

**THE DEVELOPMENT OF
IMMUNOLOGY AND ITS
EFFECTS ON THE
MEDICAL SCIENCES**

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**Inaugural address delivered on accepting the Chair of Medical Laboratory Sciences
at the University of the North on
Wednesday, the 31st March, 1982.**

PIETERSBURG

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Phil. cand. (Lund) D.Sc (Pret.)

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Mr. Vice-chancellor, ladies and gentlemen,

1. Introduction

When bacteriology was discovered about 100 years ago, all diseases were believed to be due to infections. Today immune reactions are being incriminated as being involved in most disease processes and perhaps this is not completely unwarranted since it is realised that immunological concepts apply to diverse medical conditions ranging from the appearance of a simple furuncle in the skin to the means whereby the body combats the spread of cancer.

Fundamental discoveries in immunology have influenced the development of every branch of the medical sciences. Diseases like cancer, degenerative diseases, rheumatology, nephritis etc. have an immunological basis as have dermatological disorders, neurology, G-I disorders, allergy and psychiatric diseases. It is realised that a growing number of patients have immunological deficiencies or abnormal immune responses as their sole basis for their diseases. Furthermore immunological investigations have helped in our understanding of inflammation — the basis of pathological changes and tissue repair.¹

Not only are concepts in immunology related to the causation of disease but principles of immunology are used in the treatment and prevention of infection. Pharmacologists must be aware of the fact that chemotherapeutic agents alter the individual response to infections or to any immunological stimulus, and that drugs can cause severe allergic reactions. Major operations depend on the availability of blood selected by immunological methods. Organ transplantation is made possible by our understanding of the Major Histocompatibility Complex. Many diagnostic methods are based on sensitive immunological tests like RIA*. In haematology and histopathology immunological methods are used as diagnostic aids. Microbiology is to a large extent based on immunology. In this lecture I will discuss some of the major developments in immunology and show their influence on the medical sciences.

2. Immune System

The immune system is a complex network consisting of cells, receptors for antigens on the cell surface, and molecules-including antibody molecules which interact with one another in a genetically controlled manner which then leads to differentiation of the B-cell into a plasma cell, or of the T-cell into a sensitised T-cell. In addition products of the Ir-genes are involved. The cells which belong to the immune system are the phagocytic cells, lymphocytes and plasma cells.

*Radio immuno assay

That the inflammatory reaction is important in the expulsion of foreign bodies including micro-organisms was recognised in the 18th century, but it was not until the middle of the 19th century that it was conclusively shown that white cells were involved in the destruction of micro-organisms.² Since these white cells could ingest foreign bodies they were called "phagocytes" which means cell-eating and until the end of the 19th century the prevailing view was that phagocytosis was the keystone of body defence. There are two main types of phagocytic cells in the body, the polymorphonuclear (PMN) cells and the macrophages.

The PMN migrate to the area of infection due to chemotaxis and kill bacteria through phagocytosis. Depression or absence of PMN cells is a life threatening condition where there is a rapid bacterial spread and this can occur after taking certain drugs or chemicals, and also in virus infections. However, the inflammatory response can also cause tissue damage and the contribution of PMN cells to this destructive process can be seen in diseases like nephritis, rheumatoid arthritis, gout, etc.

The second type of phagocytic cells are the macrophages. These cells are derived from the bone marrow and first circulate in the blood as monocytes and only when they migrate to the tissues do they reach maturity and become macrophages. In this process they develop motility, phagocytic capability, and enzymes like esterases, lipases, and hydrolases and are able to attack and digest the lipid-rich bacteria.²

The macrophages are also essential in the initiation of some immunological responses: that is, certain micro-organisms must first be processed by the macrophages before lymphocyte activation can take place. Macrophages have membrane receptors for antigen and complement so that they can ingest antibody-coated bacteria and destroy them, which is important in the body's defence mechanism.

The other type of cells involved in the immune response are the lymphocytes which are present in blood, lymphnodes, spleen (white pulp), tonsils and appendix. The lymphocyte is a very simple cell with a nucleus surrounded by a thin rim of featureless cytoplasm. This simplicity in morphology misled scientists for two centuries and only recently has it become clear what an intricate role this cell has in the immune response or actually that the lymphocyte is the immune system.³

In the early 1950s the evidence linking the lymphocyte to the immune response was unsatisfactory and the function of this cell an enigma, and it was only in the decade of 1958/68 that rapid advances were made; and today the lymphocyte is the most-studied cell in the body, and has contributed the knowledge of many fundamental cellular processes e.g. organization of cell membrane, and how specific proteins are assembled according to genetic instruction and then packaged and secreted across the cell membrane. The study of the lymphocyte has shown the presence of a cytoskeleton consisting of micro filaments and micro tubules and clarified their function.³

The lymphocytes can be divided into two main classes which both originate in the bone marrow from pluripotential stem cells. The lymphocyte programmed to become a T lymphocyte goes to the thymus where it matures to a T lymphocyte and it is then released into the circulation to help populate the thymus dependent area of the lymphnode and spleen.

The B lymphocyte also originates in the bone marrow, but where the maturation of the cell takes place in humans is not known although in birds this process occurs in the bursa of Fabricius. The cell migrates to the thymus independent areas of the lymphnode and spleen. Both T and B lymphocytes have specific receptors on their surface which can recognise and react with antigens.

These receptors show specificity that is a particular receptor can only bind one type of antigen. The receptors on the B lymphocyte are immunoglobulins while the receptors on the T cell have not yet been identified. When a B cell is stimulated by the interaction of antigen with the receptor on the cell surface it becomes transformed to a blast cell, and then to a plasma cell, which then starts synthesising antibodies against the antigen that caused its stimulation. Due to recombination and gene re-arrangement we are able to respond to 10^7 antigenic determinants including some antigens not yet detected⁴.

When a T cell is activated by an antigen it also changes into a blast cell and then becomes a sensitised T-cell responsible for the delayed type of hypersensitivity of cellular immunity with the formation of cytotoxic cells and lymphokines like MIF, MAF, interferon etc. The cytotoxic cells can cause lysis of the antigen and the lymphokines activate the macrophages so that they become more active. During the last five years it has been realised that the T cells are a heterogenous group of cells consisting of helper cells, suppressor cells and killer cells. Helper cells are involved in the augmentation of the antibody formation and suppressor cells inhibit antibody formation. For maximum antibody formation to occur a complex interaction must take place between macrophages, B and T cells at least in vivo and probably the situation is similar in vivo. The macrophage takes up the antigen, processes it and presents it to the T-cell together with the Ir-gene product. On the T-cell one half of a receptor on the cell surface is coded for by the VH gene and this part is specific for a particular antigen. The other part of the receptor binds to the product of the Ir-gene from the macrophage.⁵

The T-cell then passes a similar product to the B-cell and antibodies are formed with the same specificity as the receptor on the cell surface. In the meantime the suppressor T-cell has also been activated by the macrophage product and a signal goes out from the suppressor cell to the helper cell and tells it to stop helping the B-cell, and antibody production stops. Due to these complex interactions the synthesis of antibodies is well controlled. If the proliferation of B-cells were not controlled there would be an over production of antibodies as seen in diseases like multiple myeloma, lymphomas and leukaemia.

The products of the B-lymphocyte activation are antibodies or immunoglobulins. These are proteins which can combine with antigens and in this way render antigen susceptible to engulfment of macrophages, or the antigen-antibody complex may activate the complement system with resulting lysis and destruction of micro-organism,

The presence of antibodies in serum was discovered in 1880 by Behring and Kitasato⁶ although they did not know which cells were responsible for antibody synthesis. It was only in 1948 that it was conclusively shown that plasma cells were involved by using a fluorescent technique.⁷ That specific antibodies were produced by plasma cells was shown by Coons⁸. In this case a rabbit was injected with diphtheria toxoid, the lymphnode removed, and frozen sections made. The antigen, in this case the toxoid, was then allowed to react with the cells in the lymphnode and fluorescein - conjugated diphtheria anti-toxin added, and the presence of antibodies in the plasma cell was shown indicating that the plasma cells were responsible for the synthesis.

Today immunofluorescence techniques are used extensively to show the presence of either antigen or antibody in tissues or cells, and it has greatly aided the classification of e.g. lymphomas, so that more specific treatment can be instituted. However, before this it was observed that serum from animals immunised against toxins of diphtheria contained anti-toxins and that this serum would confer passive immunity when injected in other animals. This led to active immunisation using vaccines or toxoids and this is considered to be the greatest scientific and medical revolution in our time until anti-microbial drugs were discovered in the late 1930's³.

During the second world war progress was made in the fractionation of plasma using the newly-developed techniques of ultracentrifugation and electrophoresis, and it was established that the globulin fraction could be used for the prevention of hepatitis A infections.⁹ Today injection of gammaglobulins is used for prophylaxis when an epidemic is expected or when travelling to countries where infectious diseases are not yet controlled and vaccines are not available. If selected donors are used more specific antiglobulins are obtained, and if serum is taken from patients after a recent infection hyperimmune serum is obtained. E.g. Availability of hyperimmune serum is the only treatment which can be given to patients with Lassa fever or Marburg disease since no drugs are available for these diseases, and it is also given as prophylaxis to the medical and nursing staff. Gammaglobulins from patients with herpes zoster (chicken pox virus) are used to prevent children with leukemia from getting chicken pox which could be fatal. Blocking antibodies are used in Rh negative women to prevent them from being sensitised by the red cells from a Rh positive foetus if they escape into the maternal circulation.

3. Immunology and transplantation

A field which could not have developed except for the advances in immunology is transplantation of organs from one individual to another. In the beginning of this century it was observed that if tumour cells from one

mouse were injected into an unrelated mouse they failed to grow, and also, if the same animal was injected a second time the growth of the tumour was curtailed sooner. It was at first believed that this failure of the tumour cells to grow, was due to starvation — that is, that they were unable to get sufficient nutrients.

Later investigators found that the transplanted tumour had much in common with an immune response but it was only with the work of Medawar that there was an integration of immunology and transplantation.¹⁰ Medawar was involved with the treatment of burns during the second world war when he transferred skin grafts from one individual to another and rejection occurred.

The first graft usually survived for two weeks and the second graft for 7-8 days if from the same donor. If the second graft was from a different donor it survived for 14 days and the conclusion was drawn that memory must be involved, and further studies developed the concept that the accelerated rejection of a second graft was analogous to the delayed type of hypersensitivity seen in the tuberculin reaction in sensitised individuals.

It was also realised that it was not anti-bodies that were involved in graft but sensitised lymphocytes. These studies on graft-rejection led to the concept of tolerance which means that the body doesn't lodge an immune response against its own tissues. For some time already it had been observed that non-identical cattle twins sharing the same blood circulation before birth can tolerate cells of their twin partner even if they are genetically different. Burnet and Feiner came to the conclusion that non-responsiveness to one's own body constituents depend on their presence at a critical stage of embryonic development and that conversely, if an organ is removed from embryonic life and later put back, rejection occurs. So tolerance to foreign material can be produced by administering material in the appropriate dose, route and time in the animal development.³

These studies in turn led to the hypothesis that each lymphocyte or clone of lymphocytes can respond to only one particular antigen, and to account for the large variety of lymphocytes which must be present somatic mutation takes place. Those lymphocytes which have receptors from the body's own antigen are killed during embryonic life and therefore no immune response occurs to the body's own protein. This will explain why normally our own tissues are not destroyed by antibodies or sensitised cells, or that what Ehrlich called "Horror Autotoxicus" is avoided.³ The ability of the immune system to recognise tissues from a different individual is determined by tissue antigens present on all cells of the body except the red cells. The genes responsible for these antigens are present in the MHC, and close to this complex are the genes which control the immune response. Before a transplant can be undertaken extensive testing must be done in an attempt to match donor and recipient histocompatibility antigens, and the more similar they are the better the chances that the transplant will take. However, there are still problems to overcome in prevention of graft rejection and typing of tissues since even if the histocompatibility antigens

are identical in two persons who are unrelated one gets rejection so further research in this respect is necessary. It is hoped that in the future tissues may be transferred at will providing the immune reactions are controlled, e.g. by removing the reacting cells by plasmaphoresis, or with the help of monoclonal antibodies.¹¹

Autoimmune Diseases

The study of the HLA system has greatly enhanced progress in genetics and in the individual's susceptibility to disease, e.g. certain HLA phenotypes are associated with particular diseases. So for example, HLA type B27 with arthritis, B8 with myasthenia gravis, chronic active hepatitis, SLE etc., indicating that in certain individuals there exists a tendency to produce an immunopathological response to infections. Hence, although the immune response is usually beneficial it can lead to autoimmune disease.¹²

It is known that a stereo chemical similarity exists between cell surface antigens and certain structural components of products of bacteria, and the immune system will develop antibodies against the bacteria and these will cross-react with the body's own antigens. All B-cells have receptors for Epstein-Barr Virus so when infected with this virus one gets polyclonal activation of B-cells, and antibodies are synthesised against a whole lot of antigens like influenza, tetanus, SBRC or whatever the B-cell was programmed to make. But normally the response is weak due to immune regulation. But in persons with missing suppressor cells or with hyperactive B-cells antibody production goes on as in SLE where the B-cells will synthesise antibodies against many self-determinants like DNA, smooth muscle etc. It is hoped that with further studies a drug will become available which can rectify the defect, or perhaps one can do HLA typing on the foetus and transplant suppressor cells if necessary, or activate existing suppressor cells.

Allergy

Another condition due to some aberrations in the immune system is allergy. In persons susceptible to allergy small soluble proteins that are not toxic, or irritant to non-allergic persons, become allergens. The allergy can be of the inhalant type where pollens, spores or mite allergens cause hay fever; or of the non-inhalant type due to food allergens, insect venoms and penicillin. In both types the allergy is due to the synthesis of Ig E antibodies which can get stuck onto the surface of mast cells; and, in a second contact with the same antigen histamin is released together with eosinophil chemotactic factors. The etiology of allergy is probably multifactorial where several genetic and non-genetic factors interact. However, there is a hypothesis that a genetic capacity to synthesise high levels of Ig E antibodies confers an advantage in combating disease among populations that have evolved in tropical and subtropical regions. Once these diseases are eliminated or reduced the high capacity to synthesise Ig E renders a high proportion of the population vulnerable to allergy towards common environmental agents. E.g. Ethiopian school children have Ig E levels 5-6 times higher than those in healthy Swedish school children, and other studies have

indicated that in general Ig E levels and atopic diseases are higher in individuals originating from areas where parasitic disease are common.¹³ So studies in non-white populations will help in determining the general relevance of HLA association as is seen in Whites. It may be that in certain individuals due to a lack of suppressor cells allergy develops, and perhaps one can stimulate the suppressor cells specifically or eliminate the Ig E producing cells by the help of monoclonal antibodies. Another type of allergy is contact sensitivity caused by many products when they come into contact with the skin and cause a sensitisation of the T cells. This may be a small price to pay for good T-cell immunity.

Human surveillance

An important function of the immune system is immune surveillance where circulating T cells are on the look-out for any abnormal cells which may be present, and destroy them. These abnormal cells may display a different type of antigen on the cell surface due perhaps to the presence of a virus or the result of a mutation. If the T cells are not very active these abnormal cell will grow and cause a malignancy. The etiology of cancer is unknown and probably multifactorial but with the help of immunology great advances have been made in our understanding of the pathogenesis of cancer and its treatment — particularly by the use of immunotherapy. Immunotherapy in cancer is aimed at restoration and enhancement of general and specific immune processes which can control or eradicate neoplastic disorders.¹⁴ Non-specific immunotherapy stimulates the monocyte-macrophage series of cells increasing their enzymatic activity, e.g. by the injection of BCG or Pseudomonas vaccine. With specific immunotherapy one injects tumour cells or extracts of tumour cells, and thus activating specific T cells. Local immunotherapy has been used successfully for skin cancers where agents enhancing the immune response are injected, E.g. BCG was injected to patients with melanoma and metastatic breast cancer and complete regression occurred in 50% of cases.¹⁴

Immuno-deficiency

The occurrence of disorders due to immuno-deficiency has only recently been recognised. As a result of the advances in our understanding of the differentiation and maturation of lymphocytes we have a better understanding of the pathogenesis of immuno-deficiency disorders on both a cellular and molecular level, and the therapy has improved.¹⁵ When B cell defects are present one gets an increased incidence of bacterial infections, while patients with T cell defects develop infections due to fungi, viruses and protozoa. It is important to know the immune status of a person since vaccination with live agents like polio, measles etc. can cause the disease if impaired immunity is present. Therapy includes bone-marrow transplantation from histo-compatible donors to avoid graft versus host disease. If no suitable donors are available one can use transplants of fetal thymus or liver when reconstitution of both B and T cells occurs.¹⁸

Monoclonal antibodies

One of the most exciting recent discoveries in immunology is the monoclonal antibodies. These are antibodies which can be made in unlimited numbers to a specific antigen by means of the formation of hybridoma cells made by fusing a stimulated lymphocyte with a myeloma cell. This technique was invented by Milstein and Köhler at the MRC in Cambridge.¹⁷ Unfortunately they did not take out the patent rights on this technique and it is now a multi-million dollar industry in the USA while Milstein and the MRC did not get a single dollar. The monoclonal antibodies will prove to be useful in 3 major aspects:

1. isolation and purification of rate antigens and antibodies e.g. interferon
2. diagnosis
3. treatment.

Monoclonal antibodies, for example, can be made to bind individual cell types so they can home onto the cell surface of tumours in a patient either to kill the tumour cell or carry radio-labels which will localise a tumour deposit.¹⁸ The antibody can then be coupled to a toxin or a drug which will destroy the cell. If malignant cells are present in the bone marrow, one can remove the bone marrow and let the cells interact with monoclonal antibodies made against the malignant cells and then reinfuse the remaining normal cells. Monoclonal antibodies can be used to lower or deplete the T cell population in patients with kidney grafts and so decrease the possibility of rejection. Monoclonal antibodies can be used in the treatment of infections, for the production of vaccines and for the standardization of antibodies used in RIA.¹⁸

Infections have to a large extent been controlled by immunisation, antibiotics, better hygiene and nutrition but certain problems still exist which can be solved by immunological approaches. E.g. a gonococcus strain has developed which is resistant to antibiotics and a world wide epidemic threatens: it is hoped that a vaccine will be developed, perhaps with the help of monoclonal antibodies and the disease eliminated. Immunology is making a valuable contribution in tropical parasitic diseases like malaria, schistosomiasis, trypanosomiasis, etc. common in large areas of the world where measurement to control them has so far been unsuccessful.¹⁹ Parasites do induce an immune response in the host but are not very effective when compared with bacterial and viral diseases. Immunology could contribute to the control of parasitic diseases by several means e.g. improving diagnostic criteria (more sensitive and simple immuno-diagnostic tests) by getting a better understanding of the pathogenesis of the lesions, and by preparing vaccines with the help of monoclonal antibodies.

Nutrition and Immunity

Lately a lot of attention has been focused on the interaction between nutrition, immunity, diseases and aging.^{21 22} It has long been recognised that a well-balanced diet is necessary for the maintenance of optimum health, and thus nutritional deficiency leads to susceptibility to infection.

The thymus and other lymphoid tissues are sensitive to nutritional deficits and the T lymphocytes are reduced in number as a result of less thymic hormone activity. When nutritional therapy is given the function of the thymus is improved and the number of T cells are restored to normal. Many patients with serious and chronic illness suffer from malnutrition which leads to an impairment of the immune response, but this returns to normal when nutritional support is given and the health of the patient improves. Excessive dietary intake also affects the immune system and is associated with auto immune diseases, cancer, infections and degenerative diseases. Thus immunocompetence is a sensitive and functional barometer of nutritional status, and immunological tests can be of prognostic significance of impaired immunocompetence in predicting disease vulnerability and can lead to nutritional intervention programmes, to improve the immune response and health. It has also been recognised that when a defect in cell mediated immunity is present the life expectancy is decreased, so it seems as if the immune system is essential for the maintenance of optimum health. It is also believed that the primary event in the aging process would be that the thymus stops forming T lymphocytes and that all other aspects are secondary so one suffers from cancer, autoimmune diseases, infection, sclerosis etc.²²

With the knowledge we have of the immune system we will perhaps in the future be able to improve the quality of life and increase the life expectancy by stimulation of the immune system or by immuno therapy. We could infuse cells from healthy young HLA compatible donors or, even better, take away cells or part of the thymus in adolescence, store them and when needed, infuse the cells or implant part of the thymus.

So in future a scientifically modified diet along with cellular, molecular and hormonal engineering can be applied and give us freedom from many disorders and make us have 100 years of healthy life.

CONCLUSION

The development of immunology has given us a better insight into human diseases, their etiology, pathogenesis and pathology. It has revolutionised the diagnostic and therapeutic procedures. These developments could not have taken place without the concerted effort of research workers trained in different fields. Today scientists are needed who have a good theoretical background in biochemistry, molecular biology and all the branches of pathology; and, just as important, practical experience so that they can plan and initiate and perform experiments which will be of help in our understanding of the etiology and pathogenesis of disease and may so, it is hoped, lead to prevention. I am therefore sure that the graduates from the department of Medical Laboratory Science will make a valuable contribution in this respect.

Mr. Vice-chancellor, I hereby accept the Chair in Medical Laboratory Science.

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