15 Immunology and Skin Diseases

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General Preface to Series

The impact of immunological thought on medical practice has been increasing at a steady rate now for nearly twenty years. There appear to be very few fields to which the immunologist cannot contribute. Initially the immunological approach was limited to assistance in diagnosis and in sera and vaccine production. New approaches in the field of therapy are not only in the use of vaccines, sera and immunosuppressive agents, but also in the more rational use of conventional therapeutic agents. Immunological knowledge is especially necessary in the field of tumour therapy, particularly in the balanced use of surgery and radiotherapy. Moreover, immunological knowledge in other fields has allowed us to understand more readily the mechanisms whereby a single aetiological agent can produce a wide range of different clinical manifestations. Different disease patterns occur depending on the nature of the immunological reaction causing tissue damage. A completely different symptom complex from reactions involving soluble immune complexes reacting with the complement cascade will be found in those involving the reaction of specifically sensitized lymphocytes with antigen as part of a cell-mediated or delayed hypersensitivity reaction.

As a massive amount of new scientific material accumulates in this field, the clinician is frequently left behind and perplexed. Each year a new scientific journal is published specializing in fields as diverse as immuno-genetics, immunochemistry or immuno-logical techniques. We have journals emanating from continents as well as countries. The wealth of material is often bewildering. Simple textbooks of immunology are often too simple, whereas review articles may be too complicated for the specialist physician or surgeon who wants a treatise on those aspects of the subject particularly relevant to his own field of interest. It is hoped that this series will fulfil some of these needs by giving comparatively short reviews that will lay emphasis on immunological subjects which should appeal to both clinicians and those working in clinical laboratories. The aim is to provide the busy clinician in a particular field of medicine with a short volume relevant to his practice written by a specialist. It should introduce the reader to the immunological approach to his subject and indicate how modern immunological thought might influence his day-to-day work in the wards or clinical laboratory.

JOHN TURK

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Preface

In the last decade many scientific disciplines have undergone rapid advances. Immunology is one of them. It has now become very widely pervasive, being involved in many biological and medical sciences. The fundamental advances made in immunology are being increasingly applied to dermatology as much as to any other branch of medicine. Such applications have helped us to solve many intricate problems of dermatology but still there are many skin disorders in which primary pathological events are not yet clear. However, recent knowledge of immunology has helped us to look even at these less clearly understood disorders in a new light. It has thus become very necessary for a dermatologist to have a thorough knowledge of immunology in order to understand immunological aspects of skin disorders.

The purpose of this book is to describe normal immunological processes and to show that derailment in these processes at various levels may cause a variety of skin disorders. But to produce a volume dealing with all aspects of the normal immune system as well as immunological aspects of skin disorders would be a very difficult, if not impossible, task. For this reason, and to keep the volume to a reasonable size, we have eliminated much traditional information. The contents and format of the book have been so prepared as to take into account only recent concepts of immunological aspects of dermatology.

The book begins with a chapter which describes the development and differentiation of highly diversified cells that defend the body against foreign substances and which are derived from a single kind of precursor. The second chapter deals with the skin antigens, most of which are the targets of immunological responses in various skin diseases. Early parts of the remaining chapters describe normal effector systems or cells that exist in normal individuals, whereas, in later parts of these chapters, efforts have been made to pinpoint the alterations at various steps of the immune system that cause particular skin disorders. Detailed description of pathology has been avoided. As a whole, though the depth of coverage of this book had to be sacrificed because of considerations of length of the book as well as its intended audience, it must be emphasized that the treatment of each topic remains thorough and reasonably sophisticated.

Amsterdam
1980

RHC
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Contents

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Introduction

For as long as medical history is recorded, it has been suspected that persons who recover from infectious disease do not suffer again from the same disease for a considerable period of time. In other words, they become immune. In 1890, Behring and Kitasato published a report in which they demonstrated that animals made immune to an infection developed a neutralizing principle in their serum. These observations created enthusiasm to isolate and identify the neutralizing principle. Later on, the inoculated substance that evoked an immune response was termed antigen and the neutralizing principle which appeared in the serum was termed antibody.

Following these discoveries, it was considered for a long time that immunity was concerned with the production of antibodies which react with antigen to neutralize its toxic effects. Scientists are now beginning to learn that this is far from the entire story, that the mechanism of immunity is much more complex than it was ever thought to be. It is recognized now that in response to foreign or self-antigens, micro-organisms, malignant transformed cells that result in cancer or transplanted foreign tissues, the body produces a number of immunological reactions. Some of these reactions are humoral and some cellular. Humoral reactions require antibodies, a complex group of proteins, namely complement, and some cells, namely polymorphonuclear leucocytes and macrophages. Cellular reactions require mainly macrophages and T cells. Other cells that would be involved are K cells (killer cells) which have been demonstrated to kill target cells sensitized with antibody *in vitro*.

Since antibodies are derived from B lymphocytes we prefer to call humoral reactions B cell (B lymphocyte) mediated immune reactions or B cell mediated immunity (BCMI). Cell-mediated reactions will be called T cell (T lymphocyte) mediated reactions or T-cell mediated immunity (TCMI). These reactions cover a large group of immunological and clinical phenomena that require effector T cells (sensitized T cells) and are independent of free serum antibodies and may or may not be dependent on macrophages. These two types of responses are summarized in Fig. 1.1.

Before we enter into the description of mechanisms of these two types of immune response, it will be worthwhile to give a brief description of the cells that participate in immune reactions.

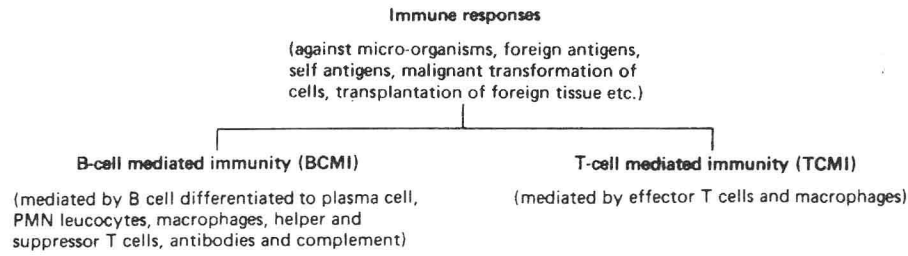

Fig. 1.1 Diagrammatic illustration of two types of immune responses.

Generation of cells that participate in immune reactions

All the blood cells originate in blood islands of the yolk sac mesoderm. This organ contained progenitor cells called stem cells, which can at later stages differentiate into various types of blood cells. From the yolk sac, stem cells migrate to the liver, then to the spleen and then to the bone marrow. Stem cells which are precursors of lymphocytes may also migrate to the thymus. Depending on the micro-environment and humoral factors they can differentiate into red blood cells, megakaryocytes, granulocytes (neutrophils, eosinophils and basophils), monocyte-macrophages and T and B lymphocytes. For example, differentiation of B lymphocytes takes place in the liver, that of T lymphocytes in the thymus, and that of granulocytes and the monocyte-macrophage cell line in the bone marrow. These observations have been described in detail in some excellent reviews (Greaves *et al.*, 1973; Owen, 1974; Cooper and Lawton, 1974a; Cooper, 1975; Cline, 1975 a, b, c, d, e, f, g; Owen, 1977).

Generation of B lymphocytes

On migrating from the yolk sac to the liver some of the stem cells are influenced to begin differentiation into B cells. The first step is the production of IgM which subsequently appears on the cell membrane. Still within the liver, IgM-synthesizing cells undergo division producing daughter cells that synthesize IgG. This is considered as the second step in the differentiation process. Other immunoglobulin (IgA, IgD and IgE) synthesizing cells are generated by a similar switch-over mechanism.

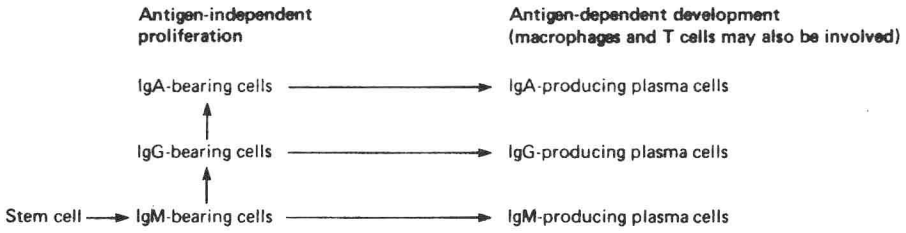

Fig. 1.2 Probable pathways of B-cell differentiation to diverse plasma cells.

The initial generation of class diversity, i.e. the generation of various kinds of B lymphocytes capable of synthesizing different immunoglobulin classes, occurs in the absence of T cells and under minimal antigen exposure. But when these virgin B cells migrate to the blood and are exposed to antigen, they differentiate further to mature antibody secreting plasma cells (Fig. 1.2) or memory cells. This triggering of conversion of B cells to plasma cells or memory cells may be either by direct interaction of antigen with surface antibodies on B cells or via antigen-activated T cells or T-cell factors during B-T cell surface-to-surface interaction. These facts have been reviewed in detail by Greaves *et al.*, 1973; Cooper and Lawton, 1974 a, b; Cooper, 1975; Owen, 1977.

Generation of T cells

When stem cell precursors of T lymphocytes enter the thymus under the influence of thymic hormones (see review by Trainin, Small and Kook, 1977) they are converted to T lymphocytes. T lymphocytes found in the thymus are known as thymocytes, to differentiate them from those that have left the thymus. Most, but not all, thymocytes are immature as regards their ability to recognize and respond to antigens. T cells leave the thymus for good and enter the blood stream. They enter certain areas of peripheral lymphoid tissue called 'thymus-dependent areas'. These may be in the lymph nodes and the spleen. In the thymus-dependent areas T cells that have developed antigen receptors on their surface after contact with antigen undergo cell divisions. They then leave these areas, enter the lymphatic circulation and re-enter the blood stream where the possibility of contact with antigen is increased. This subject has been reviewed by Greaves, Owen and Raff, 1973; Cooper and Lawton, 1974b; Sprent 1977.

Generation of the monocyte-macrophage cell line

The youngest identifiable and presumed precursors of human monocyte-macrophage cell lines are monoblasts. They are very rare in bone marrow but are frequently seen in monocytic leukaemia. Monoblasts are non-motile, non-adhesive and non-phagocytic cells. When they develop a complex Golgi apparatus and granules they are called promonocytes. Promonocytes have been identified by Nicolas *et al.* (1971) in human bone marrow. Promonocytes are glass adherent and show endocytosis but little phagocytosis. They are self replicating and during replication give rise to monocytes. Monocytes are slowly motile, have well developed Golgi apparatus and numerous lysosomal granules. They are phagocytic cells capable of division. They may enter the circulation. They give rise to immature macrophages when they enter the tissues. Immature macrophages are also capable of cell division but when they become mature they lose this property. Mature macrophages may fuse together to give multinucleated giant cells. The continued maturation of these cells results in epitheloid cells seen in chronic granulomatous reactions. These giant cells are very rich in granules and hydrolytic enzymes. This sequence of development is summarized in Fig. 1.3. Intermediate cell types may be distinguished from each other on the basis of morphological features (Cline, 1975g).

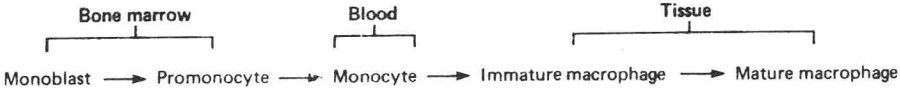

Fig. 1.3 Sequential development of monocyte-macrophage cell lines. Cells up to the immature macrophage stage are capable of cell division.

Generation of granulocytes

The granulocyte series consist of three cell lines – neutrophils, eosinophils and basophils – that are morphologically distinct. All three lines arise from stem cells in the bone marrow (see Fig. 1.4). Stem cells that are progenetors of these cell lines are not identifiable but are presumed to exist on an experimental basis. During mitotic divisions in bone marrow, stem cells are converted to neutrophilic, eosinophilic and basophilic promyelocytes. During the conversion of stem cells to promyelocytes, myeloblast intermediates appear to be formed in the case of the neutrophil and basophil series. Myeloblasts do not contain granules whereas promyelocytes do. Further mitotic divisions of neutrophil, basophil and eosinophil promyelocytes result in the production of myelocytes, metamyelocytes and finally mature neutrophils, basophils and eosinophils respectively. Some authorities believe in a band form in between metamyelocytes and mature cells. The intermediate cells produced during maturation of all the three types of granulocytes are identifiable morphologically. This subject has been reviewed in detail by Cline, 1975 b, c, d.

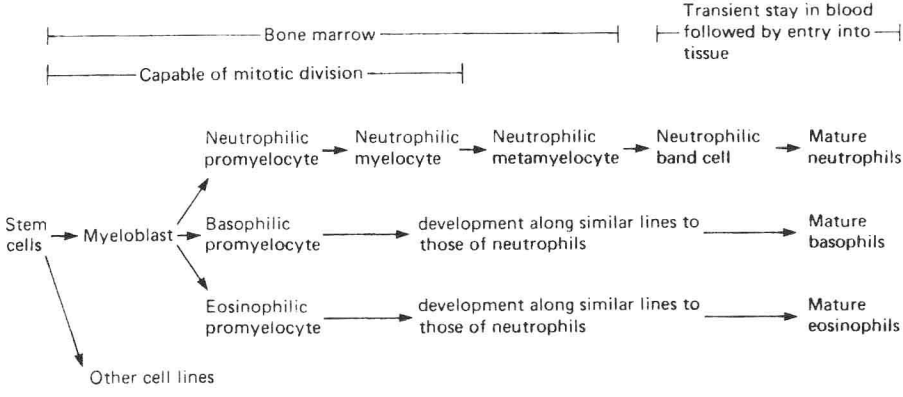

Fig. 1.4 Diagrammatic representation of the development of granulocyte cell lines.

Although this model of development of the immune system has been constructed mostly, though not solely, on the basis of animal experiments, it may easily be extended to the human immune system. Direct evidence to this effect comes from immunodeficiency diseases. In chronic granulomatous disease, defects in the bacterial killing mechanism are present in granulocytes as well as monocytes (Davis *et al.*, 1968). Patients with severe combined immunodeficiency associated with deficiency of adenine deaminase (ADA) lack ADA in lymphocytes as well as in red cells

(van der Weyden and Kelley, 1976) suggesting a common stem cell origin for both cell types. Similarly, lack of primordial lymphoid tissue development in autosomal recessive agammaglobulinaemia (Swiss type) results in the lack of both B and T cells (Good, 1970) suggesting their common origin. The lack of fully developed B cells in patients with X-linked agammaglobulinaemia makes these patients immunoglobulin deficient while their T cell system remains intact (Good, 1970). On the other hand, patients who develop a deficiency in plasma cells and antibodies at a later stage of life often have the normal number of B lymphocytes with all immunoglobulin classes on their surface, suggesting that the defect lies at the stage of conversion of B cells to plasma cells (Hermans *et al.*, 1976). Children born without a thymus or with hypoplasia of the thymus (Di George syndrome) lack T cells and T cell mediated immunity, while plasma cells, circulating immunoglobulins and B cell mediated immunity remain intact (Di George, 1968). Patients with selective deficiencies of IgG and IgA (Schur *et al.*, 1970; Buckley, 1975) may have a developmental arrest at the level of the switch-over mechanism described above. The same may be the case with IgG_2-deficiency (Schur *et al.*, 1970). These observations, together with the fact that infants born without a thymus have been treated successfully by thymus grafting and infants lacking both T and B cells with bone marrow and fetal liver transplants (Wells and Fundenberg, 1974), suggest that the development of the human immune system probably follows the same course as that of the mammalian immune system, as worked out by animal experiments.

General characteristics and functions of cells that participate in immune reactions

B and T cells

Although B and T cells can be distinguished from other cells on a morphological basis, a distinction between B and T cells can also be made on the basis of the markers they possess on their surfaces. For example, human T lymphocyte antigen (HTLA) and receptors for sheep erythrocytes are found on thymocytes and blood T cells but not on B cells. Receptors for measle viruses are found on human T cells but not on B cells. Similarly, receptors for IgG (Fc part), the third component of complement (C3) and Epstein-Barr viruses have been found on human B but not on T cells. Some surface markers of human B and T lymphocytes have been listed in Table 1.1.

B and T cells are distinct not only in their surface markers but also in their functions. B lymphocytes can differentiate into antibody-producing cells, namely plasma cells, and thus can initiate BCMI. On the other hand, T lymphocytes after activation (sensitization) do not produce serum antibodies but produce lymphokines and can initiate TCMI in conjunction with, or even in the absence of, macrophages. T cells also show helper and suppressive function in antibody production by plasma cells. Some T cells have also been shown to suppress other T cells. These different functions of B and T cells are the basis for two different immune responses, namely BCMI and TCMI respectively. These are discussed in detail in some of the subsequent chapters.

Table 1.1 Some surface markers of human lymphocytes

Markers	B-cell	T-cell	References
Human T lymphocyte antigen (HTLA)	–	+	Smith *et al.*, 1973
Sheep erythrocyte receptors	–	+	Bach, 1973 Coombs *et al.*, 1970
Measles virus receptors	–	+	Vald: narsson *et al.*, 1974 a, b
Markers against which antibodies are produced in infectious mononucleosis and lupus erythematosus	–	+	Wernet and Kunkel, 1973
Surface immunoglobulins	+	–	Preud'homme and Seligmann 1972 a, b
C3 receptor	+	–	Ross *et al.*, 1973
Fc receptor	+	low affinity receptors	Basten *et al.*, 1972; Moretta *et al.*, 1977
Epstein-Barr viruses and many others, such as mitogens	+	–	Jondal and Klein, 1973

Monocyte-macrophages

Macrophages have Fc and C3 receptors on their surface which facilitates their phagocytic capacity. Besides this they influence BCMI and TCMI in several ways. They process and present antigen to T cells and thus activate them. Since macrophages possess migration inhibition factor (MIF) receptors, they are themselves activated by MIF released by effector T cells and become cytotoxic. They influence antibody production induced by T cell dependent antigens via T cell activation. These functions are described in detail in Chapter 7.

Granulocytes

Cells of the granulocyte series, neutrophils, basophils and eosinophils, have certain properties in common. All are attracted chemotactically towards the site of inflammation and all of them are phagocytic, though basophils less avidly than neutrophils and eosinophils.

In spite of the similarities in certain properties, these cells appear to have different functions. Neutrophils are involved in the digestion and removal of immune deposits during BCMI and they also cause tissue injury and inflammation, as their granules are rich in proteolytic enzymes and vascular permeability-increasing proteins. Basophils are rich in histamine and heparin and release these pharmacologically-active compounds in response to a variety of stimuli, such as

immune complexes containing IgE, proteolytic enzymes, exposure to cold, trauma and alimentary hyperlipaemia. Basophils, by virtue of their ability to release platelet-activating factor (PAF), can make platelets also release histamine and thus increase the vascular permeability and help in immune complex entrappment during experimental serum sickness and in circulating immune complex diseases, as we shall see in Chapters 3 and 4.

On the other hand, eosinophils appear to have properties antagonistic to those of basophils. They are able to antagonize the effect of histamine (Vercauteren, 1953) and bradykinin (Archer *et al.*, 1962) and may destroy slow reacting substance of anaphylaxis (SRS-A) (Wassermann *et al.*, 1975). Thus the phagocytosis of immune complexes by eosinophils is expected to limit the inflammatory response, since immune complexes are removed and those substances are released which antagonize rather than produce inflammatory reactions.

After this preliminary introduction of immune responses and the cells that mediate and regulate these responses one chapter will be devoted to the nature of antigens in the skin and one to the role of antibodies in skin reactions. A further chapter will be devoted to complement. T-cell mediated reactions in the skin will then be discussed and will be followed by a discussion of neutrophils and macrophages.

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2

Skin antigens

Introduction

It is obvious from recent data in the literature that a large number of antigens occur in the human skin. We think it useful to discuss some aspects of these antigens at the beginning of this book, because in most instances they are the targets of various immunodermatological responses and therefore are of clinical relevance. At least three main classes of antigens can be distinguished, self-antigens, altered self-antigens and non-self-antigens.

Table 2.1 Epidermal antigens

Stratum corneum antigens
Stratum spinosum antigens
Intercellular antigens (cellular surface)
(a) pemphigus antigen(s)
(b) blood group antigen(s)
(c) histocompatibility antigens
Cytoplasmic antigens
Nuclear antigens
(a) DNA: native double-stranded molecule (dsDNA); denatured single-stranded molecule (ssDNA)
(b) RNA
(c) nuclear proteins
(d) histones (DNA complexes)
Specific cell antigens
Langerhans cell (surface) antigens
Melanocyte (surface) antigens
Basal cell antigens
Basement membrane antigens (basement membrane zone Ag)
Pemphigoid antigen(s)
Cicatrical pemphigoid antigen(s)
Herpes gestationes antigen(s)

The altered self-antigens are the result of injury to skin or interaction with non-self-antigens. For details on the nature and characteristics of the non-self-antigens the reader is referred to the various textbooks of virology, bacteriology, parasitology and mycology. It seems to us more appropriate within the framework of this book to deal more or less in detail with self-antigens. These antigens occur in two compartments, the epidermal and the dermal compartments (see Tables 2.1 and 2.2). These compartments are separated by the basement membrane which can also become a target for antibodies.

Table 2.2 Dermal antigens

Collagen (certain types)
Nuclear antigens (see epidermal antigens)
Endothelial cell antigens

The most striking demonstration of skin antigenicity is the rejection of transplanted allogenic or xenogeneic skin grafts. Skin appears to be more antigenic than most other organs, and at least fourteen different soluble antigens have been demonstrated in guinea-pig epidermis, although most are not unique to skin and are present in other organs as well (Aoki *et al.*, 1970).

Antigens can be distinguished by (a) their anatomical localization in the skin; (b) their immunogenicity; and (c) their distribution in various species and in other organs. Some antigens are immunogenic only in unrelated species, while others are immunogenic in man (alloantigens) and, more importantly, in the patient himself (autoantigens). Only the latter two types of antigens are clinically relevant.

Some antigens are present in all or most cells of the body, while others are present only or mostly in a single tissue (tissue specific antigens) (Bystryn, 1977).

Based on their localization in the skin, the following classification of skin antigens can be made (see Table 2.1). Each class of skin antigen will be discussed here in detail.

Stratum corneum (SC) antigens

Although the localization of SC offers little or no access to the immune apparatus, almost all humans have antibodies against SC antigens (Krogh *et al.*, 1974). It has been reported that antibodies to stratum corneum are detected in 83 to 100 per cent of normal persons. We must discuss how autoantigens in SC may stimulate antibody production, considering the fact that these sequestered antigens normally have no access to the immune apparatus. Moreover, they are firmly bound to the tissue and drastic extraction procedures are needed for their release *in vitro*. It has therefore been assumed that antibodies to SC reflect heteroantibodies to exogenous cross-reacting antigens, e.g. to micro-organisms in the body sharing common antigenic determinants with the antigen in SC.

According to Krogh (1973), the SC antigens can be divided in two groups,