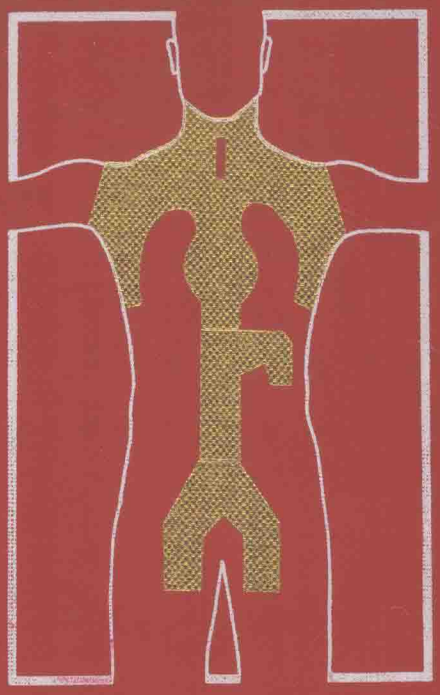

Primary and Secondary Immunodeficiency Disorders

EDITED BY

Ranjit Kumar Chandra

CHURCHILL LIVINGSTONE

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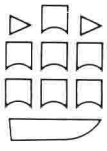

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Preface

The tiny bud of immunology has blossomed to full bloom. Immunologic techniques have found application in virtually all branches of investigative bioscience and immunologic mechanisms are invoked in the explanation of many human disorders. We owe much of our current knowledge in immunology to the pioneering observations of clinicians who correlated characteristic clinical patterns of disease to histomorphologic findings. It soon became clear that deficiency of an immunity mechanism involving an antigen-specific factor, such as antibody, or an antigen-nonspecific factor, such as phagocyte, results in impaired inflammatory response and susceptibility to frequent infection of varied severity. These primary defects of immunocompetence are often congenital and may be inherited. During the past decade, ever expanding knowledge of human primary immunodeficiencies and their counterparts in veterinary medicine has contributed to voluminous literature which is summarized in several excellent monographs and collected works. However, not even one of these texts deals with the commoner problem of secondary immunodeficiency except in passing.

It is now recognized that secondary deficits in immunocompetence also may result in enhanced susceptibility to infection. Nutritional deficiency, infection and infestation, cancer, immunosuppressive drugs, trauma, and radiation are associated with significant alterations in immunity. These pathological conditions affect a large portion of the world's population. In recent years, considerable clinical and experimental work has identified the nature and extent of secondary immunodeficiency in various disease states and clarified the etiopathogenetic mechanisms involved.

The stimulus for this publication came from the Scientific Group on Immunodeficiency convened by the World Health Organization in 1977. Many of the participants of that small meeting have contributed to this volume. The text has been written assuming a minimal initial knowledge of basic immunology. It describes the essential features of the primary immunodeficiency disorders and explains in detail those conditions that contribute to the much broader and more frequent problem of secondary immunodeficiency. The chapters are self contained and may be read in any order.

I wish to acknowledge the excellent contributions of my co-authors. The publishers were extremely helpful. The quiet and dedicated assistance of Enid O'Brien and Paula Kavanagh is sincerely appreciated. Shakti, Sujata, Amrita, Tarang and Rahul (who was born during the writing of Ch. 14) were generous in their patience.

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Contents

PART ONE

Introduction

1

Introduction

R.K. Chandra

Immunodeficiency disorders are a varied group of illnesses resulting from one or more primary or secondary abnormalities of host resistance. The main clinical consequences of impaired immunocompetence are infection, cancer, autoimmunity, allergy and failure to thrive, all of which can threaten survival. The main bulwarks of host protective mechanisms are depicted in Figure 1.1. These can be grouped into antigen-specific responses (cell-mediated immunity and immunoglobulin-antibody systems) and non-specific factors (for example, skin and mucous membranes, mucus, cilia, phagocytes, complement system, lysozyme, interferon and others). A breakdown in any of these barriers increases susceptibility to infection and other complications. For instance, the

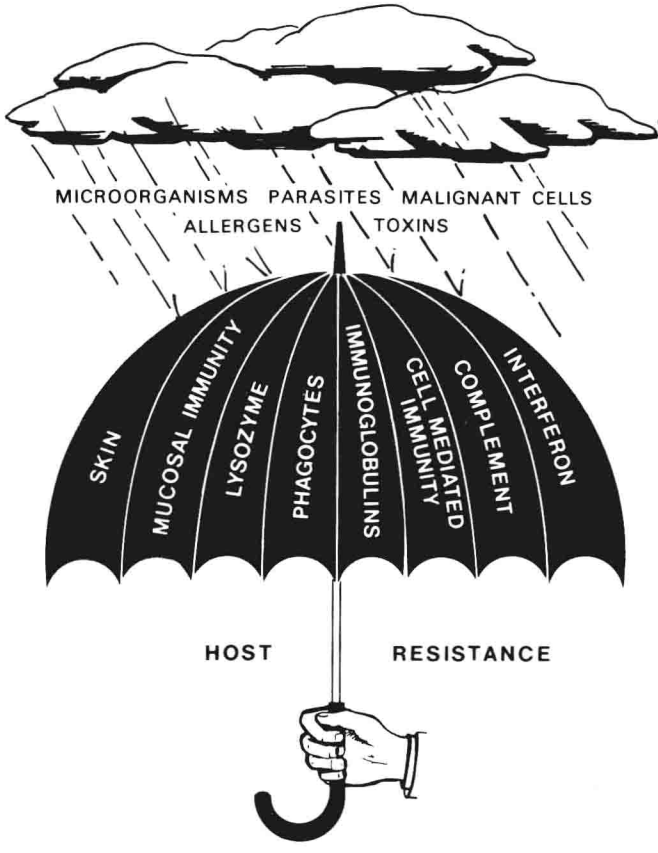

Fig. 1.1 Host protective factors. A concert of non-specific barriers and antigen-specific immune responses protect man from extraneous and internal injurious agents. (From Chandra R K 1981 Immunodeficiency in undernutrition and overnutrition. Nut Rev 39: 225–231.)

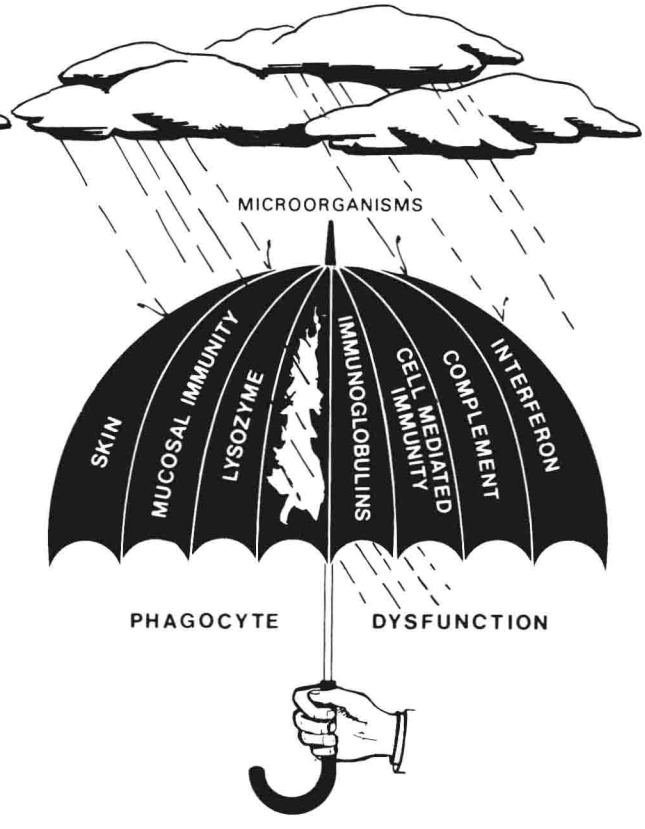

Fig. 1.2 Phagocyte dysfunction. Impairment of one protective mechanism may lead to recurrent severe infections affecting multiple systems. (Source as in Fig. 1.1.)

phagocyte defect in chronic granulomatous disease enhances the risk of pyogenic infections caused by certain bacteria and fungi (Fig. 1.2). At other times, a partial defect in one immune function may be compensated by other aspects of immunocompetence thereby producing no clinical manifestation at all. An example of this is selective IgA deficiency; the majority of individuals with this disorder are asymptomatic.

The initial stimulus for the study of immunity mechanisms was derived from careful observations made by astute clinicians. Patients with a defined set of clinical features were investigated comprehensively and a pattern of underlying immunologic abnormalities was discerned. These 'experiments of nature' led to the recognition and characterization of several primary immunodeficiency diseases. The primary immunodeficiency disorders generally are congenital and inherited, thus the affected patients often present to the health professional in infancy and early childhood. More recently it has been recognized that many systemic diseases disrupt the immunologic apparatus and impair immune responses. These include nutritional deficiencies and excesses, cancer, infections caused by bacteria and viruses, and parasitic disorders. Certain age periods are characterized by impaired immunity, e.g. the newborn and the elderly. Furthermore, certain therapeutic measures suppress the immune system, e.g. corticosteroids and cytotoxic drugs, irradiation, surgical trauma and burns. These secondary immunodeficiencies produce multiple rents in the protective umberalla of host defense (Fig. 1.3) and outnumber by far the primary immunodeficiencies.

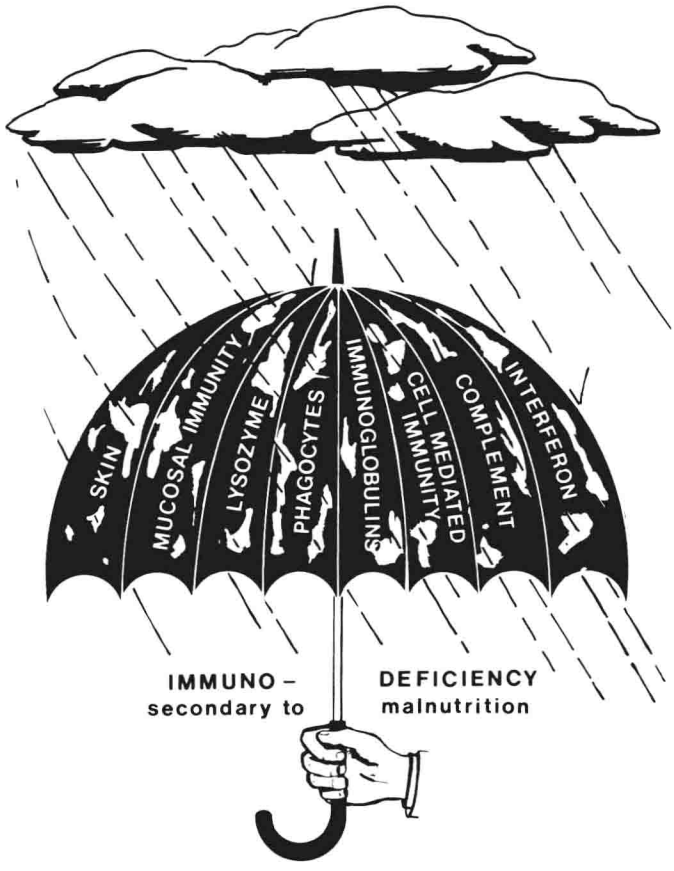

Fig. 1.3 Malnutrition. Nutritional deficiency robs the host of many host defenses. Some bulwarks of immunity are impaired more often and to a greater extent than others. (Source as in Fig. 1.1)

THE IMMUNE RESPONSE

Host reaction to an exogenous (e.g. microorganisms) or an endogenous (e.g. cancer cells) non-self antigen constitutes the immune response. If the individual has encountered the same antigens earlier, the immune response is quick and vigorous since a memory of past experience and sensitized clones of cells probably exist and readily recognize the familiar antigen. The main participants and mediators of the immune response are listed in Table 1.1. The major components of the reaction are phagocytes, antibody production, cytotoxicity and cellular interactions. The nature, dose and route of antigen exposure are critical determinants of the type and intensity of immune response generated.

Table 1.1 The main participants and mediators of the immune response

Cellular	Soluble
Lymphocytes	Mediators released by stimulated T lymphocytes ('lymphokines')
T	Immunoglobulins
B	Mediators produced by macrophages
Null	Complement components
K cells	Interferon
Macrophages	Lysozyme
Neutrophils	Histamine, slow reacting substance of anaphylaxis and other products of eosinophils and mast cells
Eosinophils and mast cells	

FUNCTIONAL ANATOMY OF THE IMMUNOLOGIC APPARATUS

Lymphoid tissues subserving the immune system can be subdivided into the central and peripheral components.

The *central lymphoid tissue* consists of the thymus and the bursa-equivalent, the cloacal lymphoid appendage in birds and probably the bone marrow in man. These two sites are responsible for the development of the two major populations of lymphocytes, the thymus-dependent T cells and the bursa-dependent B cells. The *peripheral lymphoid tissue* consists of the spleen, the lymph nodes and the mucosal-associated lymphoid aggregates in the intestine, respiratory tract and genitourinary systems. In these locations, more or less discrete areas contain mainly T lymphocytes or B lymphocytes although some overlap inevitably occurs.

Thymus

The thymus in man originates from the endoderm of the 3rd and 4th branchial pouches and is soon populated by lymphoid cells, precursors of T lymphocytes. There is a clear distinction between the outer cortex densely packed with thymocytes and the inner medulla containing reticular epithelial cells and characteristic Hassall's corpuscles and few lymphocytes. The lymphocytes undergo rapid proliferation and diversion in the thymus as if driven by a strong antigenic force although it is now established that cellular activity in this organ is independent of antigenic stimulation and presence of other organs. Most of the thymocytes die within the organ in 3–4 days. The biological purpose of this phenomenon is not clear. It may be a device for the elimination of the forbidden clones against 'self' antigens and for generation of antigen-response diversity. A few cells which mature within the thymus leave the organ to populate the peripheral lymphoid tissues. The complex though stereotyped process of the differentiation of cells into functionally mature T lymphocytes is facilitated by a soluble mediator, thymosin. This hormone-like substance can be demonstrated to be present in medullary epithelial cells and is released physiologically to convert primitive bone marrow cells into functionally competent T lymphocytes. The frequent association of thymic morphologic abnormalities with immunodeficiency syndromes clearly points to the important function of the thymus, particularly in early life.

Bursa and bone marrow

The removal of the bursa of Fabricius has a marked effect on immunoglobulin levels and antibody production. In mice, lethal irradiation and reconstitution by selected immunocompetent cells has emphasized the role of different subsets of cells in the maturation of B lymphocyte lineage and antibody response. 89-Sr treatment of the bonemarrow knocks out a third (M) population of cells.

Spleen

The main function of the spleen is to filter the blood pouring into it. The white pulp consists of lymphocyte aggregates whereas the red pulp consists of columns of macrophages and sinusoids. The periarteriolar lymphoid collection is T cell-dependent, the germinal centers are largely B cell containing areas. Plasmablasts and mature plasma cells abound in the marginal zone. The unique morphology of the splenic pulp makes it mandatory for all pathogens and foreign particles to interact with various types of immunocompetent cells, including phagocytes, plasma cells and lymphocytes.

Lymphnode

The lymphnode has distinct zones of the cortex and medulla with the paracortical region in between. Lymphoid follicles mainly located in the cortex are sites of intense cellular activity involving B lymphocytes. On antigen stimulation, the primary follicles transform into secondary follicles consisting of a densely packed rim of B cells enclosing a germinal center containing macrophages, plasma cells and small lymphocytes. In patients with congenital hypogammaglobulinemia, the lymph nodes have few poorly developed follicles.

Cell traffic

The life span of peripheral blood lymphocytes varies from 3–4 days to as long as 20 years. Similar lymphocyte subsets with disparate life spans have been demonstrated in the spleen. It is likely that cell death is not a preprogrammed event but follows contact with an appropriate antigen. Many of the long-lived lymphocytes participate in recirculation from the blood into peripheral lymphoid tissues and then back into the blood. The whole cycle takes a few hours. Much of the information on cellular traffic has been gleaned from studies of efferent lymphatics draining lymph nodes and of the thoracic duct effluate.

IMMUNOREGULATION

Recent studies have highlighted the complexity and sensitivity of immunologic networks. To elicit an immune response to an antigen is generally host protective. At the same time, regulatory mechanisms must exist which keep the immune response within reasonable limits and terminate it at an appropriate time.

The physiochemical characteristics of substances which induce an immune response, 'antigens', include large molecular size > 10 000 daltons, protein in nature, presence of antigenic determinants on the outside of the three-dimensional conformation, and charged residues within the molecule. Some antigens induce antibody synthesis directly by stimulating the conversion of B lymphocytes into plasma cells and release of immunoglobulins. Other antigens require the help of T lymphocytes.

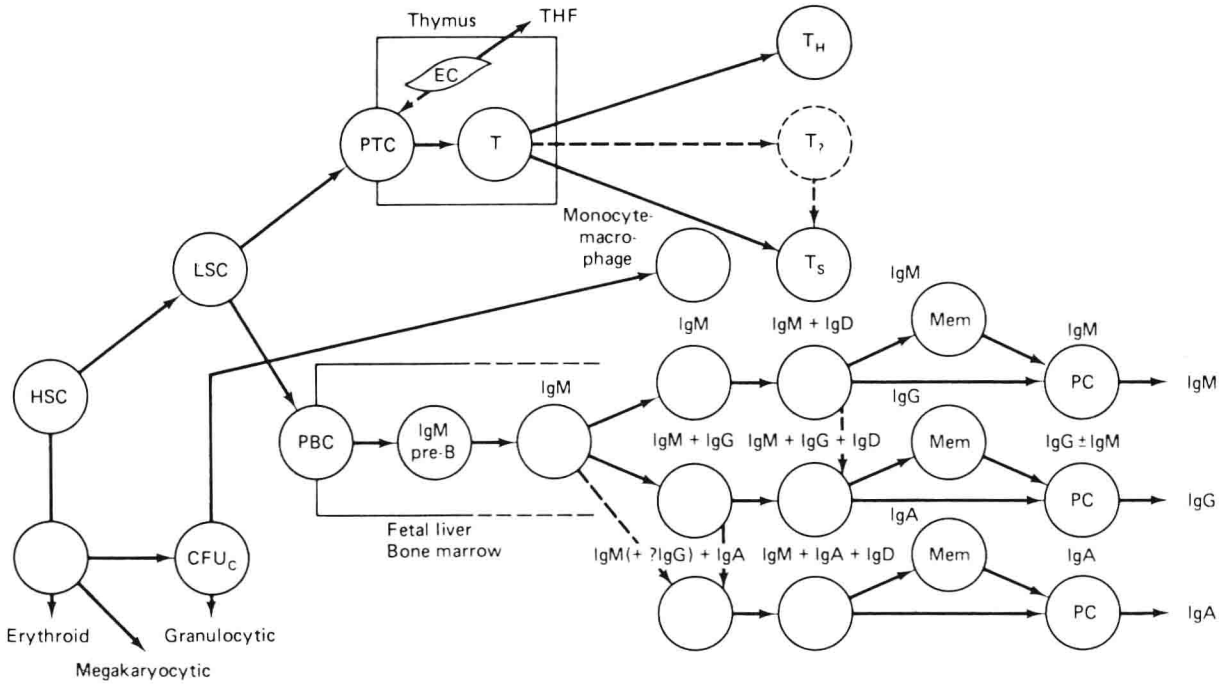

Fig. 1.4 Development of lymphocyte subpopulations. (From WHO Scientific Group 1978 Tech Rep Ser 630, Geneva.)

The dose of antigen is an important determinant of immune response. Repeated large doses induce a state of hypo- or unresponsiveness. This phenomenon of tolerance occurs earlier and more readily in T lymphocytes and is age-dependent. When the antigen is removed from the environment of the cell, tolerance wanes in a few weeks to months. Repeated subimmunizing doses may induce low zone tolerance mainly involving T lymphocytes.

Both cellular and soluble components of the immune response (Table 1.1) can provide either amplification or inhibition. The presence of different subsets of lymphocytes derived from the stem cell (Figs 1.4, 1.5) and their distinct functional attributes potentially capable of either

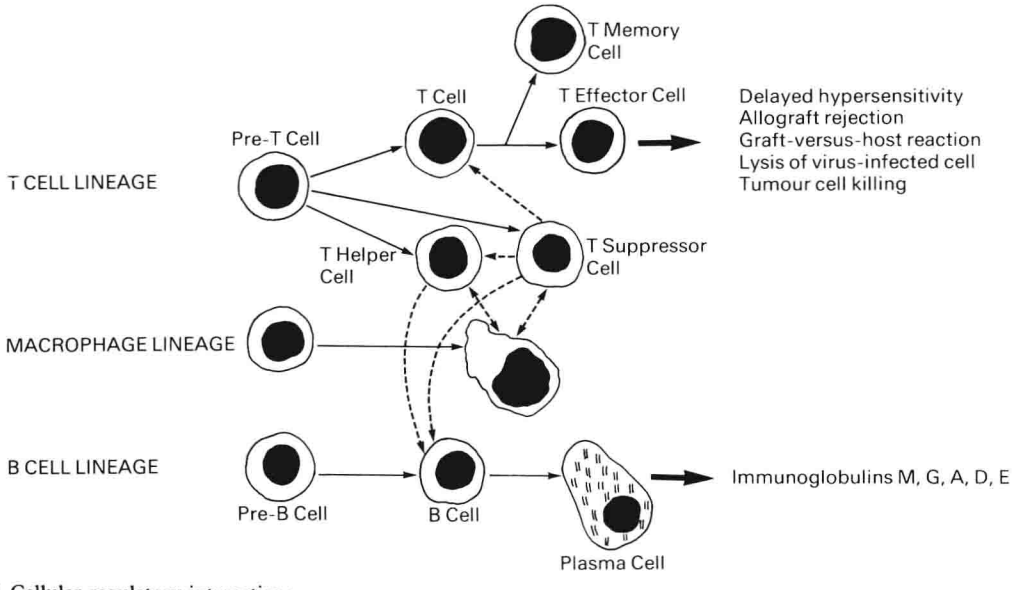

Fig. 1.5 Cellular regulatory interactions.

Table 1.2 Primary specific immunodeficiencies (from WHO Scientific Group 1978 Immunodeficiency WHO Tech. Rep. Ser 630.)

Designation	Usual phenotypic expression		Presumed level of basic cellular defect[a]	Known or presumed pathogenetic mechanism	Inheritance[b]	Main associated features
	Functional deficiencies	Cellular abnormalities				
1. Severe combined ID	CMI, Ab and phagocytes	↓ T, B, and phagocytes	HSC	Unknown	AR	—
(a) Reticular dysgenesia						
(b) 'Swiss type'	CMI and Ab	↓ T and B	LSC	Unknown	AR	—
(c) ADA deficiency	CMI and Ab	↓ T ± B	LSC or early T	Metabolic effects of ADA deficiency	AR	± chondrocyte abnormalities
(d) With B lymphocytes	CMI and Ab	↓ T (B lymphocytes without or with normal isotype diversity)	Early T ± early B	Unknown	X-linked or AR	—
(e) Others (see section 4.4)						
2. Thymic hypoplasia (Di George's syndrome)	CMI and impaired Ab	↓ T	Thymus	Embryopathy of 3rd and 4th pharyngeal pouch area	Usually not familial	(1) Hypoparathyroidism (2) Abnormal facies (3) Cardiovascular abnormalities
3. PNP deficiency	CMI ± Ab	↓ T	T	Metabolic effects of PNP deficiency	AR	Hypoplastic anaemia
4. ID with ataxia telangiectasia	CMI and Ab (partial)	↓ T and plasma cells (mainly IgA, IgE ± IgG)	Early T and defective terminal differentiation of B lymphocytes	Unknown ? Faulty thymic epithelium ? DNA repair defect	AR	(1) Cerebellar ataxia (2) Telangiectasia (3) Ovarian dysgenesis (4) Chromosomal abnormalities
5. ID with thymoma	Ab and impaired CMI (variable)	↓ pre-B and B ± ↓ T	HSC	Unknown	none	(1) Thymoma (2) Eosinopenia (3) Erythrobiastopenia (4) Aplastic anaemia
6. X-linked agammaglobulinaemia	Ab	↓ B	Pre-B	Unknown	X-linked	—

Table 1.2 (*cont'd*)

Designation	Usual phenotypic expression: Functional deficiencies	Usual phenotypic expression: Cellular abnormalities	Presumed level of basic cellular defect[a]	Known or presumed pathogenetic mechanism	Inheritance[b]	Main associated features
7. Transcobalamin II deficiency	Ab and phagocytosis	↓ plasma cells	Failure of terminal differentiation of B lymphocytes	Metabolic effects of vitamin B_{12} deficiency	AR	(1) Pancytopenia with megaloblastic anaemia (2) Intestinal villous atrophy
8. Selective IgA deficiency	IgA Ab	↓ IgA plasma cells ± ↑ Bα lymphocytes ± ↓ T	Terminal differentiation of Bα lymphocytes impaired	(1) ? ↑ T_S (2) ? ↓ T_H (3) ? intrinsic B-cell defect	Unknown > Ar > AD; frequent in families of patients with varied ID	(1) Occasional 18-chromosomal deletions (2) Anti-IgA antibodies
9. Selective deficiency of one other Ig class or subclass	Ab	↓ plasma cells ± ↓ T	Unknown	Unknown ? ↑ T_S	Unknown	—
10. Secretory piece deficiency	Secretory IgA Ab	↓ Intestinal IgA plasma cells	Mucosal epithelial cell	Unknown	Unknown	—
11. Ig deficiencies with Increased IgM	Ab	↓ IgG and IgA plasma cells, ↑ IgM plasma cells, ± ↑ B lymphocytes	Failure of terminal differentiation of Bγ and Bα lymphocytes	Unknown	X-linked or AR or unknown	—
12. Ig deficiencies with IgM production and without γ and α cells	Ab	Absent Bγ and Bα lymphocytes	Pre-B or B	Faulty isotype diversification	AR or unknown	—
13. Transient hypogammaglobulinaemia of infancy	Ab	↓ plasma cells	Impaired terminal differentiation of B lymphocytes	? ↓ T help	Frequent in heterozygous individuals in families with various severe combined ID	—
14. Antibody deficiency with normal or hypergammaglobulinae-	Impaired Ab for some antigens (mainly primary response)	↓ B	Pre-B or early B	? reduced clonal size or diversity	AR in some	—

15. Kappa chain deficiency	Ab	↓ B_k	Pre-B	Unknown	Unknown or familial	—
16. Wiskott-Aldrich syndrome	Ab to certain antigens (mainly polysaccharides) and CMI (progressive)	↓ T and B (progressive)	Unknown	Unknown	X-linked	(1) Thrombocytopenia (2) Eczema
17. Varied ID (common and largely unclassified)						
(a) Predominant Ig deficiency	Ab ± CMI	± ↓ B	Pre-B or B in some	(1) Intrinsic B-cell defect (2) Underproduction of B cells (3) ? ↑ T_S (4) ? ↓ T_H (5) Autoantibodies to B cells	Uknown or familial	—
(b) Predominant T-cell deficiency	CMI ± Ab	↓ T	Early T or T_H	(1) Unknown (2) Autoantibodies to T cells	Unknown or familial	—

↑ ↓ = Increase or decrease in level.
[a] HSC = haemopoietic stem cell; LSC = lymphopoietic stem cell.
[b] AR = autosomal recessive; AD = autosomal dominant.

Table 1.3 Complement deficiencies (From WHO Scientific Group. 1978. Immunodeficiency. WHO Tech Rep Ser 630.)

Deficiency	Inheritance[a]	HLA linkage	Symptom
Clq	AD	—	Infections
C1r	AR	—	SLE-like syndrome
C4	AR	+	SLE-like syndrome
C2	AR	+	SLE-like syndrome: vasculitis; polymyositis, arthritis
C3	AR	—	Recurrent pyogenic infections
C5	AR	—	SLE
C6	AR	?	Neisserial infection
C7	AR	—	Neisserial infection
C8	AR	—	Neisserial infection
C1 inhibitor	AD	—	Hereditary angio-oedema
C3b inactivator	AR	—	Recurrent pyogenic infection

[a] AR = autosomal recessive; AD = autosomal dominant.

Table 1.4 Primary phagocyte defects (From WHO Scientific Group. 1978. Immunodeficiency. WHO Tech Rep Ser 630.)

Designation	Functional defect	Affected cells[a]	Defective mechanism	Inheritance[b]	Associated feature
Chronic granulomatous disease	Bacterial killing	N, M	Peroxide and superoxide production	X-linked	Mothers have cutaneous lupus erythematosus
Chronic granulomatous disease	Bacterial killing	N, M	Peroxide and superoxide production	AR	
Myeloperoxidase deficiency	Bacterial killing	N	Peroxide and superoxide production	AR	
Leucocyte G6PD deficiency	Bacterial killing	N	Peroxide and superoxide production	?	
Leucocyte pyruvate kinase deficiency	Bacterial killing	N	?	?	
Chediak-Higashi disease	Mobility and bacterial killing	N, M	? cell distensibility	?	Hair pigment change, granules in phagocytes
Actin-binding deficiency	Mobility	N	Actin-binding	AR	
Shwachman's disease	Mobility	N	?	AR	Pancreas malfunction, bone abnormalities, etc.
Wiskott-Aldrich syndrome	Mobility	N, M	? Abnormal production of lymphocyte-derived chemotactic factor	X-linked	CMI defect
Others	Mobility	N	?	?	
Defective clearance	Particle clearance	M	?	Polygenic	

[a] M = macrophage; N = neutrophil.
[b] AR = autosomal recessive.

enhancing or suppressing the immune response provides fine tuning for the response in terms both of magnitude and duration. Following recognition of the antigen by T lymphocyte, specific antibody is synthesized and released by B cells-plasma cells. The antibody can bind to Fc receptors on macrophages, leaving the specific combining site still available for binding with additional antigenic molecules. Furthermore, recruitment of both T and B cells occurs with resultant increase in specifically sensitized cell population. Complement system and soluble mediators produced by activated macrophages and lymphocytes provide secondary nonspecific recruitment.