

Chapter 2

Pathogenesis

Immune Tolerance

In World War II, British fighter pilots defending England from bombing by the Nazi Luftwaffe, sometimes survived with terrible burns to the face and hands. This caused surgeons to attempt to heal them with skin grafts and led Medawar to study the fate of grafts performed between rabbits [1]. He found that second set grafts were rejected faster than first set ones, in conformity with immune system mediation of the graft rejection. Becoming interested in preventing allograft rejection by artificial induction of immune tolerance, non-reactivity to specific antigens, Medawar and his colleagues inoculated new-born mice with specific cells and showed that sometimes this produced non-reactivity when the animals had become adult [2]. This led to the idea that in animals, around the time of birth, there is a **D day**, when the immunity system changes from permanent non-reactivity (tolerance) to antigens, which will be host ones, to reactivity to new antigens, which will be foreign ones on invading microbes.

Nossal's Key Experiment

In a beautiful experiment, shown in Fig. 2.1, Nossal and Pike [3], culturing bone marrow cells from adult animals, showed that **D day, for change from tolerance to an antigen to immune reactivity against it**, is not a stage in the life of an animal, but a stage in the life of every new lymphocyte clone. This enables the histocompatibility antigens, major, minor and HY (the male histocompatibility antigen), always present where lymphocytes are multiplying, to police the immune repertoire by deleting any new B or T lymphocyte clone with a complementary antigen receptor [4]. By natural selection of reproductive advantage, sets of **immune response genes**, coding for histocompatibility antigens and antigen receptors on B and T lymphocytes, have evolved, over many generations, to maximise defence against current microbial diseases and to minimise autoimmune disease [5].

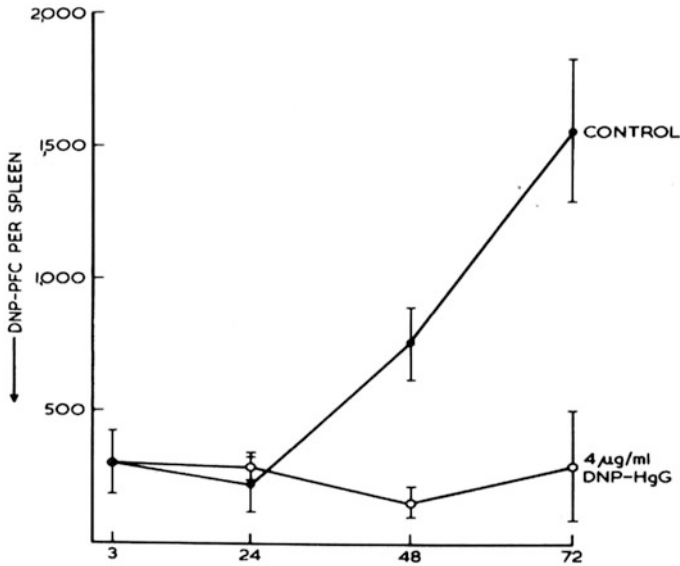


Fig. 2.1 Evidence for clonal abortion by antigenic contact in immature bone marrow lymphocytes from adult mice. These cells differentiate during 72 h in culture, to acquire antibody-secreting capacity (curve labelled “control”) as shown by the plaque-forming cell (PFC) technique. If an antigen (in the experiment illustrated, dinitrophenol on human gamma globulin, DNP-HgG) is present in the medium, reactivity to it does not develop (curve labelled 4 µg/ml DNP-HgG). This experiment shows that D day for the switch from tolerance to immune reaction is not a stage in the life of an animal, but a stage in the life of every new lymphocyte clone, arising by the frequent somatic mutations in the V genes of multiplying lymphocytes [3]

Discovery of the Structure of Antibody Molecules

Serum, which is blood from which red cells and white cells have been removed, contains dissolved proteins, including the gamma globulins that are now called immunoglobulins because they are the antibodies. How could the atomic structure of such a great mixture of molecules be determined? Henry Kunkel solved this problem by using blood from patients with multiple myeloma, a cancer in which a lymphocyte cell becomes malignant, producing large amounts of a single antibody molecule. Kunkel’s pupil, Gerald Edelman, broke the disulphide bonds holding antibodies together, revealing that each antibody molecule is comprised of four amino acid chains, two long ones and two short ones, the disulphide bonds holding them together to form a functional antibody. Rodney Porter [6] successfully split antibody molecules into their constituent amino acid chains, by using the weak proteolytic enzyme, papain. This produced three fragments, a Crystallizable Fragment, FC, the constant region, and two identical Fragments, FAB, each of which formed identical Antigen Binding sites. Figure 2.2 shows this structure.

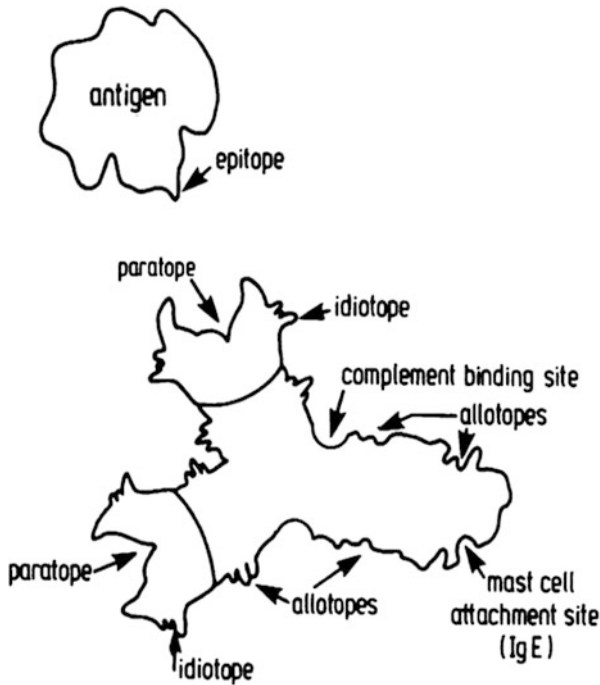


Fig. 2.2 An antibody molecule of IgG class showing the two identical *paratopes* (combining sites for antigen) and the complimentary *epitope* of the antigen molecule. Also shown are the *idiotopes* (constant region epitopes) and the attachment sites for the C1q molecule of the complement system. Additionally, an attachment site for mast cells present on IgE class antibody molecules is depicted [4]

Discovery of T and B Lymphocytes

Some years after Haldane had discovered the histocompatibility system, as described below in **Genetics**, his nephew, Mitchison [7], in a classical experiment, showed that rejection of allografts is not mediated by antibodies, but that lymphocyte cells are necessary, the rejection therefore being appropriately described as “cell-mediated.” This was the discovery of the **cytotoxic T lymphocytes** that bear the CD8 (cluster of differentiation antigens 8) surface marker and are essential for defence against virus infection. Mitchison also discovered the **helper T lymphocytes** that bear the CD4 surface marker and are necessary for firing off the cytokine secretions that mediate the cell cooperation involved in an immune attack on an invading microbe. The lymphocytes which act by secreting antibodies became known as **B lymphocytes**, because of their origin from the bone marrow, whereas **T lymphocytes** are named for their origin in the thymus.

Types of T Lymphocytes (T Cells)

There are three.

1. **Helper T cells** stimulate B lymphocyte activity, multiplication and antibody secretion, also production of cytokines involved in immune defence.

The crucial importance of helper T cells in defence against infection is strikingly demonstrated by acquired immunodeficiency syndrome (AIDS), in which the HIV-1 virus attaches to the CD4 molecule of helper T cells, depleting them and causing dangerous susceptibility to infection [8]

2. **Cytotoxic T cells** kill virus-infected host cells and, in the form of forbidden clones, kill normal host cells, including the pancreatic islet β cells, causing Type 1 Diabetes [9, 10], pericytes, causing diabetic retinopathy [11, 12] and probably other autoimmune diseases with specific parenchymal cell destruction. (Fig. 2.3)

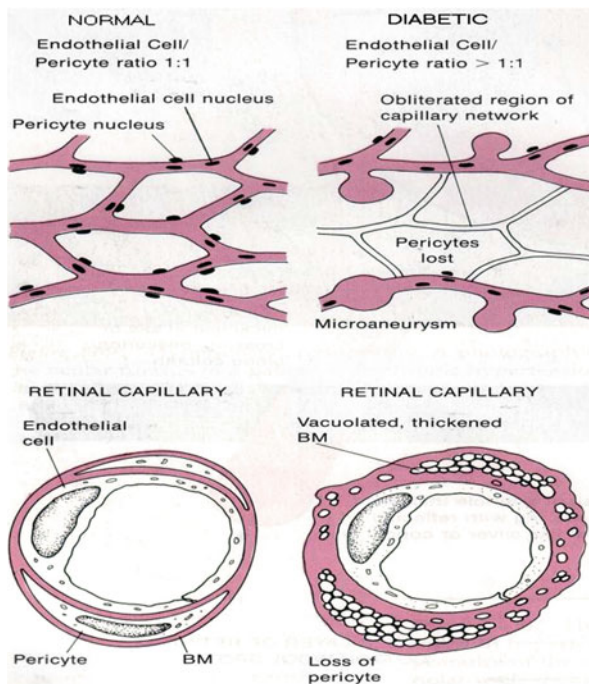


Fig. 2.3 Association of pericyte loss with collapse of the retinal vasculature in diabetic retinopathy., Adams has postulated that the pericytes are destroyed by forbidden clones of cytotoxic T cells, antigenically-related to those that destroy the pancreatic islet β cells. So therapy should be immunosuppression, not ineffective strict glycaemic control. (Clin Ophthalmol 2008; 2:295–8.). From [12]

3. Suppressor T cells inhibit immune reactions.

This was discovered in Japan by Sakaguchi and colleagues [13], who found that neonatal thymectomy caused autoimmune destruction of ovaries in mice, and in Scotland, where Irvine and colleagues [14] found that autoimmune thyroiditis in T cell-depleted rats could be suppressed by normal lymphocytes.

After development of **monoclonal antibody technology** had enabled discovery of the many clusters of differentiation (CD) antigens on lymphocytes [15], the CD4 cluster were found on helper T lymphocytes and the CD8 cluster on cytotoxic lymphocytes that destroy virus-infected cells. The CD25 cluster was found on suppressor T cells and to be part of the cell's receptor for the cytokine, interleukin-2 (IL-2), which was originally known as **T cell growth factor**, because it enabled T cells to be grown in vitro.

Regulation of Immune Responses

Natchtigal, Zan-Bar and Feldman [16] provide an explanation for the mechanism by which T cells regulate immune responses, as shown in Fig. 2.4. They postulate that

1. **Immature T cells**, meeting complementary antigen, differentiate into suppressor T cells, which suppress the specific immune response.
2. **Mature T cells**, become helper T cells.

This regulatory function of T cells effectively controls the magnitude of an immune response, preventing it continuing on indefinitely until somatic mutations

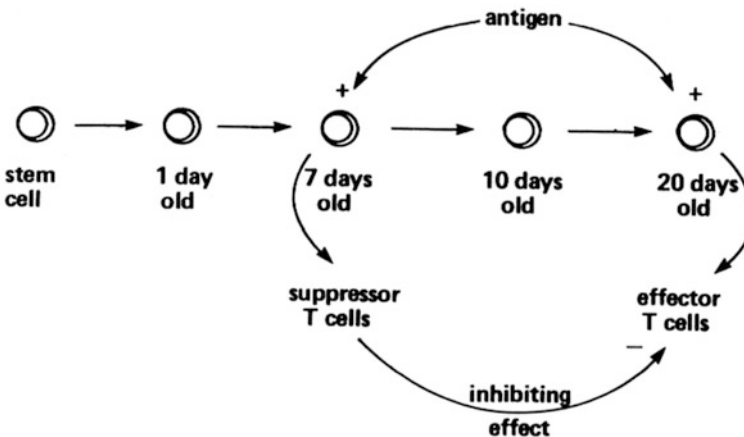


Fig. 2.4 The hypothesis of Natchtigal et al. [13]; immature T cells, meeting complementary antigen differentiate into suppressor T cells, in contrast to mature T cells which become effector T cells. This mechanism effectively controls the magnitude of an immune response, inhibiting both leukaemia and autoimmunity [16]

in the multiplying lymphocytes lead to leukaemia or autoimmune disease. Hence, suppressor T cells are a vital element of the functioning of the immune system [4].

Suppressor T Cells as the Cause of the Autoimmune Diseases

Allison, Denman and Barnes [17] postulated that loss of suppressor T cells is the cause of the autoimmune diseases. This was a very popular idea, but key purported evidence for the concept, repeated by Knight and Adams with larger numbers of mice and adequate statistics proved that the effect was not there [18].

In 1995, Sakaguchi [19], using lymphocyte cell-sorting technology and transfer of cells into lymphocyte-deficient mice, made the seminal observation that animals deprived of CD25+ lymphocytes develop autoimmune disease. After showing the existence of CD4+ CD25+ suppressor T cells in man, Shevach [20] reflected on their enormous potential for therapeutic use, but noted that no way of achieving this had been devised.

The gene, FOXP3, a transcriptional repressor that inhibits activation-induced IL-2 gene translation, has been shown to be both necessary and sufficient for the development and function of naturally arising CD4+ CD25+ suppressor T cells [21]. Children with defects of the FOXP3 gene die of immune-dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) [22]. Furthermore, animals depleted of FOXP3+ lymphocytes, die of autoimmune disease.

In the last few years, efforts to use suppressor T cells for treatment of autoimmune diseases, or allograft rejection, or to remove them to enhance attack on tumours, have all been unsuccessful [23].

Loss of Suppressor T Cells does not Cause the Autoimmune Diseases

As Shevach [24] notes, apart from IPEX, no autoimmune disease has been identified whose pathogenesis is secondary to a deficiency of suppressor T cells. Fortunately, the technology needed for selectively destroying the forbidden clones that do cause the autoimmune diseases is already available, as described below.

Solution of the Pathogenesis of Autoimmune Disease

Jerne's Selection Theory of the Immune Response

Because antibodies were known to fit their antigens closely, it was reasonable to think that they were built around the antigen, an idea that was expressed by

Horowitz as the template theory. However, after Watson and Crick's epochal solution [25] of the structure and function of DNA, Jerne [26] had the crucial realisation that cells' easy DNA to RNA to polypeptide manufacturing capacity, meant that antibodies could be pre-formed, in myriad diversity, awaiting contact with an antigen that fitted, like ready-made shoes in a shop awaiting a customer with the right-sized foot.

The Immunological Clone

If a potato is divided into pieces and these are put in the ground, the resultant group of genetically identical plants is known in horticulture as a "clone". Burnet [27] introduced this term to immunology to describe a group of immunocytes with identical receptors for antigen. Implicit in the clonal concept are two assumptions, namely;

- (1) That a single immunocyte produces antibody of only one specificity and
- (2) That antibody of a single specificity is produced by more than one immunocyte. Both these fundamentally important assumptions now have experimental confirmation.

Burnet's Clonal Selection Theory of the Immune Response

Building on Jerne's selection theory, Burnet realised that it is not antibodies that are selected, but the cells that make them, and that these are the **lymphocytes**. Furthermore, he realised that lymphocytes exist as clones of cells with identical receptors for antigen, there being millions of cells in each clone and millions of clones in a person. This is the Clonal Selection Theory of acquired immunity [27], today in general acceptance and illustrated in Fig. 2.5.

Burnet's Forbidden Clone Theory of Autoimmune Disease

As a bacteriologist, Burnet had counted mutation rates in populations of bacteria multiplying on blood agar plates. He realised that mutations would occur similarly in populations of multiplying lymphocytes. Coining the apt term "forbidden clone," for lymphocyte clones that react with a host antigen, Burnet postulated that these arise by somatic gene mutations in multiplying lymphocytes and are the cause of the autoimmune diseases [28]. This was confirmed for Graves' disease by demonstration that in individual patients, the thyroid-stimulating autoantibodies contain only one of two possible immunoglobulin light chain types, λ or κ , but

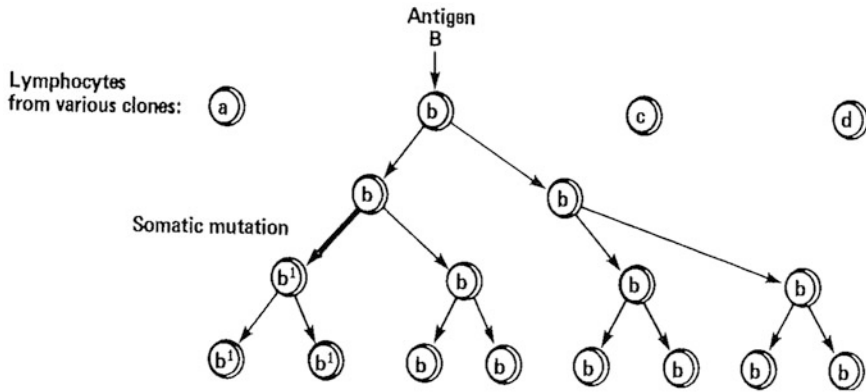


Fig. 2.5 Clonal selection by antigenic stimulation and clonal diversification by somatic mutation. Concept of Jerne [26] and Burnet [27] (Adams [4])

never both, and therefore arise from a single lymphocyte by somatic mutation in its V genes [29].

Cytotoxic T Cell Forbidden Clones

Sherwin's epic research on diabetes [9] has been capped by the discovery that the exquisitely-specific destruction of the pancreatic islet β cells that causes **Type 1 Diabetes** is caused by cytotoxic T cells [10]. Following this up, Adams has postulated that antigen receptor-related cytotoxic T cells destroy the retinal pericytes, which Klintworth [11] has shown to occur in **diabetic retinopathy** and that this is the cause of the vascular collapse of diabetic retinopathy [12] (Fig. 2.3). This indicates the need for replacement of tight glycaemic control as treatment for diabetic retinopathy by trial of immunosuppression.

Graves' Disease, a Paradigm for Autoimmune Disease

In 1986, at the University of Pisa, Professor Aldo Pinchera initiated and led an International Symposium on Thyroid Autoimmunity [30].

This was a culmination of understanding of the pathogenesis and genetics of autoimmune disease. Of all the autoimmune diseases, those involving the thyroid gland had unique advantages for study because of the presence of iodine in thyroid hormone, the hormone receptor nature of the Graves' disease autoantigen and the control of thyroid activity by the pituitary gland. Clear evidence, from world wide research supported the Forbidden Clone theory of the pathogenesis, and the H Gene theory of the genetics, described below [31].

Table 2.1 Discovered pathogenic forbidden clones and others awaiting discovery

Disease or disorder	Autoantigen	Cell type of the forbidden clone
Graves' disease	TSH receptor [34]	B cell, plasma cell
Myasthenia Gravis	Acetylcholine receptor [35]	"
Goodpasture's disease	On glomerular and lung basement membrane[36]	"
Pernicious anaemia	Intrinsic factor [37]	"
Systemic lupus erythematosis	An intracellular component made copiously available by cytolysis [38]	"
"Thrombosis by lupus anticoagulant [40]	Platelet cell wall phospholipid [39]	"
Hypocomplementaemia	Alternative pathway C3 convertase abnormally stabilised by C3 nephritic factor [41]	"
Haemolytic anaemia	Red cell surface component [42]	"
Thrombocytopenia	Platelet surface component [43]	"
Rheumatoid arthritis	Type X1 collagen [44, 45]	"
Schizophrenia	A neuronal dopaminergic receptor [46, 47]	"
Manic depressive	?Another neuronal receptor	"
Systemic scleroderma	?Fibroblast receptor causing excessive collagen formation [48– 50]	"
Paget's disease	?Osteoclast receptor, causing bone resorption [51]	"
Post-streptococcal glomerulonephritis	?Intra-cellular glomerular component exposed by nephritogenic strep toxin	?B cell, as Ig is in the lesion [52]
Rheumatic fever	Heart component cross-reactive with streptococci [53]	?T cell as the heart autoantibodies also occur in uncomplicated strep infection [54]
Diabetes type 1	Islet β cell surface component	Cytotoxic CD8 T cell [9, 10]
Diabetic retinopathy	?Vascular pericyte cells	Cytotoxic T cell, CD8 [11, 12]
Autoimmune hepatitis	?Hepatocyte surface component	?Cytotoxic T cell, CD8 [55]
Addison's disease	?Adrenocortical cell surface component	?Cytotoxic T cell [56]
Primary biliary cirrhosis	?Ductal cell surface component[57]	?Cytotoxic T cell, CD8
Multiple sclerosis	?Oligodendrocyte surface component	?Cytotoxic T cell, CD8 [58]
Polymyositis	?Muscle cell surface component	CD8 α/β T cell [59]

Pathogenic Forbidden Clones; Discovered Ones and Ones Awaiting Discovery

These are shown in Table 2.1. Initially, discovery of forbidden clones depended on particular expertise in various non-immunological fields, such as endocrinology, with radioactive iodine for Graves' disease and neurology, with acetylcholine receptors from the electric eel and bungarotoxin from poisonous India arrows, for myasthenia gravis.

A promising way to seek new forbidden clones is to use the receptor-ligand technology invented by GP Smith [32, 33]. Patients' serum or cerebrospinal fluid can be screened on bacteriophage peptide display libraries to seek antibodies that are confined to certain autoimmune diseases. The blood–brain barrier may result in clones proliferating on the brain side of the barrier without significant representation on the blood side, where the stimulating antigen may not exist. Hence for seeking autoantibodies causing psychoses, cerebrospinal fluid may need to be the starting material.

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Autoimmune Disease

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