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Robert Volpé

Auto-immunity in the Endocrine System

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Robert Volpé, M. D., F.R.C.P. (C), F.A.C.P.

Professor, Department of Medicine,
University of Toronto;
Physician-in-Chief,
The Wellesley Hospital,
Toronto, Ontario M4Y 1J3,
Canada

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Preface

The present monograph will concern itself with those disorders of the endocrine system, either associated with destruction, interference with function or hyper-function, which are considered to be due to auto-immune processes.

Endocrinopathies	Non-endocrine auto-immune disorders associated with the endocrinopathies
Graves' (Basedow's, Parry's) disease	Pernicious anaemia
Hashimoto's thyroiditis	Vitiligo
Idiopathic Addison's disease	Myaesthenia gravis
Insulinopenic diabetes mellitus	Sjögren's syndrome
Auto-immune oophoritis and orchitis	Rheumatoid arthritis
Auto-immune hypoparathyroidism	Idiopathic thrombocytopenic purpura
Auto-immune hypophysitis	Chronic active hepatitis
Possibly some cases of infertility due to anti-sperm antibodies	Primary biliary cirrhosis

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The above table indicates those organ-specific endocrinopathies considered to be due to auto-immune factors, as well as those non-endocrine, organ-specific auto-immune disorders which may be associated with them (Volpé 1977). It is evident that such disorders, occurring without any obvious external cause, raise the very elementary question of how immune processes directed against self-constituents could be initiated. Generally, of course, the immune system acts as a regulatory and defence mechanism, and disorders of auto-immunity represent breakdowns in this regulatory system. The following chapters will be concerned with the individual components of the endocrine system so affected by auto-immune processes; it will first be necessary to provide an initial chapter for the purpose of summarizing some general principles of immunology, in order to place the immune disorders of the endocrine system in context.

It is commonplace to observe that the field of immunology is of very great magnitude and is evolving very rapidly. The chapter on general principles therefore will not be all-embracing, but will select those elements which will be necessary for a comprehension of the disorders to be discussed later. Moreover, the chapters which follow will not offer comprehensive citations of the literature, but rather references will be made to studies considered most appropriate, most important or representative or to many of the extensive and excellent reviews which have recently appeared on topics appropriate to this text.

While the reviews of the endocrinopathies which follow the introductory chapter will cite the views of many workers, the perspectives will not be neutral. The author

will infuse his own interpretations on the various observations collated herein, in an effort to derive a unitary hypothesis which will then encompass most, if not all, of the auto-immune organ-specific endocrinopathies (and those non-endocrine, organ-specific auto-immune disorders associated with them). These views have evolved from consideration of studies in the author's laboratory and of many others, as distilled through innumerable discussions between the present writer and many colleagues. Particular gratitude is expressed to Vas V. Row, my research associate, and many previous research fellows: Drs. Jean Dussault, Eric Laryea, Joseph McConnon, Lamk Lamki, Peter Clarke, Robert Munro, John O'Donnell, Andrew Knox, Merrill Edmonds, Christian von Westarp, Jay Silverberg, Akira Sugenoya, Krinos Trokoudes, Arthur Kidd, Nobumitsu Okita, Mark Lewis, Jacques How, and Duncan Topliss. These young men have been a source of constant stimulation over the years, for which the author is greatly indebted.

It is important also to express gratitude to the unsung heroes of this monograph; to my secretaries, Mrs. Sarah McLaughlin and Mrs. Ursula Besteman, for their efforts in typing, arranging and organizing this work; to Mrs. V. Empey, Medical Librarian, Wellesley Hospital, and her staff for their assistance with the background references; to the Medical Art Department, Wellesley Hospital, for the diagrams; and finally, to my wife and family, and my skiing and tennis partners for their forbearance during the long months of preparation of this manuscript.

Toronto, July 1981 Robert Volpé

Contents

1 General Principles of Immunology (as Related to Auto-immune Disease)

1.1 Immunity and the Immune Response

The term "immunity" may be defined as those physiological mechanisms which endow the organism with the capacity to recognize substances as foreign, and to neutralize, eliminate or metabolize them without injury to its own tissues. Responses to such foreign substances may be divided into two types, i.e. those which are non-specific, and those which are specific immunological responses. Non-specific responses may occur following the initial and even subsequent exposure to foreign antigen, and are not dependent on specific recognition. A non-specific response involves the participation of cellular and chemical mediators, such as macrophages, lysozymes, properdin, interferon, prostaglandins and complement (Playfair 1975).

Although the term "complement" was originally designated to imply an auxiliary factor in serum that, acting upon an antibody-coated cell, would lead to lysis of the cell, the complement system is now known to be a complex cascade of interacting proteins. It is evident that the complement sequence consists of nine functional entities or eleven discrete proteins. These have a variety of different molecular weights and properties. The terms applied to these components include Clq, Clr, Cls, C2, C3, C4, C5, C6, C7, C8 and C9. The components of complement cause the accumulation of neutrophils from the circulation (chemotaxis). Complement products are capable of neutralizing viruses, producing kinin-like substances which contract smooth muscle and cause increased vascular permeability, producing immune adherence, intensifying an inflammatory reaction, and perhaps affecting cell surfaces, thus resulting in cell damage or death. The phenomenon of rapid red cell destruction may be closely related to that of immune adherence.

Specific immunological response (also called adaptive immunity) is restricted primarily to chordates (Hildemann and Reddy 1973). In this form of immune response, the organism demonstrates its ability to select from the entire spectrum of possible foreign substances those to which it is actually exposed, and to react against them in a specific manner. Moreover, this specific response can then be expanded, either to combat a continuing invasion, or for subsequent use, by means of immunological memory (Bellanti 1978). The specific response is mediated by lymphocytes; the crucial role of lymphocytes in the immune response will be discussed below.

Terminology to be employed in this chapter and monograph is of importance. A substance giving rise to antibody is called an antigen. A determinant not antigenic on its own, but against which antibody can be formed, is called a hapten. The additional determinant required to convert a hapten into an antigen (usually by stimulating a T-lymphocyte) is called a carrier. The term "immunogen" refers to substances capable of giving rise to actual immunity or protection. A substance

capable of non-specifically stimulating the formation of antibody to unrelated antigens is termed an adjuvant (Playfair 1975).

1.1.1 The Role of Lymphocytes in the Immune Response

Immunological responses serve three functions—defence, homeostasis and surveillance (Fudenberg et al. 1976). The first function, defence against invasion by micro-organisms, was a matter of scientific inquiry over many generations, and was the route by which the explosion in knowledge regarding immunological processes has occurred. The second function, homeostasis, allows the organism to preserve uniformity of a given cell type. Removal of damaged cellular elements, such as circulating erythrocytes or leucocytes, may be performed by ordinary degradative or catabolic functions, which are immune in nature.

Finally, immune surveillance is a function which monitors the recognition of abnormal cell types which constantly arise within the body. This immunoregulatory system is complex and will be discussed in the latter portion of this chapter.

1.1.2 Types of Lymphocytes

There appear to be two major categories of lymphocytes. While all lymphocytes are initially produced in the bone marrow, some are processed by the micro-environment of the thymus [possibly by a thymic hormone, thymopoietin (Goldstein 1975), thymosin (Goldstein et al. 1972), thymic serum factor (Bach et al. 1977, 1978)], and are thus termed thymus-dependent or T-lymphocytes. Most of the remainder of bone marrow-derived lymphocytes are not processed by the thymus, but rather in another specific inducing micro-environment, probably within the bone marrow itself, and are considered analogous to those lymphocytes which come from the avian bursa of Fabricius (bursa-equivalent or B-lymphocytes) (Bellanti 1978) (Fig. 1.1). There is evidence that some cells which appear to be lymphocytes morphologically may be neither T- nor B-lymphocytes, e.g. null cells. Moreover, it is now evident that there are many subclasses of T-lymphocytes which have different function.

T-lymphocytes have specific surface components which permit identification with specific antisera (Elliott et al. 1980). The first demonstration of this means of identification was with the theta-isoantigen system in mice, but identification of the T-lymphocytes in other species (including humans) by similar techniques has been accomplished (Miescher and Muller-Eberhard 1976). T-lymphocytes are responsible for "cell-mediated immunity", and have a variety of functions in the immune response. While the T-lymphocyte cannot produce antibodies itself (except as surface receptors), it can cooperate with appropriate B-lymphocytes which in consequence then do produce such antibodies (Katz and Benacerraf 1972). The production of IgG in particular always requires the participation by T-lymphocytes in addition to B-lymphocytes. When T-lymphocytes co-operate with and direct groups of B-lymphocytes in this manner to produce antibodies, they are termed helper T-lymphocytes. T-lymphocytes may also be involved in the direct killing of target cells, the activation of some functions of macrophages, and the production of a variety of soluble products (lymphokines); the variety of functions of these lymphokines may be mediated by structural specificity for each function or for a few related functions (Dumonde and Maini 1971). Lymphokines include macrophage

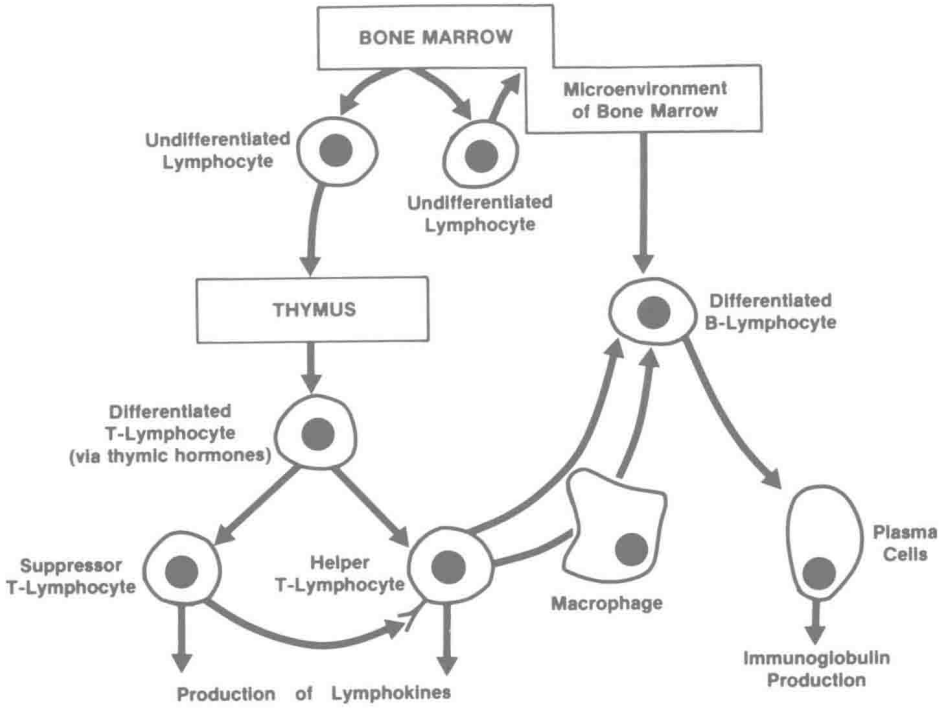

Fig. 1.1. Simplified version of lymphocyte differentiation. (See text for discussion.) (Okita et al. 1981)

migration inhibition factor, macrophage aggregation factor, macrophage-spreading inhibitory factor, migration inhibition factor for other cells (T-lymphocytes, polymorphonuclear leucocytes), chemotactic factor, mitogenic factor, lymphotoxic factor, skin reactive factor, interferon, inhibitors of proliferation and DNA synthesis and lymph node permeability factor. Secondly, T-lymphocytes belonging to a subset act as suppressor T-lymphocytes, i.e. they suppress other T-lymphocytes (such as helper T-lymphocytes), as well as B-lymphocytes. Finally, T-lymphocytes exert a regulatory function, which is considered to be by the action of a third subset of T-lymphocytes, and affect feedback regulation of helper and suppressor T-lymphocytes. These cells, which are also involved in self-recognition, will be the subject of a fuller discussion below. In any event, deficiency of T-lymphocytes can result in severe infections, and possibly malignancy (Bellanti 1978; Miescher and Muller-Eberhard 1976). New techniques are gradually becoming available to identify the three subsets of T-lymphocytes by means of conventional hetero-antibodies, monoclonal antibodies produced by hybridomas, auto-antibodies from patients with systemic lupus erythematosus, allo-antibodies, and receptors for isotype specific Fc receptors (Evans et al. 1977; Moretta et al. 1977; Reinherz and Schlossman 1979; Reinherz et al. 1979).

B-lymphocytes are the precursors of the cells which secrete antibody. A deficiency in B-lymphocytes generally results in bacterial infections. It appears that antibody production can come directly from B-lymphocytes, or via transformation of B-

lymphocytes to plasma cells. B-lymphocytes may be identified by their surface immunoglobulin molecules, which are being produced by these cells, although primitive B-lymphocytes may not have such markings (Fudenberg et al. 1976). The latter, however, have the ability to transform into cells capable of producing immunoglobulins. Immunoglobulins are of several types, namely, IgA, IgE, IgG, IgM and IgD (Bernier 1978). IgG, the most abundant of the immunoglobulins, is thought to contribute to immunity against many infecting agents, including bacteria, viruses, parasites and some fungi. In addition, most auto-antibodies are of this type, and thus the IgG class of immunoglobulins is of particular interest in relation to auto-immune disorders, and will receive most attention in this volume. IgA, the second most abundant serum immunoglobulin, contributes to the immunity of the individual in the external secretory system (gastro-intestinal, respiratory and genito-urinary tracts). IgM, the largest of the immunoglobulin molecules, is restricted almost entirely to the intravascular space. These macromolecules are capable of agglutinating particulate antigen, such as bacteria and red blood cells, and of fixing complement efficiently. IgD has not yet been assigned a clear biological role, but may act as a specific B-lymphocyte surface receptor in the initiation of the immune response (Elliott et al. 1980). Finally, IgE, the reaginic antibody, is present in only trace amounts in the serum; it appears to initiate aspects of the "acute allergic reaction".

All antibodies are immunoglobulins (Ig), and the terms are virtually interchangeable. A single organism can produce millions of slightly different antibodies of different specificities, producing a wide repertoire of antibodies capable of responding to an equally wide range of antigens that may possibly be encountered (Bernier 1978).

IgG antibody molecules consist of two heavy polypeptide (H) chains and two light (L) chains, which are linked by disulphide bonds. The molecular weight of IgG is approximately 160 000. Differences between antibodies which permit response to different antigens are attributable to differences, which may be very extensive, in the N-terminal parts of the H and L chains. Thus, this part of the molecule is termed the variable (V) region, and each region is called a domain. Indeed, less marked differences in other domains of the H chain permit the mediation of other biological functions, such as fixation to macrophages. The "antigen-binding site" or "antibody-active site" of the immunoglobulin molecule is the region that combines with a specific antigen. An antigen can only select from the already available molecules those which happen to fit it best, and thus the production of antibody is selective. After such an antigen-antibody union, there is preferential amplification of the response though selective stimulation and multiplication of the specific clone of B-lymphocytes. The B-lymphocytes producing the highest affinity antibody bind the greatest amount of antigen, leading to their being most highly stimulated. This results in multiplication of clones with high affinity antibodies, leading to a progressive increase in the avidity of the specific antibody for the antigen in question (Katz and Benacerraf 1972). Since this also involves specific helper T-lymphocytes, it is presumed that these too are sensitized, and also take part in the amplification process (Waldman and Munro 1973). Such "high avidity" antibody is generally found late in the primary immune response to an invading antigen, but more quickly in a secondary response, i.e. when the same antigen is encountered again.

Auto-antibodies are those antibodies which react against self-constituents, and are at the core of the discussion in the latter part of this chapter and in later chapters. A special form of auto-antibody is the anti-idiotypic antibody, which is an antibody reacting against an antibody produced by self or against an immunocompetent cell in the same organism (Wigzell et al 1978). It is now felt that auto-anti-idiotypic immunity is a normal part of the conventional immune process, and may have as a consequence potentiation or elimination of a select immune function if this is dependent on the presence of a given clone of idiotype-positive cells. Such antibodies may thus be important as one of the means of normal regulation of the immune processes, but also, under some circumstances, may mimic auto-antigens. Thus there may be a complex network of anti-idiotypic antibodies, not only participating in immuno regulation (along with other mechanisms), but possibly activating or potentiating an immune process (Jerne 1975). Thus these specialized antibodies carry the potential to selectively change the immune course in already immune individuals. For example, anti-idiotypic antibodies formed against auto-antibodies could theoretically prevent certain biological effects of the original auto-antibody, while perhaps producing another biological effect resulting from the immune complex so formed.

In the circulation T-lymphocytes constitute about 55%–60% of the total. In the thymus, over 90% of the cells are T-lymphocytes, whereas in the bone marrow the majority of the cells are B-lymphocytes. In lymph nodes and spleen, the ratio is approximately equal. Cells of both types appear to be capable of recognizing individual foreign substances, so that only one clone of cells from each type ultimately responds to a given foreign antigen. (Actually, as mentioned above, several clones initially respond, but the clone with the highest affinity for the antigen is selected on the basis of that affinity.) Each B-lymphocyte carries only one type of surface antibody molecule, and thus is apparently capable of responding to only one specific antigen (or perhaps a few very closely related antigens). T-lymphocytes, on the other hand, may have the capacity of recognizing a slightly broader range of closely related antigens, although this point is controversial. Once they have come into contact with their complementary antigen, the reacting cells amplify the response quickly, replicating in both the T- and B-lymphocyte series. Even after the antigenic challenge has disappeared, this amplification of response may be recalled, presumably either by an expanded population of cells or by a clone of memory cells (Fudenberg et al 1976; Bellanti 1978).

1.1.3 Processing of Antigen

Antigen itself may be considered the part of the cellular environment that induces the development of immune responsiveness. Following the introduction of an antigen, a variety of sequential steps occurs. The antigen is first met by a macrophage, which appears to be important, even essential, for the processing of antigen, so that the antigen can interact with the cells of the lymphoid series (Möller 1978). Macrophages, which are activated by means of surface receptors, have many functions, which are beyond the scope of this brief review; for further discussion of the various roles of the macrophage, the reader is referred elsewhere (Möller 1978; Elliott et al. 1980). Following this processing by the macrophages, the antigen stimulates specific lymphocytes to proliferate and differentiate into immunocom-

petent cells; both T-lymphocytes capable of producing lymphokines and B-lymphocytes capable of forming antibody. Some of the T-lymphocytes so induced assist or help the B-lymphocyte response. Thus, not only is the response specific, but it is soon amplified so as to produce a completely appropriate response to the introduction of the antigen. When the antigen subsequently disappears, the population of immunocompetent cells undergoes involution. Some of these cells persist as "memory" cells, which are capable of carrying out certain functions if the same antigen is encountered at a later time. These functions consist of calling forth a much more rapid response (secondary response) of the same clones of T- and B-lymphocytes required once again to elicit a specific response to a specific antigen (Herscowitz 1978; Williams 1975).

Specific antigen receptors exist on the surface of both T- and B-lymphocytes (Davie and Paul 1972; Elliott et al. 1980). While certain antigens can directly stimulate B-lymphocytes so that they can consequently transform into plasma cells and produce antibody, most antigens require the interaction of helper T-lymphocytes, which co-operate with and direct groups of appropriate B-lymphocytes to then produce antibody, as previously briefly discussed. Another subpopulation of T-lymphocytes (suppressor T-lymphocytes) is capable of suppressing the immune response. This subpopulation will be discussed further below.

1.1.4 Genetic Control of the Immune Response

Many aspects of the immune response have now been shown to have a genetic basis. The immune system consists of a highly complex network of components, both cellular and soluble, most of which are specifically encoded for by genes. It is evident that a large number of specific immune response genes exist that control the specific responses to a variety of antigens. It is equally clear that genes may control the cellular interactions within the immune system, as well as the transmission of antigenic specificities from generation to generation.

The major histocompatibility complex (MHC) which is found in mammals is a single genetic region having a major influence on graft rejection. This region has been found to control not only the rejection of heterologous grafts, but also such immunological processes as the immune responsiveness to certain antigens and (more germane to the present discussion) susceptibility to the development of auto-immune diseases. The two MHC systems most extensively studied include the histocompatibility (H-2) system in the mouse and the human leucocyte antigen (HLA) system in man (Bach and van Rood 1976; Dausset 1978; Dausset and Contu 1980; Mc Devitt 1980; McDevitt and Landy 1972; Ritzmann 1976; Rose et al 1978; Svejgaard et al. 1980). The HLA system in man is located on the short arm of chromosome 6 (see Fig. 1.2). A recent excellent review deals with the relationship of HLA to endocrine disease specifically (Farid and Bear 1981).

In addition to the function listed above, this system is also involved in the killing of virus-infected cells and the synthesis of several complement components. However, the various complicated effects of these genes are not directly assessed when testing for disease associations in man. For such purposes, the HLA cell-suface "antigens" are used, because they are relatively easy to identify and because many frequent alternative genes (i. e. many common alleles) are know for each locus. At least four loci determine the classic transplantation antigens identified by

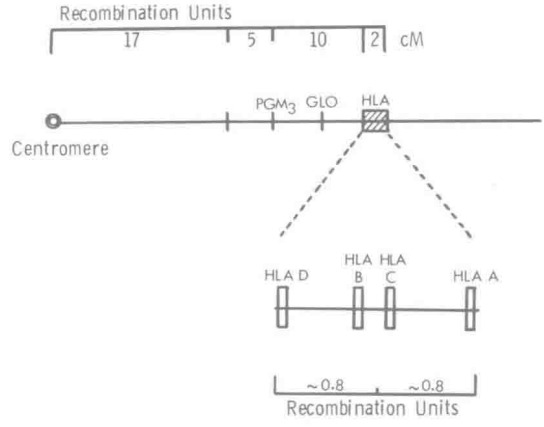

Fig. 1.2. The HLA complex on chromosome 6. This HLA complex is shown relative to other markers (PGM_3, phosphoglucomutase-3; *GLO*, glyoxylase). These markers are all on the short arm of chromosome 6 and distance are indicated in centimorgans (*cM*). The *lower part* of the figure depicts an expanded version of the HLA complex; again, distances between the HLA loci are indicated in centimorgans

serological methods. Eight well-defined and 11 provisional antigens are recognized as A-locus products, and 8 well-defined and 12 provisional antigens as B-locus products (WHO-IUIS Terminology Committee, 1975). The C-locus determines another series of serologically detected antigens, but their functions are not yet clarified, and only a few of the alternative alleles at this locus have been provisionalle defined. D-locus antigens (formerly called mixed-leucocyte culture or MLC antigens) cannot be detected by conventional serological typing. However, lymphocytes from two individuals with different D-locus antigens become activated and form large "blast" cells when cultured together in vitro, while lymphocytes from two D-locus compatible individuals generally will not activate each other in mixed cultures. By using "typing cells" of known specificity in mixed cultures set up so that only the unknown lymphocytes can proliferate, D-locus antigens of the unknown cells can be determined (Svejgaard et al. 1975). Recently, methods have been developed which allow the serological definition of a set of antigens which are closely related to, if not identical with, the HLA-Dw antigens as defined by mixed lymphocyte culture; these are termed HLA-D related (HLA-DR) (van Rood et al. 1975).

Genetic loci are linked if they occur together on the same chromosome in such approximation that they are not separated from each other during meiosis as often as genes on different chromosomes. Linkage can be demonstrated by analysing experimental crosses or the segregation of genes in family studies. HLA complexes are generally inherited intact. Each person receives one HLA complex from his father (his paternal haplotype) and the other from his mother (his maternal haplotype).

Linked alleles which occur together in the same haplotype more frequently than expected are said to be in linkage disequilibrium. Linkage disequilibrium is frequently observed amongst HLA genes, and its occurrence may be necessary to demonstrate certain disease associations. Currently, since it is not yet possible to state that a particular HLA gene is *responsible* for a disease, the HLA antigens should only be considered as convenient inherited markers of disease susceptibility. Incidentally, linkage disequilibrium may be detected in population studies, but not in family studies.

There are two general approaches to investigating associations between HLA antigens and disease (Friedman and Fialkow 1978). In population studies,

frequencies of HLA antigens are compared in patients and matched control persons. In assessing apparent population associations between HLA antigens and a disease, it is necessary to determine the strength of the associations and their statistical significance. The strength of the association is generally expressed as relative risk, i. e. the chance of the disease appearing in a person with a given antigen compared to the chance in a person lacking that antigen. On the other hand, family studies are valuable in evaluating HLA disease associations since they illuminate the inheritance of disease susceptibility.

Family studies require kinships in which two or more siblings or other relatives (but not a parent and a single child, who always share one haplotype) are affected with the same disorder. Since complete HLA haplotypes are almost always inherited as units, family studies can be used to demonstrate HLA-linked disease-predisposing genes, even if they are not associated with any detectable antigen in the population (i. e. there is no linkage disequilibrium). In contrast, detection of an HLA disease association in population studies may sometimes depend on the occurrence of linkage disequilibrium.

It is striking that so many of the organ-specific endocrinopathies are associated with the same HLA-D antigen, at least in Caucasians (Table 1.1). It is not yet known whether these disorders all have different Dw3-associated susceptibility genes or whether the susceptibility for these conditions depends on a common Dw3-associated factor, which could conceivably encode a defect in immune regulation. The fact that in none of the Dw3-associated diseases is there an excess of HLA homozygotes indicates that the mode of inheritance of the susceptibility gene is rather a dominant one (with relatively low penetrance) (Albert and Scholz 1979). From this it may be concluded that the mechanism of pathogenesis is not the lack of reactivity, but rather some abnormality in immune activity. Since it is known that

Table 1.1. Some HLA-associated diseases[a]

Disorder	HLA-A	HLA-B	HLA-D/DR
Acute lymphocytic leukaemia	A2		
Haemochromatosis	A3	B14	
Ankylosing spondylitis		B27	
Behcet's syndrome		B5	
Subacute thyroiditis		Bw35	
Multiple sclerosis			Dw2/DRw2
Type I (insulinopenic diabetes)			
Ir1 (Ib)		B8	Dw3/DRw3 (Caucasian)
Ir2 (Ia)		B15	Dw4/DRw4 (Caucasian)
		BJ22	DYT (Japanese)
Addison's disease		B8	Dw3/DRw3
Chronic active hepatitis		B8	Dw3/DRw3
Myaesthenia gravis		B8	Dw3/DRw3
Graves' (Basedow's) disease		B8	Dw3/DRw3 (Caucasian)
		Bw35	Dw12 (Japanese)
		B46	– (Chinese)
Hashimoto's thyroiditis			DR5
Rheumatoid arthritis			Dw4/DRw4
Coeliac disease			Dw3/DRw3

[a] In Caucasians unless otherwise stated.