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Introduction

Humans have 100 or so specialized genes that controls the growth of cells. If they mutate, a single DNA base may change or whole sections of the message are lost [1].

Certain virus oncogenes are inserted into the DNA and these may be responsible for harmful mutations. Most mutations occur in parts of the DNA that do not contain meaningful instructions, or mutations may effect critical areas of the DNA essential for survival of the cell [2].

In discussing the general biological significance of immune reactions in maintaining the integrity of the cellular systems of the body, there must be many millions of error or mutation occurring everyday of life in the cell population resulting to immunological anomalies [3]

This review unravels the details of the immunological properties underlying the inducement, generation and control of these errors, the antigenic changes in the cells themselves,

Review Article

How to induce, generate and control Immunological Anomalies in humans?

Abstract

This review unravels the details of the immunological properties underlying the inducement, generation and control of immunological errors, the antigenic changes in the cells themselves, and the extent and activities of the immune response arising as a result of these changes.

The immunological anomalies in humans which includes graft rejection, tissue transplantation, immunosuppression, immunoenhancement, malignant diseases, tumour immunology, hypersensitivity, immunopathology, immunodeficiency and autoimmune diseases were fully discussed as well as their immunological properties which will serve as a guide to immunological research activities and disease control.

In this article, we reviewed the antigenic properties of the transformed cells and the ability of the host to mount an immune response to such antigens. Immunological errors itself can have effects on the immune system and these have to be taken into consideration in designing immunotherapeutic measures for the control of chronic and debilitating infectious diseases i.e. HIV is not a transforming virus and is therefore not directly responsible for the lymphomas and skin tumours found in AIDS patients.

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The immunological anomalies in humans which includes graft rejection, tissue transplantation, immunosuppression, immunoenhancement, malignant diseases, tumour immunology, hypersensitivity, immunopathology, immunodeficiency and autoimmune diseases were fully discussed as well as their immunological properties which will serve as a guide to immunological research activities and disease control.

The ability of normal cells to proliferate in response to cell loss is rigidly controlled within an organ or tissue. In some pathological states, the stimulus for cell proliferation exceeds that required for replacement leading to polyclonal expansion and hypertrophy of tissue [5].

In most circumstances, the expansion and hypertrophy of tissue comes under control with reduction of the growth stimulus. For cells to proliferate out of control requires a transforming event so that the daughter cells continue to proliferate independent of external growth control [6].

The immunology of tissue transplantation

The tissue cells of animals contain molecular structures that are specific for the species of origin of the cell, and which if implanted into an animal of another species will induce an immune response. The response rapidly destroys the implanted cells and has the characteristics of the primary and secondary immune response as already described for antigens in general [7].

In addition to species- species antigens, differences also exist between individual members of the same species so that transfer of tissue cells between members induces a similar immune reaction [8].

The closer the relationship between two individuals of the same species, the more likely are implanted cells to survive. In the case of identical twins, survival is assured. Inbred strains of animals, particularly mice, have been developed which are genetically identical and these are widely used in experimental work on tissue transplantation immunology [9].

Terminology used in transplantation studies (older terminology in bracket) (Table 1)

Table 1:

Relationship between donor and recipient	Term applied to relationship	Prefix applied to graft, antigen or antibody
Of different species	Xenogeneic (Heterogeneic)	Xeno- (hetero)
Of same species but different genetic constitution.	Allogeneic (homologous)	Allo- (homo)
Of same inbred strain (genetically identical)	Syngeneic (Isogeneic) (Isologous)	(Iso-)
Same individual	Autologous	Auto-

In man, surgical techniques are available to enable transplantation of many organs and tissues but unfortunately, a high proportion of organ transplants fail because of rejection by the immune response or because of the side-effects of attempts to suppress the immune response, due to toxicity of the drugs or their depressive effect on resistance to infection [10].

The immunology of graft rejection

Passenger antigen- presenting cells in the graft are believed to provide the main stimulus for graft rejection and include dendritic cells and monocytes expressing MHC class II molecules [11].

These cells present graft antigens to CD_4^+ T- cells along with interleukin-1 (IL-1) and initiate an immune response with the production of effector T-cells and plasma cells. Effector cells

that destroy the graft develop from both CD_8^+ and CD_4^+ subsets of T-lymphocytes [12].

In addition to cytotoxic effects, interferon-gamma is produced that increases expression of MHC encoded molecules on graft tissue that make the graft more vulnerable to destruction by effector cells [13].

There are two main types of graft rejection process.

(a) The so-called "first set" response which occurs about 10 days after a first graft from an unrelated donor [13].

(b) The "second set" response occurring in about 7 days in an animal which had previously received a graft from the same unrelated donor. The phenomenon of first and second set rejection can be compared to primary and secondary immunization- the accelerated secondary response brought about by stimulation of an already sensitized or "primed" immune system [14].

Experimental evidence has shown that only a low percentage of the lymphocytes infiltrating a graft are specifically reactive to graft alloantigens. Lymphokines secreted by Helper T- lymphocytes may be responsible for the migration and proliferation of the majority of the infiltrating inflammatory cells [15].

Graft rejection can be inhibited by in vivo administration of antisera against lymphokines. Adoptive transfer experiments on T-lymphocytes - depleted mice indicate that CD_4^+ T-cells are critical to skin- graft rejection in mice [16].

Furthermore, injections of interleukin- 2 can greatly enhance heart graft rejection in rats. Other cell types may influence graft rejection and it has been found that monocytes and macrophages accumulate in large numbers early in human renal graft rejection [17].

It can therefore be seen that the reaction against a graft depends upon a complex series of interrelated phenomena, some of which are specifically induced by the foreign nature of graft antigens. Other phenomena are non-specific in the immunological sense and occur as part of an inflammatory process [18].

The immunology of clinical transplantation

The first successful kidney transplant was carried out in 1954. Improvements in techniques including the use of immunosuppressive drugs have reduced the incidence of complications. The use of cyclosporine and monoclonal antibody therapy have greatly improved the success rate. Transplant therapy is now also available with the likelihood of success for heart, liver and pancreatic grafts and has transformed the outlook for patients with chronic and debilitating disease of these organs. The most successful transplants are those given at an early stage of the disease [19].

Donor selection normally depends on ABO and HLA compatibility and testing by cross- matching of patient's serum and donor tissue. Improved immunosuppression and

preoperative conditioning procedures have enabled donor tissue to be used that shares 2, 1 or no haplotypes with the recipient [20].

Preoperative random blood transfusion is correlated with improved allograft survival believed to be due to development of suppressor T- cells or anti-idiotype antibodies [21].

Advances in histocompatibility typing, prevention of graft-versus-host (GVH) disease and supportive care have resulted in successful transplantation of bone marrow for several previously fatal diseases. It is the treatment of choice for severe combined immunodeficiency (SCID) and is used with varying degrees of success in aplastic anaemia, acute and chronic myelogenous leukaemia and acute lymphoblastic leukaemia [22].

Efforts to use marrow from partially matched family donors or phenotypically matched unrelated donors show increasing success. "Purging" techniques with monoclonal antibodies against leukaemic neoplastic cells are in the process of development [23].

Liver transplant rejection appears to be due to different mechanisms than kidney rejection. Donor selection depends more on ABO matching rather than HLA (Histocompatibility antigens). Liver seems to be able to resist acute rejection but the mechanisms are not understood [24].

Cyclosporin therapy has had a major effect on the results of transplantation. In heart transplantation, evaluation of donor tissue and recipient depends on HLA typing and detection of any preformed anti-HLA antibodies. A mononuclear cell infiltration of the tissue is found if rejection is taking place along with electrocardiographic abnormalities [25].

There is a 70% survival rate at 5 years. In bone transplantation autografts, or autografts in conjunction with allografts, are the most commonly transplanted tissue. Allografted cells induce antibody production and cell-mediated immunity with resulting bone destruction [25].

Slow revascularization usually occurs and new cartilage and bone is laid down. About 10% of grafts fail. Conventional immunosuppression is rarely used in bone transplantation. A new technique is under development in which donor bone is coated with a biodegradable cement that covers HLA antigens for sufficient time for them to lose their antigenicity [26].

The immunology of immunosuppression

This means prevention of sensitization of immune reaction and also tolerance to graft antigens. Graft rejection, as has been noted, involves a sequence of separate phenomena developing from initial contact of the foreign antigens with the host immunological system through to rejection itself [27].

The steps include establishment of lymphatic drainage, antigen release, its contact with the cells of the immune system, proliferation of antibody-forming cells of the lymphoid tissues, the inflammatory response and release of pharmacological mediators and cytotoxic effects of lymphoid cells and/or antibody on the graft tissues [28].

Interference with any of these stages would likely interfere with the rejection process. One of the most interesting approaches, which is yet unfortunately only at the experimental stage, is interference with what might be termed the afferent arc of the process of rejection, namely the initial sensitization of the lymphoid cells [29].

If it were possible to induce immune tolerance to the strong histocompatibility antigens of tissue grafts, then immunological rejection or immunosuppression will not take place [30].

The tolerant animal although unable to react against the antigen to which it is tolerant can still respond to other antigens such as potentially infective agents like bacteria, fungi or viruses; and this obviates one of the greatest difficulties associated with immunosuppressive procedures [31].

The immunology of immunological enhancement

Another phenomenon relevant to the maintenance of incompatible grafts is "immunological enhancement". This is brought about by antibody produced against graft antigens that can under certain circumstances protect the graft from attack by cells of the immune system. This system has been used successfully in rats with incompatible kidney grafts, the animals being previously immunized with tissue from the protective donor [32].

The grafts exhibit normal renal function for a year or more afterwards. The method has been applied in a few instances to human kidney grafts and the results suggest that the method may be of considerable future value [33,34].

In practice, there are, at the moment, three main approaches to the problem of immunosuppression.

1. X- irradiation to knock out the lymphoid tissues and abolish the immune response.
2. Immunosuppressive drugs – antimetabolites and anti-inflammatory agents to prevent proliferation of antibody-forming cells.
3. Immunological methods – antilymphocyte serum (ALS) produced, for example, in the horse, to attack the lymphocytes directly and destroy them before they attack the graft [35]

The immunology of immunosuppressive therapy

Most immunosuppressive drugs in current use are capable of inhibiting the immune response non-specifically. The aim is to develop agents (drugs, monoclonal antibodies, cytokines) with the ability to act on specific components of the immune system [36].

Among the most commonly used drugs are corticosteroids that are effective in suppressing inflammatory processes and immune responses [37].

Four cytotoxic drugs are in clinical use for immunosuppression: cyclophosphamide, azathioprine, methotrexate and chlorambucil. They are not selectively toxic for lymphocytes and to varying degrees effect all the cells of the immune system (and non-lymphoid proliferating cells) resulting in increased susceptibility to opportunistic infections [38].

Side-effects include pancytopenia, gastrointestinal disturbances and reduced fertility. These drugs are used to treat autoimmune diseases including rheumatic disorders.

Cyclosporin is a more selectively immunosuppressive agent and is able to act on T-helper cells without affecting other T-cell functions, B-lymphocytes, granulocytes or macrophages. This drug has been used for the prevention of transplant rejection. Its major activity appears to be inhibition of IL-2 synthesis and secretion and may impair T-helper cell responses to IL-2 [39].

Corticosteroids and cyclosporine act synergistically. Cyclosporin like other cytotoxic drugs has been associated with B-cell lymphomas and can have effects on CNS, and can cause liver and kidney disease. Cyclosporin is used to act on T-helper cells, inhibit IL-2 production and also for possible reduction of IL-2 receptors. The toxic effects is that it can cause liver and kidney damage, hypertension, neurotoxicity and haemolytic uraemic system [40].

The immunology of tumour and malignant diseases

The ability of normal cells to proliferate in response to cell loss is rigidly controlled within an organ or tissue. In some pathological states, the stimulus for cell proliferation exceeds that required for replacement leading to polyclonal expansion and hypertrophy of tissue.

In most circumstances, the expansion and hypertrophy of tissues under control with reduction of the growth stimulus [41].

For cells to proliferate out of control requires a transforming event so that the daughter cells continue to proliferate independent of external growth control. Humans have 100 or so specialized genes that controls the growth of cells. If they mutate, a single DNA base may change or whole sections of the message are lost. Certain virus oncogenes are inserted into the DNA and these may be responsible for harmful mutations [42]

Most mutations occur in parts of the DNA that do not contain meaningful instructions, or mutations may effect critical areas of the DNA essential for survival of the cell [42].

In discussing the general biological significance of immune reactions in maintaining the integrity of the cellular systems of the body, it should be pointed out that in man in whom more than 10^{14} cells are constantly reproducing, there is sufficient evidence to make it likely that in any given genetic locus an error occurs with a frequency in the range of 10^{-5} to 10^{-7} per replication [43].

This means that in the cell population, there must be many millions of error or mutations occurring every day of life. It seems inconceivable that complex and long-lived multicellular

animals could have evolved unless some means of dealing with this eventuality had been developed [44].

Recently, however, doubt has been expressed on this view and it has been suggested that this daily development of malignant cells is not supported by the experimental evidence, and that spontaneous malignant transformation in vitro appears to be dependent more on cell-to-cell interactions than to be an intrinsic property of single cells [45].

The role of immunological mechanisms in the suppression of malignant cells has been appreciated since the work of Paul Ehrlich at the beginning of the century, but it is only in the last 10 years or so that immunologists have begun to unravel the details of the immunological processes underlying the control of tumours, the antigenic changes in tumour cells themselves and the extent and activities of the immune response arising as a result of these changes [46].

Tumour immunology requires knowledge of the antigenic properties of transformed cells and the ability of the host to mount an immune response to such antigens. Tumour growth itself can have effects on the immune system and these have to be taken into account in designing immunotherapeutic measures to control tumour growth [47].

The immune mechanisms in tumour

There is increased incidence in thymectomized mice of tumours induced by chemical carcinogens and viruses. This seems likely to be due to a deficiency of the cell-mediated immune mechanisms which are under the control of the thymus. Therefore neonatally thymectomized animals are unable to reject incompatible tissue grafts and do not give delayed hypersensitivity reactions of the tuberculin type [48].

These activities depend on intact cell-mediated, thymus-dependent immune reactivity and it is the absence of this reactivity which allows tumour cells to grow unhindered. The experimental evidence in support of this view is conflicting. Thymectomy of mice does appear to increase the incidence of skin tumours to certain chemical carcinogens (polycyclic hydrocarbons) and of tumours induced by DNA viruses [49].

However, early thymectomy seems to have no significant effect on development of spontaneous tumours in mice and there are reports of a decreased incidence of tumours, such as mouse mammary carcinoma, following thymectomy. It therefore appears that the effects of thymectomy are variable and depend to some extent on other factors, such as the agent responsible for tumour development [50].

Another example where deficiency of the cell-mediated immune mechanisms is associated with tumour formation is in a condition known as graft-host-disease. This condition is produced in mice by injecting spleen cells into an unrelated recipient, the reaction of the spleen cells against the host resulting in the destruction of its lymphoid tissues. This can be demonstrated by using two inbred strains of mice, e.g. CBA and C57 black, and injecting the spleen cells of one of the parents into the offspring of such a mating. CBA cells injected into a

CBA /C57B recipient will recognize the C 57 B component of the host –lymphoid cells as foreign but will not be themselves rejected because the recipient itself carries the CBA antigens [51].

The destruction of the recipient's lymphoid tissues, and therefore its cell-mediated immune response, produces a defect in the control of neoplastic cell proliferation leucocytes into virus containing cells capable of continuous growth. The virus appears to have a predilection for cells of the lymphoid organs and it cannot yet be excluded that the virus is a "passenger" trapped within lymphoid cells present in the tumour rather than the prime cause of the tumour [52].

Recent evidence suggests the possibility that the herpes virus may act indirectly on cells by activating a latent RNA tumour virus. Ultraviolet light irradiated herpes simplex virus, whilst unable to destroy mouse cells, resulted in the activation of an endogenous virus similar to the RNA tumour viruses. The possible involvement of a transmissible viral agent in human sarcomas has been proposed in the last few years. A common surface antigen has been found in sarcoma cells derived from bone, cartilage, fat and muscle and induces a detectable antibody response in patient's serum. This antigen can be transferred to normal human fibroblasts by exposing them to the filtered culture medium from sarcoma cells [53].

That the antigen is transmissible to other individuals is suggested by the finding that cohabitants of sarcoma patients have the anti-sarcoma antibody in their serum.

Papillomaviruses have been recently implicated as the cause of neoplastic changes along with herpes viruses in cervical tumours [54].

The immunology of retroviruses, oncogens and tumours

The Rous Sarcoma Virus (RSV) that induces sarcomas in chickens was the first of the retroviruses to be implicated in tumour formation. These mice frequently develop tumours of the lymphoid tissues having many of the features of Hodgkin's disease of humans [55].

A herpes virus (Epstein- Barr) has been isolated from the human lymphoid tumour known as Burkitt's lymphoma and it has been proposed that the tumour is of virus aetiology.

Evidence in patients with Burkitt's lymphoma has added considerable support to the significance of cell-mediated immune mechanisms in the control of tumour. Only 1 of 12 patients, on skin testing with extracts of their own tumour cells, had positive delayed hypersensitivity reactions. However, when the tumour growth was suppressed with cyclophosphamide, skin tests become positive in 7 of the 12 indicating a recovery of the cell –mediated immune mechanisms which is associated with remission of the tumour [56].

Serological studies have demonstrated a strong association between the presence of high titres of antibody to EB virus in both Burkitt's lymphoma and postnasal carcinoma. However, antibody to the virus is widespread throughout the world and

association can be found with a number of diverse disease states [57].

The virus can be found, not only in leucocytes of patients with Burkitt's lymphoma but also in leucocytes of patients with infectious mononucleosis and even in some normal individuals. The virus appears to be able in vitro to transform leucocytes into virus containing cells capable of continuous growth [58].

It consists of two genetic subunits, one being required for viral replication in the host cell and other determining its capacity to induce sarcomas. This latter subunit is termed an oncogene- in this case src-and is not required for normal viral growth [59].

Using radioactive DNA probes synthesized from RSV using reverse transcriptase, the src oncogene could be demonstrated in normal chicken eggs. Since then, oncologists have shown that the src oncogene is present in a wide variety of species. The gene appears to be a normal cellular gene that was in some way picked up by the virus. Its finding has led to the identification of some 20 retroviral oncogenes that can be subdivided into families that share sequences [60].

The way the cellular oncogene is activated so that a virus –infected cell becomes transformed to a tumour cell appears to be by the insertion of proviral DNA that carries sequences that function as control centres for gene expression. The sequences activate the oncogene and lead to overproduction of its protein product and transformation of the cell [61].

Several of the protein encoded by oncogenes are likely to be abnormal versions of cell surface receptors for growth factors and at least one encodes a portion of a growth factor itself [62].

Several of the proteins are found on the inner surface of the plasma membrane so that they may serve to transduce signals received from growth factors acting outside the cell. Such activation phenomena are likely to happen only rarely in virus-infected cells, as viral DNA seems to enter the chromosome of the host cell in a random way. It appears that every human cell contains sets of genes (at least 20 and less than 100) that may become oncogenes when incorporated into retroviruses. These findings emphasize the need for an understanding of growth factors and their controlling mechanisms so that tumour cell formation can be elucidated [63].

HIV is not a transforming virus and is therefore not directly responsible for the lymphomas and skin tumours found in AIDS patients. The crucial factor in AIDS is associated immunodeficiency that interferes with normal immune surveillance mechanisms. These tumours can therefore be compared to the opportunistic infections characteristic of AIDS. Papillomas resulting from human papilloma virus are commonly associated with immunodeficiency states as are EBV-induced tumours (Burkitt's lymphoma) [63].

The immunology of immunity to tumours

Carcinomas of the gastrointestinal tract can be shown to contain an antigen absent from normal adult gut cells

but present in those of embryos. The antigen termed carcinoembryonic antigen (CEA) has been found in the blood of patients with such tumours and their lymphocytes appear to be able to act *in vitro* against their cultured tumour cells in contrast to control lymphocytes that have no effect [64].

The T-cell response to tumour antigens with the help of antigen-presenting cells is responsible for the activation of the immune system. CD_4^+ and CD_8^+ T-cell responses are of major importance in tumour immunity and can mediate eradication of the tumour. The table below summarizes the roles of various cells in the immune system [65].

Summary of immunity to tumour cells (Table 2)

Table 2:

Natural Immunity	Natural killer cells, neutrophil polymorphs, activated macrophages.
Acquired immunity positive	Natural killer cells amplified by gamma-interferon from T-cells activated by tumour antigen. Macrophages acted on by lymphokines MIF, MAF and chemotactic factor from T-cells activated by tumour antigen. Macrophages and k-cells that recognize antibody on tumour cells by their fc receptors (antibody-dependent cell-mediated cytotoxicity -ADCC) complement components produced in inflammatory response that are chemotactic for neutrophils and cause enzyme release from macrophages.
Negative effects	PGE_2 from macrophages and tumour cells suppress NK cells activity.

Antitumour antibody is sometimes found in patient serum and can act by complement-mediated lysis or by antibody-dependent cell-mediated cytotoxicity (ADCC). ADCC may be a more important mechanism than complement lysis. Natural killer cells particularly if activated by cytokines such as IL-2 and IFN- γ are cytotoxic for tumour cells and are believed to be a first line of defence against tumours as well as being recruited later after T-cell stimulation [66,67].

Cytolysins for tumour cells include; natural killer cells, cytotoxic factor, perforins, cytolysins, lymphotoxins and tumour necrosis factor. Their mechanisms of action are not understood. Perforin in mice, which shows a 27% amino acid homology with C9, has a similar molecular mass and shares antigenic determinants [67].

The immunology of cancer immunotherapy

There are four main approaches that are under investigation for the immunotherapy of tumours.

Non-specific immunotherapy has a long history starting with the use of microbial products and more recently synthetic agents and cytokines.

The use of tumour-specific antibodies (passive-immunotherapy) to mediate the effector functions of antibodies or as carriers of radiochemicals, chemotherapeutic agents, or toxins.

Transfer of T-cells from a donor who has been immunized with tumour antigens (adoptive immunotherapy)

Active immunization to induce protective immunity against emergent or existing cancer cells [68-70].

The immunology of tumour antigens

For the immunological system to react against tumour cells, these cells must be changed in such a way so that they are no longer recognized as self. That this is indeed so is substantiated by many examples of tumours which have been found to develop new antigens as part of their cell structure [56,57].

Tumour antigens can be divided into two major categories; those that are unique to a particular tumour, i.e; tumour-specific, and those that whilst found on normal cells are qualitatively or quantitatively different on tumour cells; these are termed tumour-associated antigens [59].

The first category are much more likely to be good targets for the immune response. The latter category is best characterized by the oncofetal antigens. These antigens may be expressed on some normal cells at a particular stage of differentiation. A well-known example is carcino-embryonic antigen (CEA) found in tumours of the gastrointestinal tract. This glycoprotein is not normally found on adult colon but only in fetal gut. CEA can be found in the serum but is unfortunately not a reliable marker for the presence of a tumour as inflammatory lesions such as pancreatitis and colitis, can also lead to the expression of the antigen [60].

Monitoring the level of CEA is however useful in predicting the response to therapy of colonic tumours. Another oncofetal antigen, alphafetoprotein normally secreted by fetal liver is found in the serum of patients with liver and germinal cell tumours [61].

Other antigens found in normal cells may be produced in excess by tumour cells and include T-cell antigens such as CD_5 in chronic lymphatic leukaemia and CD_{10} in acute lymphatic leukaemia. There are numerous examples of tumour formation which seem to be associated with these changes. The SV_{40} virus induces tumours in monkeys, the Rous sarcoma virus (RSV) in chickens and the polyoma virus in mice [62].

Restrictions in tumour immunity includes immune suppression by tumour cell components, excessive tumour size, enhancing or blocking factors, antigenic modulation of human antigens, development of T-cell suppression and tumour cells situated in sites inaccessible to immune system [63].

The immunology of immunopathology

The immune system has been condensed in relation to its role in protection from infection or tumour development and in graft rejection or reaction to transfused blood cells (agglutination). Such responses can be considered as advantageous to the host in terms of removal of foreign material. Protection is sometimes associated with disadvantageous consequences to the host, as is illustrated by the finding of immune complexes with their effects in the kidneys and elsewhere [64].

In other situations, the functioning of the immune system is affected by its exposure to infective agents and in rare instances by inherited defects causing diseases [65].

In normal individuals, self tolerance and the ability to discriminate between self and non-self was an essential feature in the development of the immune system. The ability of the cells of the immune system is not absolute and conditions (largely ill-defined) can arise where self-reactivity, or autoimmunity occurs [66].

These disadvantageous immune responses or immune pathology are under three headings; hypersensitivity, immunodeficiency and autoimmunity [67].

The immunology of hypersensitivity

Immunity was first recognized as a resistant state that followed infection. The immune system protects the host not only from infectious agents but reacts against foreign material such as tissue grafts, blood products and various chemical substances, none of which bear any relationship to infectious agents. However, some forms of immune reaction, rather than providing exemption or safety can produce severe and occasional fatal results. These are known as hypersensitivity reactions and result from an excessive or inappropriate response to an antigenic stimulus [68].

The mechanism underlying these deleterious reactions are those that normally eradicate foreign material but for various reasons, the response leads to a disease state. When considering each of the four hypersensitivity states, it is important to remember this fact and consider the underlying defence mechanism and how it has given rise to the observed immunopathology [69].

Various classifications of hypersensitivity reactions have been proposed and probably the most widely accepted is that of Coombs and Gell. This recognizes four types of hypersensitivity i.e. Type I ; Anaphylactic, Type II; Cytotoxic, Type III; Immune Complex, and Type IV: Cell-mediated or delayed hypersensitivity [69].

TYPE I: ANAPHYLACTIC HYPERSENSITIVITY: If a guinea-pig is injected with a small dose of an antigen such as egg albumin, no adverse effects are noted. If a second injection of the same antigen is given intravenously after an interval of about 2 weeks, a condition known as anaphylactic shock is likely to develop.

The animal becomes restless, starts chewing and rubbing its nose, begins to wheeze and may develop convulsions and die. The initial injection of antigen is termed the sensitizing dose and the second injection, the shocking dose. Post-mortem examination shows contraction of the smooth muscle, especially of the bronchioles and bronchi, and dilation of capillaries. Similar reactions are seen in humans especially after a bee sting or injection of penicillin in sensitized individuals.

Localized reactions are seen in patients with hay fever and asthma. In all these situations, the host responds to the first

injection by producing IgE and it is the level of IgE produced to a particular antigen that will determine whether an anaphylactic reaction will occur on re-exposure to the same antigen [71].

TYPE II: CYTOTOXIC HYPERSENSITIVITY: If antibody interacts with an epitope on a cell, then the cell can be destroyed by a number of mechanisms: The cell can be engulfed by a phagocytic cell by a reduction in the surface charge caused by the interaction with antibody, by direct opsonization and uptake by Fc receptors, or by complement receptor uptake after activation of complement by antigen /antibody complexes.

Cell death can be mediated by the activation of complement and the action of the membrane attack complex. The cell can also be attacked by a distinct cytolytic mechanism that requires the presence of specific target cell-bound antibody. Phagocytes cannot phagocytose large targets. So, granule and lysosomal contents are released in apposition to the sensitized target causing its destruction [41].

The Fc portion of this bound antibody is recognized by the effector cells which destroy the target through an extracellular release of toxic molecules. This antibody-dependent, cell-mediated cytotoxicity (ADCC) is performed by both phagocytic and non-phagocytic myeloid cells (neutrophils, eosinophils and monocytes) and by large granular lymphocytes that have been called "Killer cells". These killer cells are almost certainly natural killer cells that recognize an unknown target cell structure in the absence of antibody but can use antibody if it is present [72].

Type II reactions can be initiated by the binding of antibody to an antigenic component of a cell and include the cytolytic effects seen in mismatched blood transfusions and in Rhesus incompatibility. The production of antibodies to a patient's own cells will give rise to autoimmune diseases [42].

Autoantibodies to an individual's own red blood cells are present in autoimmune haemolytic anaemia. Patient with Hashimoto's thyroiditis have antibodies which in the presence of complement, destroy human thyroid cells. There are many examples of these cytotoxic or cytolytic reactions which are brought about by an immune reaction to foreign substances attached to the cell membranes of erythrocytes, leucocytes or platelets [43].

One of the best-known examples of this phenomenon is Sedormid (apronal) purpura. The complexing of the drug Sedormid with platelets results in the induction of an antibody response directed against the platelet-absorbed drug. This antibody then binds to platelets that have the drug attached and causes destruction of the platelets and purpura [44].

As a result of the elucidation of the mechanism of this disease by Ackroyd in London, Sedormid was withdrawn from use. This type of reaction may be more widespread than generally recognized. A variety of infectious diseases due to Salmonella organisms and mycobacteria are associated with haemolytic anaemia. There is evidence, particularly in studies in Salmonella infections, that the haemolysis is due

to an immune reaction against a lipopolysaccharide bacterial endotoxin that becomes coated onto the patient's erythrocytes [45].

The proper functioning of many cells and processes is controlled by chemical messengers, such as hormones and neurotransmitters, that act by binding to a receptor on the surface of the responding cell. This interaction on the surface of the cell is then transmitted to the interior of the cell and signals the cell to perform the required activity [46].

For example, thyroid stimulating hormone (TSH) produced by the pituitary gland binds to a specific receptor on thyroid cells. This leads to the activation of the membrane adenylate cyclase and the production of the second messenger cyclic – AMP that stimulates the activity of the thyroid cell. Certain individuals produce an antibody against their TSH receptor that does not lead to the destruction of the cell but mimics the effect of TSH [47].

Therefore, there is stimulation of the cells and an over-production of thyroid hormones. Therefore, in type II hypersensitivity, the production of an antibody against a self molecule or to a foreign antigen bound to a cell surface an infectious agent or inert material gives rise to damaging reactions. The damage is caused by the activation of host defense mechanisms in an inappropriate setting [48].

TYPE III: IMMUNE COMPLEX HYPERSENSITIVITY: When soluble antigen combines with antibody, the size and physical form of the immune complex formed will depend on the relative proportions of the participating molecules. The amount of antigen and antibody needed to form a large aggregate will depend among other things on the class of antibody and the valency of the antigen [49].

Under appropriate conditions, the complexes formed can precipitate out of solution. This precipitation reaction is maximal at what is known as equivalence and large complexes will form. Monocytes and macrophages using Fc receptors, are very efficient at binding and removing large complexes. The same cell types can also eliminate the smaller complexes made in antibody excess but are relatively inefficient at removing those formed in antigen excess. The large complexes are also removed by neutrophils but they are inefficient at clearing the smaller, soluble ones [50].

If a situation arises that mimics antigen excess, then the complexes formed are not cleared and their persistence can trigger an acute inflammatory response. This is part of the normal host response to infection; however, if the complex persists or becomes trapped in tissues, then immunopathological reactions ensue [51].

Type III hypersensitivity reactions appear if there is a defect in the systems, involving phagocytes and complement, that remove immune complexes or if the system is overloaded and the complexes are given a chance to become deposited in tissues. This latter situation occurs when antigens are never completely eliminated, as with persistent infection with a microbial organism, autoimmunity and repeated contact with an environmental factor [52].

The tissue damage that results from the deposition of immune complexes is caused by the activation of complement, platelets and phagocytes, in essence, an acute inflammatory response. Complement activation will result in the production of the anaphylatoxins C3a and C5a, that trigger mast cells to release their granule contents. The increased vascular permeability and chemotactic factors produced lead to an influx of neutrophils that begin to remove the immune complexes. During this process, some of the neutrophils release their granule contents of proteolytic enzymes. This leads to more tissue damage and intensifies the inflammatory response. The terminal components of the complement pathway can become attached to the surface of adjacent cells leading to lysis [53].

Type IV: Cell- mediated or delayed hypersensitivity

This form of hypersensitivity can be defined as a specifically provoked, slowly evolving (24 to 48 hours) mixed cellular reaction involving lymphocytes and macrophages. The reaction is not brought about by circulating antibody but by sensitized lymphoid cells and can be transferred in experimental animals by means of such cells but not by serum. This type of response is seen in a number of allergic reactions to bacteria, viruses and fungi, in contact dermatitis and in graft rejection. The classical example of this type of reaction is the tuberculin response that is seen following an intradermal injection of a purified protein derivative (PPD) from tubercle bacilli in immune individuals [54].

An indurated inflammatory reaction in the skin appears about 24 hours later and persists for a few weeks. In humans, the injection site is infiltrated with large numbers of mononuclear cells, mainly lymphocytes, with about 10- 20% macrophages. Most of these cells are in or around small blood vessels [55].

A normal cell- mediated immune response develops when first exposure to the antigen gives rise to a population of antigen- specific memory T-lymphocytes. These cells continuously circulate around the body until they come across the antigen expressed on the surface of an antigen- presenting cell (APC) in association with MHC class II [56].

They are stimulated by this interaction to proliferate and to release lymphokines. The lymphokines are responsible for the cell- mediated host defence mechanisms [57].

Type IV hypersensitivity reactions sometimes develop following sensitization to metals such as nickel and chromium to simple chemical substances such as dyestuffs, potassium dichromate (affecting cement workers) primulin from primula plants, poison ivy and chemicals such as picryl chloride, dinitrochlorobenzene and para-phenylene diamine (from hair dyes) [20,58].

Penicillin sensitization is a common clinical complication following the topical application of the antibiotic in ointments or creams. These substances are not themselves antigenic and only become so on combination with proteins in the skin. The Langerhan's cells of the epidermis are efficient antigen – presenting cells favouring the development of a T-cell response. These cells pick up these newly formed antigens in

the skin and transport them to the draining lymph node where a T- cell response is stimulated [19,59].

Substances that cause cell-mediated hypersensitivity often become directly attached to the surface proteins of Langerhan's cells and are transported to the lymph node [18,60].

Here the specific T-cells will be stimulated to mature and will then return to the site of entry of the offending material and release their lymphokines [17,44].

In a normal situation, these would help eliminate a pathogen but in this case the continual or subsequent exposure to the foreign material leads to an inappropriate response that involve not only the attraction and activation of macrophages but also the stimulation of precursor cytotoxic T-cells into effector cells. These events lead to the elimination of the foreign material. The type IV hypersensitivity state arises when an inappropriate or exaggerated cell-mediated response occurs. Cell-mediated hypersensitivity reactions are seen in a number of chronic infectious diseases due to mycobacteria protozoa and fungi [16,34].

Because the host is unable to eradicate the microorganism the antigens persist and give rise to a chronic antigenic stimulus, therefore continual release of lymphokines from sensitized T- cell results in the accumulation of large numbers of activated macrophages that can become epitheloid cells. These cells can fuse together to form giant cells. Macrophages will express antigen fragments on their surface in association with MHS class I and II and will therefore be the targets of cytotoxic T-cells and stimulate more lymphokine production. This whole process leads to tissue damage with the formation of a chronic granuloma and resultant cell death [15,16].

Granuloma formation is the body's attempt to isolate a site of persistent infection Granulomas can also form following exposure to indigestible inorganic materials such as silica and talc. The skin rash in measles and some of the lesions in herpex simplex infections may be due to cell-mediated allergic reactions where the damage is caused by cytotoxic T-cells [14,65].

Therefore, the cell-mediated immune reactions in a situation where they do not eliminate the pathogen, can lead to tissue destruction. The site is characterized by a mononuclear cell infiltrate peaking at 48 hours The clinical symptoms in these contact dermatitis lesions include redness, swelling, vesicles, scaling and exudation of fluid i.e. eczema [13,23].

The immunology of immunodeficiency states

Immunopathology is as a result of immunodeficiency states. The World Health Organization classification for antibody deficiencies is as follows:

Transient hypogammaglobulinaemia of infancy- as maternal IgG level falls.

Congenital hypogammaglobulinaemia – X-linked or autosomal recessive i.e. male infants only.

Common variable immunodeficiency – heterogenous group of infants or adults.

Immunodeficiency with raised IgM.

Immunodeficiency with thymoma.

Selective IgA deficiency.

Selective IgM deficiency.

Selective IgG subclass deficiency [12,60].

Immune deficiency states result when the immunologically competent cells of the lymphoid tissues, derived from, renewed and influenced by the activity of the thymus, bone marrow and probably gut-associated [11,56].

Lymphoid tissues can be the subject of disease processes due either to defects in one of the components of the complex itself, or secondarily to some other disease process affecting the normal functioning of some part of the lymphoid tissues [10].

In 1953, Bruton first described hypogammaglobulinaemia in an 8-year-old boy who developed septic arthritis of the knee at 4 years of age followed by numerous attacks of otitis media, pneumococcal sepsis and pneumonia [9,11].

Electrophoretic analysis of the serum proteins showed almost complete absence of the gamma globulin fraction. The child appeared unable to give an immune response to typhoid and diphtheria immunization. It is now recognized that this form of deficiency is only one of a group of specific deficiencies affecting the lymphoid tissues which can affect both sexes manifest themselves at any age and be genetically determined or arise secondarily to some other condition [8,65].

Before considering specific defects in the acquired immune response, there are a small number of defects that need to be considered in the innate immune mechanism that possibly involve defects in phagocyte function. These defects in the innate immune mechanism may be summarized as follows:

Congenital agranulocytosis.

Chronic granulomatous disease- due to defect in NADPH pathway of neutrophils, or glucose -6-phosphate dehydrogenase (G6PD) deficiency.

Defective phagocyte responses to chemotactic stimuli.

Deficiency of complement components (rare)- most common and severe in C3 deficiency sometimes associated with autoimmune diseases.

Apart from the above clinical and immunological aspects of immune deficiency states it can also be seen to involve one or more of the different components of the immune system:

The cells responsible for making circulating immunoglobulins.

The cells concerned with the cell-mediated immune response; and

The bone marrow stem cells.

A wide range of laboratory tests are available to investigate the various forms of deficiency [7].

Assay of circulating immunoglobulins can be assessed qualitatively by electrophoresis and quantitatively by immunodiffusion tests. These tests are capable of identifying deficiencies of particular classes of immunoglobulin [6,44,45].

The ability of the patient to make specific immunoglobulin can be tested by active immunization with, for example, a bacterial pathogen such as tetanus toxoid and the antibody response measured by a tube precipitation test. The presence of the cells involved in the humoral immune response can be assayed by making use of the fact that the particular cells concerned- the B-lymphocytes - have receptors on their surface for the Fc component of the Ig molecule and for the C3 complement [5,55-57].

In the test, sheep red blood cells coated with anti-sheep red cell antibody and complement (in non-lytic quantities) are mixed with peripheral blood leucocytes by means of the Fc and C3 receptors (that combine with the antibody and complement on the red cell) forming "rosettes". The proportion of leucocytes forming such rosettes gives an estimate of the number of B-lymphocytes and is normally about 25% of the lymphocytes in human peripheral blood [4,62,63].

The immunology of autoantigenes, autoimmunity and autoimmune diseases. autoantigenes, autoimmunity and autoimmune diseases

A fundamental characteristic of an animal's immune system is that it does not under normal circumstances react against its own body constituents. Mechanisms as we have seen exist that allow the immune system to tolerate self and destroy non-self [30].

Occasionally, these mechanisms break down and autoantibodies are produced. In many individuals, auto antibodies are present but do not appear to cause any problems. However, in other situations, autoimmune diseases may be the sequel to the formation of autoantibodies [20].

There is a wide spectrum of autoimmune disorders some of the diseases where autoantibodies play a role are shown in the table below along with the antigens to which they bind. At one extreme there are the organ -specific diseases where the auto-antibodies are directed against components specific to the organ involved [17].

An example of this is autoimmune thyroid diseases which fall into three categories:

Grave's disease or hyperthyroidism, 2. Hashimoto's disease or hypothyroidism and 3. Myxedema with almost no thyroid function.

In many individuals there is a progression through these three states. The thyroid is an endocrine gland that synthesizes hormones such as thyroxin, that are essential for proper growth

and metabolism In Grave's disease, there is an autoantibody that binds to the thyroid stimulating hormone (TSH) receptor and causes the release of thyroid products in the absence of TSH [25].

This is a type II hypersensitivity reaction and gives rise to an over-reactive thyroid. In Hashimoto's thyroiditis, an antibody specific for a thyroid protein, thyroglobulin, is present. The gland becomes infiltrated with lymphocytes and phagocytes causing inflammation and goiter (enlargement of the thyroid) [39].

In addition to the cell-mediated destruction, the antibody against thyroglobulin is thought to add to the disease process by causing complement lysis of thyroid cells that are coated in thyroglobulin. The more progressive destruction seen in myxedema involves a number of immune mechanisms including autoantibodies against a number of organ- specific components. The destruction is mediated by macrophages and almost all function is lost [4].

At the other end of the autoimmune spectrum are the non-organ-specific diseases where both the lesion and antibodies are not confined to one organ Systemic lupus erythematosus (SLE) is an example of such a disease. This condition is characterized by a butterfly- shaped facial rash resembling the colouring of a wolf (Lupus being Latin for wolf), it is systemic, i.e. multi-organ involvement and erythematosus refers to the redness of the skin rash [52].

Range of autoimmune diseases (Table 3)

*Relative risk is a measure of the increased chance of developing the disease for individuals of particular HLA antigen type relative to those lacking the antigen. Autoantibodies against DNA are present but others are found that react with a number of cellular constituents. Immune complexes are formed between these antibodies and products of damaged cells, e.g. DNA [69].

These immune complexes can form or become deposited at a number of sites. Generalized inflammation will be stimulated

Table 3:

Disease	Antigen	Hla- Link	*Relative Risk
Hashimoto's thyroiditis	Thyroglobillin	DR5	3.2
Primary myxoedema	Cell surface	DR3	5.7
Grave's disease	TSH receptor	DR3	3.7
Pernicious anaemia	Intrinsic factor	DR5	5.4
Insulin- dependent diabetes	Islet cells	DR3, DR4, DR3/4	5.0, 6.8, 14.3
Good pasture's syndrome	Glomerular and Lung basement membrane	DR2	13.1
Primary biliary cirrhosis	Mitochondria	-	-
Ulcerative colitis	Colon lipopolysaccharide	-	-
Rheumatoid arthritis	IgG	DR4	4.2
Systemic lupus erythematosus	DNA, nucleoproteins	DR4	5.8

by these complexes as will antibody- dependent cell – mediated cytotoxicity and activation of phagocytes. The disease can go into remission when the source of the antigen is removed and the immune complexes are cleared away [69].

It will however return if more cell damage occurs. In between these two extremes are disorders where the lesion tends to be localized to a single organ but the antibodies are non-organ-specific [8,9].

In primary biliary cirrhosis the small bile ductule is the main target of the inflammatory cells but the antibodies are directed against an organelle found in all cells- mitochondria [9].

A number of patients with autoimmune diseases tend to suffer from more than one condition. When this happens, the disease tend to come from the same region of the autoimmune spectrum. Therefore patients with thyroiditis have a much higher incidence of pernicious anaemia than would be expected in a random population [11,16].

The same situation is found at the non-organ-specific end where SLF is associated with rheumatoid arthritis and a number of other disorders. Genetic factors appear to play a role in the development of autoimmune diseases. Autoimmune diseases are found to run in families close relatives of sufferers tend to have elevated levels of autoantibodies although these may not manifest themselves as an overt disease [12,13].

There are also strong associations between several autoimmune diseases and particular HLA specificities, suggesting that Ir gene effects may be involved. The question now arises of how antibody formation can be triggered. There are a number of ways in which the self- tolerance mechanisms could be overcome [13,14].

The first involves the exposure of the immune system to molecules that are normally sequestered within organs. It is proposed that any mishap that caused release of these molecules would provide an opportunity for autoantibody formation. Hidden or sequestered antigens do appear to exist and the best examples of these are sperm and lens tissue [14].

However, it appears that the injection of extracts of these tissues does not readily elicit an antibody response and that many of these sequestered molecules do indeed enter the circulation. Therefore, the accessibility of a molecule to the immune system does not appear to be of major importance in the generation of autoimmunity. What may be more important for the generation of an immune response is whether the molecule is presented to the immune system in a form and at a concentration that can stimulate a response [15].

For an immune response to be generated, the antigen will have to be presented on the surface of a cell in association with MHC class II molecules and this complex must be recognized by a helper T- cell. Since autoreactive B-cells can be easily detected and it appears that self peptides can associate with MHC molecules, the key to the control of autoimmunity must be at the level of the T-cell [16].

As discussed above, when considering tolerance in the normal situation T-cells can be unresponsive because of clonal deletion, active suppression caused by other T-cells or macrophages or failure of antigen presentation. There are a variety of ways in which this unresponsiveness could be altered and give rise to autoimmunity [17].

Experimental studies of tolerance evasion by altered antigens have been carried out with purified proteins, conjugates of haptens and proteins and with cellular antigens. Some of the most definitive work is that carried out by Weigle who showed that rabbits made tolerant with bovine serum albumin (BSA) and then immunized with the cross- reacting antigen human serum albumin (HSA) eventually made antibodies which could react with BSA. The same result was obtained with chemically modified BSA in place of the HAS [18].

In the tolerized state B- cells with the potential to make anti-BSA antibodies are present but they are unable to produce any antibody because of the lack of T- cell help. The BSA specific T-cells that could provide this help have been made unresponsive by the induction of tolerance. When HSA which contains some B- cell epitopes in common with BSA is injected the rabbit will be exposed to a new set of T- cell epitopes, carrier determinants that can stimulate the HSA specific T-cells to provide help for the B-cells [19].

A closer approximation to autoimmune disease is provided by experiments using thyroglobulin in rabbits not only are antithyroglobulin antibodies induced by injection of altered thyroglobulin but inflammatory lesions are also found in their thyroid glands [20].

When certain drugs bind to tissue proteins they can induce structural modifications the resulting complex drug and self molecule can give rise to a type II hypersensitivity reaction as described above [21].

However it can also generate a new carrier determinant that will induce help for autoreactive B-cells. An example of this is the autoimmune haemolytic anaemia associated with the treatment of hypertension by x- methyl dopa. A metabolic breakdown product of x- methyl dopa is thought to modify proteins on the surface of the red blood cells in such a way as to generate a structure that can give rise to a T-cell epitope. The stimulated T-cells are then able to provide help for B-cells that are reactive to the Rhesus e antigen [22].

The autoantibody produced will then bind to the patient's own normal red blood cells and cause their destruction through a complement – mediated mechanisms. There are other examples of this type of reaction; including isoniazid which gives arthritis and procainamide which stimulates the production of antinuclear antibodies. There are a number of examples where potential autontigenic determinants are present in exogenous material [23,50].

These preparations may provide a new carrier, ie; T-cell stimulating determinant provide a new carrier, i.e. T-cell stimulating determinant that provokes autoantibody formation.

The encephalitis sometimes seen after rabies vaccination

is thought to result from a response directed against the brain that is stimulated by heterologous brain tissues present in the vaccine.

Microorganisms are a source of cross-reacting antigens sharing antigenic determinants with tissue components. These may provide an important way of inducing immunity. There is an antigen in human colon extractable even from sterile fetal colon, that cross-reacts antigenically with *Escherichia coli* 014 [24].

It is possible that the inflammatory condition known as ulcerative colitis in which anticolon antibodies are found, is due to an immune response initiated by the cross-reacting bacterial antigen [25].

Similarly, the group A Streptococci which are closely associated with Rheumatic fever and antiheart antibody is found in just over 50% of patients with this condition [26].

Nephritogenic strains of type 12 group A *Streptococci* carry surface antigens similar to those found in human glomeruli, and infection by these organisms has been associated with the development of acute nephritis. Some of the immunopathology seen in Chaga's disease has been attributed to a cross-reaction between *Trypanosoma cruzi* and cardiac muscle [27].

A new helper determinant may appear on a cell due to drug modification, as described above or during viral infections these new cell surface antigens (often known as neoantigens) then promote production of antibodies against other normal molecules [28].

It has been shown that infection of a tumour cell with influenza virus produces a response towards uninfected tumour cells [29].

Infection with *Mycoplasma pneumonia* which is responsible for a disease known as primary atypical pneumonia is associated with the appearance of cold agglutinins. These IgM antibodies often directed against blood group I, react with the patient's red cells in the periphery where the temperature is lowest [30].

Another way that autoimmunity may be triggered is by some breakdown in the immune network. This could occur at the level of cellular production or at a functional level of production defects could arise that allow self-reactive cells to survive [31].

It is believed that suppressor cells play an essential role in maintaining non-reactivity to self-antigens. Interference with suppressor cells may lead to autoimmune disease by allowing the immune system to interact positively with self antigens [32].

Autoimmunity can be induced by bypassing T-cells Self-reactive cells can be directly stimulated by polyclonal activators that directly activate B-cells. A number of microorganisms or their products are potent polyclonal activators; however, the response that is generated tends to be IgM and to wane when the pathogen is eliminated [33].

Bacterial endotoxin the lipopolysaccharide of Gram-negative bacteria provides a non-specific inductive signal to B-cells by passing the need for T-cell help. A variety of antibodies are present in infectious mononucleosis including autoantibodies that are caused by the polyclonal activation of B-cells by Epstein-Barr virus [34].

Breakdown in the idiotypic network is another way of activating self-reactive cells. Lymphocytes are linked in a network through interactions involving the variable regions of their surface receptors. Because T-cells have a receptor with a variable region they can also stimulate anti-idiotypic responses and their activities can be influenced through idiotypic interactions [35].

In the normal unstimulated situation, these interactions keep the immune system in equilibrium but when antigen is introduced the network is initially tipped towards production of a response and then returns to the "ground state" through the development of suppressor signals [36].

It should be remembered that idiotypic interactions can act as either inhibitors or activators of the immune response, depending on the information received. There are a number of situations where signals could be generated that leads to an autoimmune response. The antibody produced in response to a microorganism could interact with the idiotope on a self-reactive cell to give a stimulatory signal and an unreactive response [37].

The foreign material might trigger the production of an antibody that has an idiotope that is found on other immunoglobulins or T-cell receptors (a cross-reacting idiotope or public idiotope) This cross-reacting idiotope could stimulate autoreactive cells that share this idiotope or are linked through an anti-idiotypic interaction [38].

Microorganisms use cell surface molecules as attachment sites therefore if a response is generated against the microbial structure an anti-idiotypic-antibody to this will be an autoantibody [39].

The consequences for the host control could be quite devastating since a number of microorganisms use important molecules as their site of attachment and entry. This can be extended to include other mechanisms described above. A viral infection can induce a neoantigen on the cell surface that is able to provide help for B-cells that produce antihormone antibody. The antibody will be capable of binding to the hormone-producing cells and instigating cell damage [40].

In addition, anti-idiotypic antibodies generated against this antibody will have anti-receptor activity [41].

Since proper antigen presentation is essential for the initiation of an immune response, it is possible that defects in antigen-presenting cells or aberrant expression of MHC class II antigens may lead to an autoimmune response.

Undoubtedly, autoimmune diseases have a multifactorial aetiology and a number of the proposed mechanisms may contribute in different combinations to different disorders [42].

The immunology of other diseases associated with auto-immune states

There is a large reservoir of diseases in which some form of autoantibody has been found but where neither the stimulus for autoantibody formation, nor the role if any, of immune reactions has been elucidated [43].

Among these conditions is rheumatoid arthritis in which an IgM antibody called Rheumatoid factor is present in the serum.

This antibody is detected in vitro by its ability to agglutinate red cells or latex particles which have been coated with IgG globulin. The rheumatoid factor does not appear to be directly involved in the pathogenesis of the disease and no satisfactory explanation has been offered to account for its pathogenesis [44].

The possibility has suggested that infective agents are involved, such as mycoplasma or chronic infective bacterial agents, and there are reports of the isolation of such agents from rheumatoid joints in man and arthritis in a number of other species [45].

One suggestion is that the infective agent may modify the lymphoid tissues so that there is a failure of the normal tolerance control mechanisms. This might involve activation of pre-existing autoimmune T-cells inducing polyclonal B-cell activation, or the infective agent sharing epitopes with autoantigens in host cells. Experimental arthritis can be induced in rats by the injection of Freund's complete adjuvant containing killed tubercle bacilli. This is a polyarthritis with mononuclear cell infiltration similar to the arthritis found in a human illness known as Reiter's syndrome the main features of which are urethritis and arthritis and which may occur in the presence of a mycoplasma infection [47].

Mycoplasma arthritidis can also induce acute and chronic joint inflammation in rats and mice similar to that in rheumatoid arthritis [48].

Uveitis, conjunctivitis and urethritis are also sometimes found. Mycoplasmas produce mitogen (MAM) that is a potent inducer of gamma- interferon in both murine and human lymphocytes. MAM is a member of a group of microbial toxins known as superantigens that induce a polyclonal B- cell response through an action in mice carrying I-E molecules [49].

MAM is believed to act as a bridge between T -helper cells and B-cells that express a receptor for MAM (I-E in mice) Recent evidence suggests that there may be an IgG form of rheumatoid factor present in both the blood and joint fluid of rheumatoid patients as well as the IgM type and that injection of autologous purified IgG into previously unaffected joints can induce acute arthritis [50].

Further evidence suggesting that an antigen - antibody reaction is taking place is provided by the low competent levels found in patient's joint fluid and the presence of immune complexes. Rheumatoid factors react with the Cy2 domain of

the Fc fragment of IgG (rabbit or human) but not with the Fab fragment [51].

Rheumatoid factors are sometimes found in patients with diseases other than rheumatoid arthritis. These include systemic lupus erythematosus Sjogren's syndrome, scleroderma lymphoproliferative disease in certain persistent bacterial, protozoal and viral infections [52].

Even healthy subjects sometimes have low titres of the factor in their serum, particularly in the older age groups. The mechanism underlying the appearance of these rheumatoid (antiglobulin) factors is not clear. In chronic infections, it is conceivable that the factor is a response to antigenic determinants on the IgG molecule that are exposed when IgG antibody complexes with the infective agent [53].

In the healthy individual, a low titre of rheumatoid factor may perhaps serve a physiological function as a way of clearing degraded immunoglobulin molecules arising during infective or inflammatory processes [54].

HLA-B27 individuals who become infected with Salmonella, Yersinia, Shigella and Gonococci often develop arthritis suggesting that HLA-B27 acts in conjunction with the bacterial infection to cause the development of autoantibodies [55].

Recent evidence has emerged indicating that patients with rheumatoid arthritis show enhanced responses to conserved bacterial products known as heat shock proteins and has stimulated considerable interest among immunologists and rheumatologists as a possible explanation for the pathogenesis of the disease. Heat shock proteins (HSPs) were first shown to be produced by cells in culture when their temperature was raised above 37 °C. Their production has since been demonstrated in a wide range of eukaryotic and prokaryotic cells with extensive structural homology and cross- reactivity between foreign and self HSPs. HSPs are normally engaged in the stabilization of newly synthesized polypeptides in order to ensure correct protein folding and intracellular transport of proteins for secretion from cells [56,57].

Since fever is a physiological stimulus to HSP production it may exert beneficial effects on the repair of damaged proteins in inflammation. Because of the cross- reactivity between microbial and mammalian HSPs, their generation within infected cells may lead to an autoimmune response [58].

Raised levels of antibodies to the 65KD HSP of mycobacteria have been found in the serum of patients with rheumatoid arthritis their synovial T-lymphocytes proliferate in vitro to this HSP and epitopes of the HSP can be found in the synovial tissue.

Additional evidence for the importance of HSPs in arthritis is the finding that Lewis rats that are susceptible to the development of adjuvant arthritis can be protected by vaccination with mycobacterial HSP [57].

Furthermore, the sensitivity of individual animals to develop adjuvant arthritis seems to depend on the ability of

their T-cells to respond to HSPs. It has recently been suggested that responses to HSPs may be related to a genetically inherited defect in the regulation of T-cell development so that a population of fetal type T-cells (with a $\gamma\delta$ T-cell receptor) and B-cells of B-1 (CD 5⁺) type are expanded in patients with rheumatoid arthritis.

It is hoped that these various observations will lead to a clearer understanding of the mechanisms underlying the pathogenesis of rheumatic diseases.

Diabetes mellitus of the insulin -dependent type is believed to involve both an inherited susceptibility and environmental factors in the pathogenesis. The details of these interacting factors and their role are poorly understood. Susceptibility to the disease shows linkage to HLA haplotype inheritance with families whatever the actual HLA phenotypes may be.

A child that is of identical HLA phenotype to a diabetic sibling is likely to be susceptible.

Peak incidence of the disease is between 10 and 14 years with a prevalence in white western populations of 0.25% showing seasonal fluctuation and a slight predominance in males. More than 90% of patients have HLA-DR3, - DR4 or both and there is a negative association with HLA-DR2 [59].

Patients show evidence of lymphocytic infiltration (particularly CD8 T-cells) in the pancreatic islets even before glucose intolerance is found eventually, destruction of beta cells occurs with atrophy and scarring. Autoantibody against pancreatic islet cells is found in 50– 80% of these individuals and when it is of the complement fixing type, seems to lead to islet cell damage [60].

The antibody appears early in the disease before clinically obvious diabetes and serves as a marker of Islet cell damage before progressing to insulin insufficiency. This suggests the possibility for development of measures to arrest islet cell destruction before diabetes occurs [61].

More recently an insulin autoantibody has also been found in the prediabetic preinsulin treatment phase. In diabetes, the pathological changes include the presence of inflammatory cells surrounding the islets (insulinitis) and the presence of MHC class II molecules on Islet cells.

The latter finding led to the hypothesis that the MHC class II molecule might be responsible for presenting the islet cell antigens to T-helper cells but experimental studies on hyper expression of MHC antigens on pancreatic Islet cells have not so far supported this hypothesis [61].

Local expression of interferon gamma and other cytokines in the pancreas has been shown to lead to destruction of the islet cells and raises the possibility that a virus infection with a consequent host cytokine response could be responsible for the pathological changes.

Although Coxsackie viruses are known to infect islet cells (as well as the myocardium), it has not been possible to implicate

the virus in the pathogenesis of type I diabetes. Animal models of the disease suggest that there are defects in the immune regulation with depletion of a subset of T-cells (RT6* T- cells).

The immunology of multiple sclerosis (Ms)

Another disease believed to have an autoimmune basis is associated with a variety of HLA antigens (A3, B7, DR2) with DR2 showing the highest relative risk of 4.1 compared with approximately 2 for each of the other antigens. Subgroups of DR2 also appear to be involved. In large survey of Canadian MS patients over half were DR2 compared to 285 in controls [61].

Relative risk rates have been estimated as above 5% for siblings of patients and for their parents aunts and uncles.

In contrast, it is about 1% for children of patients compared with 0.1% for the population at large. The multifactorial basis of the disease is emphasized by the finding that lapps and gypsies over 50% of whom are DR2 have a very low incidence of MS. The increased prevalence of the disease at higher latitudes appears to be accounted for by the percentage of the population of Scandinavian ancestry. A large amount of contradictory data has been reported and it seems likely that different genetic backgrounds with various environmental factors may produce different susceptibility patterns [62].

It is likely that loci in addition to HLA along with environmental influences are also involved. Recent evidence implicates particular haplotypes of the T-cell linked to pathogenesis and requires the study of T-cells isolated from lesions [63].

Like rheumatoid arthritis, the nature of the initiating event is unknown. A number of viruses produce demyelinating disease in animals such as canine distemper virus visna virus in sheep and goats and murine encephalitis viruses. This has led to the suggestion that molecular mimicry between viral antigens and host tissue antigens may exist and be responsible for auto-immunization [64].

In a recent report HTLV-like viral RNA has been found in cells cultured from the CSF of MS patients. The disease is characterized by perivascular cellular infiltrates and demyelination of the white matter of the central nervous system [63].

The plaques that are formed show a depletion of oligodendroglial cells and proliferation of astrocytes. Evidence for a possible immune pathogenesis comes from the finding of macrophage-like cells with lipid inclusions and lymphoid cells in these lesions.

Identification of the cell types has become possible using monoclonal antibodies to a variety of cell surface markers.

Large numbers of cells bearing MHC class II molecules are present at the edges of the plaques decreasing towards the center. CD₄⁺ and CD₈⁺ cells have also been found both around and within the plaques but no B-cells. These findings along with the additional presence of interleukin-1 and prostaglandin

E₂, suggest that an active immune process is taking place in the lesions of multiple sclerosis [64].

These findings in humans are supported by extensive evidence from work with animal models of the disease in which demyelination can be induced by immunization with myelin basic protein and in which susceptibility can be transferred to normal animals by spleen cells of the immunized donors.

More recently, T- cell clones have been developed with specificity for myelin basic protein that produce typical disease in rats [65].

The immunology of myasthenia gravis

The main feature of *Myasthenia gravis* is muscle weakness due to a disorder of neuromuscular transmission. The prevalence is between 2 and 10 per 100,000 and can occur at all ages. There is sometimes an association with the presence of a thymoma, thymic hyperplasia and autoantibodies [66].

Before the age of 40 and in the absence of a thymoma females appear to be more susceptible and there is an association with HLA – A1, –B8 and –DR3. In contrast patients over 40 without a thymoma show an association with HLA –A3, –B7 and –DR2 with a preponderance of males [67].

Patients with a thymoma over the age of 40 show no sex or HLA association. There is frequently an association with other autoimmune conditions (e.g. Systemic lupus erythematosus). Anti-acetylcholine receptor antibodies are found in 90% of patients. These antibodies and immune complexes induce complement –mediated destruction of the post –synaptic membrane with loss of receptor sites for acetylcholine. Anti-cholinesterase drugs and thymectomy are the mainstay of treatment as well as the use of immunosuppressive agents and/or plasmapheresis to remove the antibody [68].

In experimental models of the disease in mice, monoclonal antibodies to CD₄⁺ T- lymphocytes suppressed established disease and prevented loss of acetylcholine receptors. Similar approaches have been applied to mouse models of systemic lupus, experimental autoimmune encephalomyelitis and collagen-induced arthritis.

An interesting development is the use of monoclonal antibodies against a single T-cell clone specific for myelin basic protein that appears to protect rats from the development of experimental autoimmune encephalitis. Although the possible side –effects of therapy that is directed at lymphocyte subpopulations (e.g. susceptibility to infection) are unknown, it seems likely that this approach will be tested in patients with severe life-threatening forms of autoimmune disease in which other forms of therapy have proved ineffective [69].

The immunology of antibodies as a consequence of tissue damage

In considering the role of antibodies as a possible cause of autoimmune disease, it should be remembered that antibodies of IgM type directed at subcellular antigens, can

be readily induced by various forms of tissue damage these arise secondarily to the damage and appear to have no role in perpetuating it [69].

The table below gives some examples of autoimmune disease and the autoantibodies found (Table 4).

Antibodies of this type have been shown in the laboratory and can readily be induced in rats by the injection of the hepatotoxic agent, carbon tetrachloride. It was subsequently found that normal rats mice and hamsters have some IgM anti-tissue antibody in their serum. A possible physiological role for these antibodies is suggested by the finding in vitro of a chemotactic effect on rat polymorphs of a mixture of the antitissue antibody and its antigen [70].

Therefore the antibody might be responsible for initiating

Table 4: Examples of autoantibodies in disease

Disease	Autoantibody Specificity
Autoimmune haemolytic anaemia	Erythrocytes.
Thrombocytopenic purpura	Platelets
Systemic lupus erythematosus	Nuclear antigens and antigens of various tissues and blood cells
Rheumatoid arthritis	Immunoglobulin G
Primary biliary cirrhosis	Mitochondria
Ulcerative colitis	Colon lipopolysaccharide
Hashimoto's thyroiditis	Thyroglobulin
Thyrotoxicosis	Cell surface thyroid stimulating (TSH) receptors.
Pernicious anaemia	Intrinsic factor
Myasthenia gravis	Acetylcholine receptors (and certain muscle tissue)
Juvenile diabetes (type 1)	Islet cell surface

a phagocytic cell clearing process to deal with the breakdown products of normal cell turnover.

Conclusion

Recent evidence indicates that IgG antibody existing in the normal individual seems to be able to recognize glycoprotein determinants which appear on aged red blood cells.

The determinants are exposed following the loss of sialic acid groups from the outside of the cells on ageing. Their exposure can be reproduced experimentally by treatment with neuraminidase. The IgG antibodies bind to the exposed glycoprotein and enable the attachment of the red cell to the Fc receptors on a macrophage.

The aged red cell is then phagocytosed and destroyed by the lysosome enzymes of the macrophage. All autoantibodies are therefore not necessarily autoregressive although the history of immunity and protection inculcates the idea of antibodies acting solely as aggressive agents [71].

In this article, we reviewed the antigenic properties of the transformed cells and the ability of the host to mount an

immune response to such antigens. Immunological errors itself can have effects on the immune system and these have to be taken into consideration in designing immunotherapeutic measures for the control of chronic and debilitating infectious diseases i.e. HIV is not a transforming virus and is therefore not directly responsible for the lymphomas and skin tumours found in AIDS patients.

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