World Health Organization
Technical Report Series
No. 519

Cell-Mediated Immunity and Resistance to Infection

Report of a WHO Scientific Group

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

World Health Organization
Technical Report Series
No. 519

Cell-Mediated Immunity and Resistance to Infection

Report of a WHO Scientific Group

World Health Organization
Geneva
1973

PRINTED IN SWITZERLAND

Contents

WHO Scientific Group on Cell-Mediated Immunity and Resistance to Infection

Geneva, 19–23 September 1972

Members

Dr. A. C. ALLISON, Clinical Research Centre, Northwick Park Hospital, Harrow, England (Vice-Chairman)

Prof. B. R. BLOOM, Department of Microbiology and Immunology, Albert Einstein College of Medicine, Yeshiva University, Bronx, N.Y., USA

Dr. T. BRUNNER, Swiss Institute for Experimental Cancer Research, Lausanne, Switzerland

Dr. T. GODAL, Armauer Hansen Research Institute, Addis Ababa, Ethiopia

Dr. G. B. MACKANESS, Trudeau Institute, Saranac Lake, N.Y., USA (Chairman)

Dr. D. D. MCGREGOR, Trudeau Institute, Saranac Lake, N.Y., USA (Rapporteur)

Dr. D. S. NELSON, Department of Bacteriology, University of Sydney, Australia

Prof. J. L. TURK, Department of Pathology, Royal College of Surgeons, London, England

Secretariat[1]

Dr. R. V. BLANDEN, John Curtin School of Medical Research, Australian National University, Canberra, Australia (Temporary Adviser)

Dr. W. P. FAULK, Immunology, WHO, Geneva, Switzerland

Dr. H. C. GOODMAN, Chief, Immunology, WHO, Geneva, Switzerland (Secretary)

Dr. J. S. REMINGTON, Allergy, Immunology and Infectious Diseases Department, Palo Alto Medical Research Foundation, Calif., USA (Temporary Adviser)

Dr. J. N. SHEAGREN, College of Medicine, Department of Medicine, Howard University, Washington, D.C., USA (Temporary Adviser)

Dr. G. TORRIGIANI, Immunology, WHO, Geneva, Switzerland

[1] Unable to attend: Dr. B. D. BRONDZ, Gamaleja Institute of Epidemiology and Microbiology, Moscow, USSR.

Cell-Mediated Immunity and Resistance to Infection

Report of a WHO Scientific Group

A WHO Scientific Group on Cell-Mediated Immunity and Resistance to Infection met in Geneva from 19 to 23 September 1972. The meeting was opened on behalf of the Director-General by Dr. M. A. AKHMETELI, Director of the Division of Non-Communicable Diseases.

1. Introduction

In the early years of this century serum antibodies were shown to carry out many important protective functions, sometimes in conjunction with the complement system, e.g., neutralization of viruses, lysis of certain micro-organisms, or their opsonization for more efficient phagocytosis. Experience in human populations soon confirmed experimental observations indicating that antibody acted as a protective agent in a variety of infections. However, a group of diseases remained in which humoral immunity could not be demonstrated to influence host resistance. Tuberculosis, a notable example of such a disease, was distinguished by an additional peculiarity that had long puzzled immunologists. It was accompanied by an unusual delayed form of hypersensitivity that ZINSSER first recognized in 1921 to be a feature of several other infectious diseases as well. Although delayed hypersensitivity to tuberculin was part of the Koch phenomenon and seemed to be a defensive reaction of some sort, its precise role remained a mystery for many years. Failure to transfer the reaction by the transfusion of antibody-containing serum deepened the mystery and pointed to a possible separate mechanism of immunity.

The event that opened the way to further progress in studying both im-

munity to organisms such as the tubercle baccillus and the nature of the delayed-type hypersensitivity engendered by this class of infectious agent was the demonstration by CHASE & LANDSTEINER in 1942 that such hypersensitivity could be conferred on non-reactive subjects by transferring living lymphoid cells from sensitized donors. These observations provided the foundation for the science of cellular immunology.

The past few years have brought a wave of new knowledge about the cells that constitute the body's immunological apparatus. The most notable advance has been the demonstration that there are two types of lymphocyte each having distinctive properties and different functions. Thymus-dependent lymphocytes (T lymphocytes, or T cells), which arise from stem cells in the bone marrow and mature under the influence of the thymus, circulate throughout the body and respond to specific antigenic stimulation but do not secrete antibody. T lymphocytes are known to participate in at least 4 immune processes: rejection of allografts and tumours; delayed-type hypersensitivity reactions; activation of macrophages to resist infection; and a cooperative function with the precursors of antibody-forming cells that serves to increase antibody formation. The other class of lymphocytes – bone-marrow derived, thymus-independent lymphocytes (B lymphocytes, or B cells) and the cells derived from them – contribute to immunity by their unique capacity to synthesize and secrete antibodies.

Together with the availability of inbred strains that permit cell transfers between animals, this new knowledge concerning the cells involved in immunological processes has made it possible to analyse resistance to infectious diseases at the cellular level. This report is primarily concerned with cell-mediated immunity, i.e., with the cells that provide both a means of detecting a microbial invasion and a mechanism for resisting it without the secretion of antibody. But T cells, B cells, and antibodies interact in complex ways. While the mechanisms of humoral and cell-mediated immunity may be separated for purposes of analysis in most infectious diseases, they can act in concert to protect the host against extracellular and intracellular pathogens. The interplay between humoral and cellular immunity may also be associated with the contrasting forms of some infectious diseases, such as leprosy, and may contribute to the persistence or recurrence of others.

To investigate these complex problems new methods have been devised for studying cell-mediated immune reactions *in vitro*. The serological techniques of the past are being complemented by a new and more

sophisticated technology for manipulating living cells *in vitro*. The judicious use of these new techniques combined with a thoughtful application of older ones is gradually disclosing the basic mechanisms of defence against an ever-increasing number of infectious diseases. Every infectious disease is a distinct entity with its own particular features and each must be studied separately so that appropriate prophylactic and therapeutic procedures can be developed and tested.

2. Nature of Cell-Mediated Immunity

2.1 Induction of Cell-Mediated Immunity

Acquired resistance to infectious disease begins with the induction of a specific immune response. The precise mechanisms of the inductive process are under intensive study and constitute one of the most important issues in immunology, but for the purpose of this report it is sufficient to say that induction involves some interaction between antigen and immunocompetent lymphocytes, with a possible intermediate step consisting in the processing or presentation of antigen by macrophages.

As stated above, the cell-mediated immune response involves T cells in particular. The properties of antigen-sensitive (progenitor) T cells and the possible influence of B cells or humoral antibody on the induction of the T cell response will be discussed in more detail subsequently. In this section we are concerned with the way in which antigens must be presented in order to provoke a T cell response, for it has long been known that special conditions of immunization are often required. For example, living intracellular parasites are noted for their ability to evoke a T cell response, as evidenced by the regular occurrence of delayed-type hypersensitivity – an external sign of T cell involvement – in infected animals and man. In contrast, killed vaccines or antigen extracts containing some of the same antigenic determinants as the living organisms fail to provoke cell-mediated immunity unless incorporated in Freund-type adjuvants. The reasons for this difference are not known, but there are several possible explanations. (a) Antigens released from *infected* macrophages may differ physicochemically from those released from macrophages that have ingested dead organisms. There is evidence that chemically-modified [PARISH, 1971] or enzymatically-degraded flagellin [ICHIKI & PARISH, 1972] or red blood cell [PEARSON & RAFFEL, 1971] antigens induce cell-

mediated immunity whereas unmodified antigens induce antibody formation. These modified antigens may have determinants that are poorly recognized by B cells but are still able to stimulate T cells. Alternatively, the effective dose of a given determinant may be reduced by these modifications. Early studies have in fact shown that minute doses of certain antigens [SALVIN, 1958], particularly when complexed with antibody in appropriate proportions, can evoke cell-mediated immune responses. (b) Another possible explanation is that the surfaces of infected macrophages or other cells present antigen to T cells in a highly stimulatory form.

Further information concerning the conditions required to induce cell-mediated immunity would be particularly helpful for the prophylaxis and treatment of human disease. It could permit, for example, the production of safer, non-viable vaccines for smallpox and some other virus diseases, tuberculosis, brucellosis, Chagas' disease, and many other infections of man and domestic animals. It might also lead to more effective and rationally based immunotherapy in human cancer.

We turn now to the cellular basis of the cell-mediated immune response. There is clear experimental evidence from studies on laboratory rodents that the specific effector cells of this response arise directly from the antigen-driven proliferative response of progenitors that are members of a recirculating pool of T cells. This evidence is briefly summarized below.

Thymocytes bearing isotopic [JOEL *et al.*, 1972], chromosomal [DAVIES, 1969], or antigenic markers [MILLER & SPRENT, 1971] have been shown to migrate to thymus-dependent areas of secondary lymphoid tissue (periarteriolar sheath of spleen and paracortical area of lymph nodes) [PARROTT *et al.*, 1966], and to appear in thoracic duct lymph. Procedures that deplete the recirculating pool of T cells, e.g., neonatal thymectomy [MILLER & OSOBA, 1967], antilymphocyte serum (ALS) treatment [MEDAWAR, 1969], or adult thymectomy followed by lethal irradiation and bone marrow reconstitution [PARROTT *et al.*, 1970], profoundly suppress cell-mediated immune responses. Proliferation of T cells occurs in the thymus-dependent areas of lymph nodes [DAVIES *et al.*, 1969] and spleen during the induction of cell-mediated immunity, and stimuli that do not provoke a response in these areas fail to confer protective immunity to a variety of parasitic agents. The kinetics of this response will be discussed below. Progenitors of the specific effector cells of cell-mediated immunity appear to be present in the thymus, spleen, and the recirculating pool of lymphocytes [SPRENT & MILLER, 1971; CEROTTINI *et al.*, 1970; COOPER &

ADA, 1972; BLANDEN & LANGMAN, 1972] but seem to be scarce in bone marrow. A final indication is that antisera against markers of T lymphocytes eliminate specific effector cells from populations of immune lymphoid cells [BLANDEN & LANGMAN, 1972; BLANDEN, 1971; LANE & UNANUE, 1972].

Little is known about the life history of the progenitors of effector T cells. There is also scant information available regarding the requirement for cooperation among cell types in the induction of a cell-mediated immune response or the nature of such cooperating cells. However, on the basis of studies of graft-versus-host reactions in mice it has been proposed that induction can require cooperation between two different classes of T cell [RAFF & CANTOR, 1971; ASOFSKY *et al.*, 1971]. The two types may belong to different cell lineages or may represent different stages of maturation within a single cell line. The first type of T cell postulated (T_1) is normally present in the thymus and spleen and may decrease in number in secondary lymphoid tissue 2–6 weeks after adult thymectomy, i.e., it might be in an early stage of post-thymic maturation in these tissues. The second type postulated (T_2) is scarce in the thymus and does not decrease in number in secondary lymphoid tissue after adult thymectomy, i.e., it might be in a late stage of post-thymic maturation. It has been suggested that T_1 cells are the progenitors of effector cells and that T_2 cells act as amplifiers of the response.

Thus far, investigations of the cellular requirements for cell-mediated immune responses in other systems [SPRENT & MILLER, 1971; CEROTTINI *et al.*, 1970; COOPER & ADA, 1972; BLANDEN & LANGMAN, unpublished observations] suggest that cooperation between T_1 and T_2 cells as defined above is not essential, and that T cells at various stages of post-thymic life can act as progenitors of effector T cells. For example, mouse thymus cells transfered to lethally irradiated recipients can generate, within 1 week of antigenic stimulation, effector T cells that mediate delayed hypersensitivity to bacterial antigens, kill tumour cells, or trigger skin graft rejection. Basically similar experiments have shown that T cells mediating antibacterial resistance can arise from progenitors that have resided for less than 3 weeks in secondary lymphoid tissues. These findings are compatible with the concept that T_1 type cells act as progenitors but suggest that T_2 amplifiers are not absolutely essential for the response. Mice thymectomized as adults at least 6 weeks before antigenic stimulation can produce an unimpaired cell-mediated immune response to bacterial infection; in such animals, cells of the T_1 type would be absent.

This indicates that T_2 cells can also act as progenitors of cells mediating antibacterial resistance, i.e., that they are not functionally restricted to amplifier activity.

The possibility that cooperation between T cells (defined as a single broad cell class) is a general phenomenon in cell-mediated immune responses cannot yet be excluded.

References

ASOFSKY, R., CANTOR, H. & TIGELAAR, R. E. (1971) In: AMOS, B. D. (ed.), Progress in Immunology, New York & London, p. 369

BLANDEN, R. V. (1971) J. exp. Med., *133*, 1974

BLANDEN, R. V. & LANGMAN, R. E. (1972) Scand. J. Immunol., *1*, 379

CEROTTINI, J.-C., NORDIN, A. A. & BRUNNER, K. T. (1970) Nature (Lond.), *227*, 72

COOPER, M. G. & ADA, G. L. (1972) Scand. J. Immunol., *1*, 247

DAVIES, A. J. S. (1969) Transplant. Rev., *1*, 43

DAVIES, A. J. S., CARTER, R. L., LEUCHARS, E. & WALLIS, V. (1969) Immunology, *17*, 111

ICHIKI, A. T. & PARISH, C. R. (1972) Cell. Immunol., *4*, 264

JOEL, D. D., HESS, M. W. & COTTIER, H. (1972) J. exp. Med., *135*, 907

LANE, F. C. & UNANUE, E. R. (1972) J. exp. Med., *135*, 1104

MEDAWAR, P. B. (1969) Proc. roy. Soc. B, *174*, 155

MILLER, J. F. A. P. & OSOBA, D. (1967) Physiol. Rev., *47*, 437

MILLER, J. F. A. P. & SPRENT, J. (1971) Nature [new Biol.], *230*, 267

PARISH, C. R. (1971) J. exp. Med., *134*, 21

PARROTT, D. M. V., DE SOUSA, M. A. B. & EAST, J. (1966) J. exp. Med., *123*, 191

PARROTT, D. M. V. DE SOUSA, M. A. B., FACHET, J., WALLIS, V., LEUCHARS, E. & DAVIES, A. J. S. (1970) Clin. exp. Immunol., *7*, 387

PEARSON, M. N. & RAFFEL, S. (1971) J. exp. Med., *133*, 494

RAFF, M. C. & CANTOR, H. (1971) In: AMOS, B. D. (ed.), Progress in Immunology, New York & London, Academic Press, p. 83

SALVIN, S. B. (1958) J. exp. Med., *107*, 109

SPRENT, J. & MILLER, J. F. A. P. (1971) Nature [new Biol.], *234*, 195

2.2 Cells Involved in the Expression of Cell-Mediated Immunity

2.2.1 Specific Effector Cells

Techniques permitting the enumeration of individual antibody-secreting cells have revolutionized cellular immunology and enabled detailed studies to be made of the kinetics of the production of these cells in the course of immune responses. There is a great need to develop similar

techniques for the detection of individual antigen-specific effector T cells, obviously a much more difficult task than the detection of cells secreting specific antibody. One such method currently being developed is described elsewhere in this report (see page 55).

In vitro and *in vivo* studies of the specific effector cells of cell-mediated immunity are based on various functions of these cells that can be measured quantitatively. These include the cooperative 'helper' function in antibody synthesis; transformation to blast cells; release of mediator substances that activate macrophages; direct target-cell killing; adoptive transfer of immunity to infections, grafts, and tumours; and immunological memory. It is not known whether the same T cell can participate in all these functions or whether different T cell populations are involved. Since the nature and specificity of individual T cells in the population have not yet been determined, considerable caution is required in interpreting the available studies of the histogenesis of cell-mediated immune responses to infective agents and the biological functions of effector cell populations, discussed below.

As already mentioned, organisms that can survive and multiply intracellularly are known for their ability to induce a cell-mediated response. The magnitude and kinetics of the response are influenced by several factors, e.g., the dose and virulence of the parasite and possibly the number of effective antigenic determinants involved. The best studied examples are the responses to *Mycobacterium tuberculosis* and *Listeria monocytogenes* in mice and rats, which have been investigated with two basic techniques. (a) In mice, the histological changes and dividing cell populations in responding spleen or lymph nodes have been followed in relation to the course of infection. (b) In rats, cells harvested at different times from thoracic duct lymph of infected donors have been transferred to syngeneic recipients where their antibacterial effects and physiological properties have been studied.

The general picture emerging from these studies is as follows. Dividing cells appear in the thymus-dependent areas of lymphoid tissues within 1–2 days after infection. In the spleen, dividing cells are subsequently seen to increase in number in the red pulp. The peak of the response depends on the type of infective agent and the dose employed. With *Listeria* in the mouse, the peak occurs at 6 days [NORTH, 1972]; with tubercle bacilli, it occurs later [NORTH *et al.*, 1972]. In the early phases the dividing cells are large blasts with pyroninophilic cytoplasm, but in later phases many of them have the appearance of pyroninophilic small lymphocytes.

In mice infected with virulent tubercle bacilli, the dividing cells in the spleen have a generation time of about 11 h. Three or four divisions occur before the progeny leave the spleen and enter the blood. These data are in good agreement with the findings in other bacterial and viral infections, and with the results obtained in a system involving a response to allogeneic cells, in which sensitized lymphocytes were detected by various means within 3–6 days of stimulation.

After their generation in lymphoid tissue, specific effector lymphocytes enter the bloodstream and localize at sites of infection in other tissues. Cells generated in the spleen can enter the blood directly, whereas those generated in lymph nodes must first traverse efferent lymphatics and the main lymphatic ducts. Lymphocytes with the ability to protect normal recipients appear in the thoracic duct within 72 h of a primary listeriosis in rats. The level of resistance transferred by a standard number of lymphocytes increases to a peak on day 6 and then declines rapidly. In contrast, protective cells formed in response to BCG appear later and can be demonstrated in the lymph for at least several months. Studies using the antimitotic drug vinblastine suggest that it is the dividing cells that are responsible for transferring resistance to *Listeria*, in view of the finding that a single injection of the drug can eliminate protective lymphocytes from an actively immunized donor. There is also evidence indicating that nondividing lymphocytes perform effector functions *in vitro* and possibly *in vivo*. Protective lymphocytes from BCG-injected donors are resistant to vinblastine, provided the cells are obtained late in the infection.

An effective defence against intracellular parasites requires a mechanism for generating and accumulating sensitized lymphozytes and nonspecific effector cells, such as mononuclear phagocytes, in foci of infection. Sensitized lymphocytes, when stimulated by antigen, may serve to recruit nonspecific effector cells to such foci. This recruitment mechanism appears to be important in mousepox, for example, in which the virus, growing in hepatic parenchyma cells, produces lesions devoid of infiltrating cells until the animal becomes immune [BLANDEN, 1971]. In this case, the recognition of antigen by sensitized lymphocytes in the blood would seem to be the event initiating cellular infiltration. Other examples are the rapid initiation of the rejection process in a completely healed, uninflamed skin graft after the injection of specifically sensitized cells, and the specific localization of labelled, specifically cytotoxic T cells at site of implantation of allogeneic tumours. On the other hand, studies using radiolabelled thoracic duct cells have shown that dividing lymphocytes, regard-

less of their immunological specificity, are arrested at sites of inflammation [KOSTER & MCGREGOR, 1971]. This points to a mechanism by which inflammation, initiated either nonspecifically or by specifically sensitized lymphocytes, could be amplified in the infected host.

2.2.2 Nonspecific Effector Cells

Since there is no evidence that specifically sensitized lymphocytes are themselves able to kill micro-organisms, the collaboration of ancillary effector cells is most likely required for resistance to infection. The nature of this collaboration is discussed in the next section (2.3.1).

The principal collaborating cell appears to be a mononuclear phagocyte. The term 'mononuclear phagocyte system' has been proposed for macrophages, monocytes, and their precursor cells [VAN FURTH *et al.*, 1972]. These originate from stem cells in the bone marrow that continuously multiply and differentiate to become promonocytes, which are phagocytic and adherent to glass. Promonocytes then divide and differentiate into monocytes, which are released into the circulating blood. Blood monocytes enter the tissues and differentiate into macrophages having an increased phagocytic capacity and lysosome content. Tissue macrophages include Kupffer cells of the liver, free and fixed macrophages of the spleen, lymph nodes, and bone marrow, alveolar macrophages of the lung, macrophages of other tissues, and perhaps also osteoclasts of bone and microglia cells of the central nervous system. (Reticulum cells and endothelial cells are excluded from this category.)

Mononuclear phagocytes are distinguished by their nuclei, their phagocytic capacity, the nature and content of their lysosomes (which differ from those of poylmorphonuclear leucocytes), their adherence to glass and other surfaces, and the presence on their plasma membrane of receptors for certain immunoglobulins or immune complexes (IgG1, IgG3, and IgM) and complement (C3).

Normally, tissue macrophages turn over continuously and slowly and divide infrequently. Under pathological conditions macrophages in inflammatory lesions arise mainly from blood monocytes, although local multiplication of macrophages may also occur. Cytokinetic studies do not support the view that mononuclear phagocytes are derived from lymphocytes.

The main physiological function of macrophages is to rid the blood, lymph, and tissues of particles, including micro-organisms and effete cells. This elimination process can be considered to take place in three

stages: attachment of the particles to the plasma membrane of macrophages, phagocytosis, and discharge of lysosomal enzymes into the phagocytic vesicles containing the particles. The attachment of particles to the plasma membrane is often facilitated by antibody, especially in the presence of complement, or by other as yet unidentified constituents of normal serum collectively termed opsonins. Some kinds of particle may become attached without apparent need for serum factors. Phagocytosis probably results from plasma membrane reactions triggering the contraction of an actomyosin contractile microfilament system, with consequent infolding of the plasma membrane to which the particles are attached. Usually phagocytosis is followed by the fusion of lysosomes with the phagocytic vacuole containing the particle, but sometimes (e.g., after ingestion of live *M. tuberculosis* or *Toxoplasma* organisms) this fusion is inhibited. Whether this explains persistent infection in these cells is not yet known.

The bulk of particles or other materials ingested by macrophages is rapidly broken down in the lysosomal system. Some particles, however, undergo slow digestion or remain undigested. In the case of most antigens associated with macrophages, about 10–20% of the antigen is broken down slowly and retains immunogenicity for many hours at least. Also in this category are materials that cannot be degraded, for example, pneumococcus polysaccharide, cell wall constituents of certain organisms (including group A streptococci and mycobacteria), and inorganic particles such as carbon or silica. Part of the still undigested antigen remains on the surface of the cells and may be involved in stimulating both humoral and cell-mediated immune responses.

The mechanisms by which micro-organisms are killed in macrophages are poorly understood. Certain organisms can survive and multiply within the macrophages of normal animals, and thus give rise to many of the infections discussed in this report. Some also appear to be able to multiply in macrophages taken from immune animals, e.g., leishmaniae (section 3.5).

Unlike polymorphonuclear leucocytes, macrophages retain considerable synthetic potential and can be stimulated to form large amounts of lysosomal and other enzymes. Such stimulation or activation can be brought about in several ways, with a variety of end results. Macrophages cultured in the presence of anticellular antibody, streptococcal cell walls, or other stimulants have a greatly increased content of lysosomal enzymes. In comparison with normal macrophages, macrophages recovered

Table I. Distinguishing characteristics of T lymphocytes, B lymphocytes, and macrophages

Membrane markers	T lymphocytes	B lymphocytes	Macrophages
IgG	−	+	−
Receptor for C3 (erythrocyte – antibody – complement [EAC] rosettes)	−	+	+
Receptor for Ig or Ab-Ag complexes (Fc)	−	+	+
Thymus-specific antigens (*θ*, mouse thymocyte leukaemia antigen, etc.)	+	−	−
Receptors for sheep red blood cells (erythrocyte [E] rosettes)	+	−	−
in vitro stimulation of DNA synthesis by mitogens[a]			
Phytohaemagglutinin (PHA)	+	−[b]	−
Concanavalin A (Con A)	+	−	−
Lipopolysaccharide (bacterial endotoxin)[c]	−	+	−
Anti-Ig	−	+	−
Specific binding to antigen-coated beads	−	+	−
Mixed lymphocyte culture reactivity	+	−	−
Graft-versus-host reaction inducing capacity	+	−	−
Adherence to surfaces (glass, plastic)	−[d]	−[e]	+
Phagocytic	−	−	+

[a] These data derive mainly from experiments in mice, and their extrapolation to man is questionable.

[b] Some B lymphocytes may be recruited to divide secondarily by factors elaborated by activated T lymphocytes. B cells may also be stimulated when the mitogen is attached to a solid support.

[c] In mice.

[d] Except for blast cells.

[e] Except for mature plasma cells or when immune complexes are attached to B cells.

from animals infected with organisms that can multiply within cells show increased spreading on glass, elevated lysosomal hydrolase levels, a higher percentage of glucose metabolism by the hexose monophosphate pathway as compared with the glycolytic pathway, and increased capacity to kill or inhibit the replication of a variety of organisms. These changes are not necessarily causally related. The terms 'stimulated' or 'activated' must not be used loosely but should always be defined in terms of the agent utilized to produce the effect and the method by which the effect is