affected. Impairment of graft rejection and of delayed hypersensitivity is found in these animals, but the capacity to produce antibody is less affected On the other hand, in chickens from which the bursa of Fabricius has been removed before birth, immunoglobulin levels are low, the production of antibody is diminished or abolished, and the formation of germinal centres formation is impaired The cells concerned are therefore known as "bursa-derived" cells (B-cells).

In man and other mammals there is no convincing evidence of the presence of a structure analogous to the bursa.

However, cells originating in the bone marrow appear to behave similarly to the bursa-derived cells of birds and are therefore also known as B-cells. Evidence has recently been put forward by Wilson and Nossal[12] that in man populations of B- and T-cells co-exist in normal peripheral blood—the B-cells accounting for about one-third of the total circulating lymphocytes. B-cells are recognizable because they carry a high surface density of immunoglobulin, while T-lymphocytes (and thymocytes) have very little.[13] It is suggested that the surface coat of B-cells can recognize antigen and that the latter serves as the stimulus to activity and proliferation of the cells. At suitable sites (germinal centres) the activated B-cells are thought to undergo further development into plasma cells, which are concerned with immunoglobulin (and antibody) production.

On the other hand, when suitably sensitized, T-cells—which form the preponderant proportion of the circulating pool of lymphocytes—are thought also to be capable of stimulation by antigen to proliferate, forming an enlarged population of primed antigen-sensitive cells, and possibly to co-operate in the response to certain antigens by stimulating B-lymphocytes to antibody production. Activated T-cells are thought also to release soluble factors influencing macrophages and altering vascular permeability.

Development of Immune Mechanism

Though lymphoid tissue appears early in fetal life, the normal fetus synthesizes little or no immunoglobulin in utero. Antibodies in the blood of the newborn at birth have been transferred transplacentally from mother to infant and reflect the mother's antibody pattern. These passively transferred antibodies are all of the IgG class. The other immunoglobulins do not cross the placenta and their full intrinsic production by the child occurs sequentially in the order: IgM (0-1 yr); IgA (10-12 yrs); IgE (over the age of 12). The initial absence of synthesis of Igs is presumably due to the sterile environment in which the normal fetus exists, and the consequent lack of stimulus to intrinsic Ig production. Little or no Ig or antibody is detectable even in maturing animals maintained in a germ-free environment. On the other hand, if the fetus is infected in utero after the 20th week of gestation (as in rubella, congenital syphilis, or toxoplasmosis) then antibodies of fetal origin are demonstrable at birth. Normal development of the immune response is therefore a reaction to the stimulus of emergence into an environment full of antigenic material.

Immunological Deficiency Syndromes

Since Ig synthesis is not established at birth hypogammaglobulinaemia is a normal phenomenon between the second and sixth months of life. But in some infants there may be further delay in maturation of Ig-producing cells leading to a persistent and deepening hypogammaglobulinaemia with increased susceptibility to infection. This delay in production may affect IgG alone, or IgG levels may be normal while IgA or IgM levels, or both, may be low.

As distinct from this maturational delay in Ig production (which is usually transient), persistent immunological deficiency may occur in primary or secondary forms and may involve the humoral or cellular components separately or in combination. A large variety of conditions associated with immunological deficiency has now been described. Since the precise point of breakdown of the normal mechanism has not been identified in all cases, the classification of these diseases presents difficulties.[14 15] This account will be limited to a few of the more clear-cut conditions with passing references to others (see Table III).

PRIMARY IMMUNOLOGICAL DEFICIENCIES

Swiss-type Hypogammaglobulinaemia (Thymic Alymphoplasia)

This is the most severe variety, since it combines deficiency of both cellular and humoral immunity and is usually fatal before

TABLE III—*The Lymphocyte Cell-lines Affected in Some Immunological Deficiency States*

Type	Immunological Features	Cell-lines Affected (A = abnormal; N = normal)		
		B-cells	T-cells	Stem-cells
Transient hypogammaglobulinaemia of infancy	Delayed maturation of Ig formation (IgG primarily affected)	A	N	N
Swiss-type hypogammaglobulinaemia	Lymphopenia; hypoplastic thymus and lymphoid tissue; no detectable Igs or antibodies; defective delayed hypersensitivity and graft rejection	A	A	?A
Bruton-type hypogammaglobulinaemia	Persistent hypogammaglobulinaemia involving one or all Ig classes in boys; delayed hypersensitivity and graft rejection are slow but present; normal thymus; hypoplastic lymphoid tissue devoid of plasma cells	A	N	N
Hypogammaglobulinaemia with B lymphocytes	Persistent hypogammaglobulinaemia in both sexes and at varying ages; normal thymus, normal cellular immunity; lymphoid tissue normal or hyperplastic but lacking plasma-cells. Nearly normal numbers of B lymphocytes with surface recognition Igs responsive to antigen but incapable of plasma-cell differentiation	A	N	N
Di George syndrome	Normal Igs and antibody response to bacterial products; lymphoid tissue shows depletion of thymus-dependent areas; thymic agenesis associated with parathyroid hypoplasia; defective cellular immunity	N	A	N
Wiskott-Aldrich syndrome	Superficial infections, eczema, otitis media, thrombocytopenia, progressive lymphopenia; thymus normal; lymph nodes show progressive depletion of paracortical lymphocytes; IgA levels raised and IgM levels decreased in some cases. Macroglobulin antibodies deficient	A	A	?
Ataxia-telangiectasia	Igs normal in some but 50% with IgA deficiency and 70% with IgE deficiency; thymic aplasia; defective cellular hypersensitivity	A	A	?

the age of 2.[16] The pathological picture is striking. The thymus is difficult to identify and when found is a tiny epithelial structure without Hassall's corpuscles or thymocytes. The lymph nodes are very small and almost unrecognizable since they lack follicles and plasma cells and contain few lymphocytes. Similarly, lymphoid follicles and lymphocytes may be absent from the lamina propria of the bowel. Probably the condition arises from a deficiency of the primitive stem-cells which give origin to both B-cell and T-cell lines.

Bruton-type Hypogammaglobulinaemia

This is commoner and of varying severity.[17] The condition occurs as an X-linked recessive condition in boys and is characterized by reduced or absent production of one or more Igs associated with defective antibody production but normal cellular immunity. The thymus is normal but lymphoid tissue is deficient in all elements of the plasma-cell line (the final form of B-cells). There is impaired development of lymphoid follicles in lymph nodes, Peyer's patches, and appendix, and of Malpighian follicles in the spleen.

Clinically, the condition becomes apparent at about 6-9 months of age owing to the occurrence of recurrent infections (especially respiratory bacterial infections). These respond to therapy with antibiotics and gammaglobulin.

Immunologically, delayed hypersensitivity and graft rejection have been shown to occur slowly but to be present. Antibody formation to bacterial antigens is very poor or absent but response to viral antigens is often normal and vaccinations "take."

Arthritis has been described as a frequent complication (especially in the U.S.A.) and was originally described as being rheumatoid disease. However Lawrence *et al.*[18-20] found polyarthritis less commonly in a British series[19 20] and, noting an association with steatorrhoea in these cases, considered the joint changes to be more like the arthropathy which occurs, even in individuals with an intact immunological apparatus, as a complication of chronic intestinal disease.

The Bruton syndrome is taken to be a selective deficiency of production of the B-cells.[14]

Hypogammaglobulinaemia with B-lymphocytes

As opposed to the preceding variety of case, there is another group of patients of either sex and varying age who present with a superficially similar clinical picture of recurrent bacterial infections and who are deficient in plasma-cells and circulating Igs.[20] But in this group there are normal or even hyperplastic germinal centres in reactive or over-reactive lymphoid tissue. Nevertheless, closer examination of the cells in the germinal centres shows few, if any, mature plasma cells. In these patients, as in those of the Bruton type, a normal thymus is present and cellular immunity is normal. The designation has been coined for this group because it is suggested that though B-lymphocytes are present and respond to antigens by proliferation (as shown by the lymphoid hyperplasia), in this condition the cells cannot go on to the final phase of differentiation into plasma cells and hence Ig production and antibody response are deficient.[20]

The Di George Syndrome

The thymus, parathyroids, and thyroid all originate during embryonic development from the branchial pouches. This rare syndrome[21] is thought to be due to failure of development of the third and fourth branchial pouches, giving rise to associated agenesis of the thymus and parathyroids. From the immunological standpoint, the condition is a kind of mirror-image of the Bruton syndrome, in that lymphoid tissue and Ig levels are normal (suggesting the B-cell line is present and capable of full differentiation) but that thymic agenesis is associated with defective cellular hypersensitivity (deficiency of T-cells).

SECONDARY HYPOGAMMAGLOBULINAEMIA

This is seen after irradiation, during immunosuppressive therapy, and sometimes in association with lymphomas, chronic lymphatic leukaemia, myelomatosis, and macroglobulinaemia. In chronic lymphatic leukaemia it has been shown independently by two groups[12 23] that most (80% or more, as opposed to the normal 34% or so) of the circulating leukaemic lymphocytes are of the B-cell type—presumably diverted to neoplastic proliferation and thus not available for normal plasma-cell differentiation.

In myelomatosis and macroglobulinaemia the serum in the late stages of the disease may show a great increase of abnormal monoclonal myeloma protein or macroglobulin, respectively, with definite reduction of normal (polyclonal) Igs. It may be envisaged that proliferating clones of neoplastic plasma-cells develop at the expense of the tissue producing normal immunoglobulins.

OTHER CONDITIONS ASSOCIATED WITH IMPAIRED IMMUNITY

In addition to the conditions above, in which the nature of the defect is beginning to become clarified, in others the reason for associated immunological deficiency is not clear. These include the three conditions mentioned below. For references to others the reader is referred to reference 14.

The Wiskott-Aldrich syndrome[24 25] is a sex-linked recessive condition characterized by superficial infections, eczema, otitis media, progressive lymphopenia, and thrombocytopenia with bleeding (for example, bloody diarrhoea). No consistent pattern of immunological defect has been found though *raised* IgA levels with decreased IgM levels have been recorded in some cases.

Ataxia-telangiectasia[25-28] is also hereditary but, in this instance, characterized by multiple telangiectases and progressive ataxy starting in childhood or early adult life. Recurrent infections (especially repeated attacks of pneumonia) are common. Thymic aplasia is present and there is deficient transplantation immunity but no lymphopenia. Reduced levels or absence of IgA has been reported in about half the cases recorded and IgE deficiency has recently been noted in 11 out of a series of 16 patients.[29]

Chronic Mucocutaneous Candidiasis.—Infection with *Candida albicans* may occur in many debilitating diseases, including several varieties of hypogammaglobulinaemia. But in some patients with normal Ig levels but with chronic mucocutaneous lesions due to *Candida* infection it has been suggested that there is a specific loss of cutaneous reactivity (anergy) rather than an overall defect of the cellular immune mechanism.[30] Sensitized T-cells reacting with antigen are currently held[11 15] to release a number of soluble factors which are chemotactic for mononuclear cells, inhibit the migration of macrophages, are mitogenic for other lymphocytes, and increase vascular permeability. These factors are thought to provide the pharmacodynamic basis of specific cell-mediated immunity. Possibly deficiency of one or more of these factors (in particular, deficiency of the macrophage inhibition factor) may be the basis for the lesions of chronic mucotaneous candidiasis in some patients.[30]

Professor Charles Janeway concluded his Leonard Parsons Lecture[31] in the Birmingham medical school in 1965 by saying "It is our hope that, as knowledge of the inter-relation of the thymus, the lymphoid follicles throughout the body, and the peripheral lymphocytes increases, we may be able to activate or restore the immunological system to normal function." Some success[32 34] with grafts of thymus or bone-marrow, or both, from histocompatible donors has already been reported in some of these conditions. Probably with further progress in our knowledge of immunological mechanisms and of the ways in which these become deficient, greater insight into these rare but interesting cases and into methods for their treatment may be expected.

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Tomorrow's Buildings

New Liver Unit at King's College Hospital

FROM A SPECIAL CORRESPONDENT

On 16 February the Duchess of Gloucester was due to open a new purpose-built liver unit at King's College Hospital in London. Linked to the recently modernized 23-bedded ward for patients with liver disease on the floor below, the new unit will be devoted entirely to research. It covers an area of 6,000 sq ft (557 sq m), and will provide adequate bench space for a team of at least 50 workers from various disciplines, including biochemistry, immunology, virology, and haematology.

The plans for the new unit were first drawn up in October 1970; building started in February 1971 and has just been completed. In designing the unit the architect (who was Mr.