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The Immunocompromised Patient

SUMMARY

The number of immunocompromised persons—as well as the importance of family physicians understanding their state—is increasing. In many instances the family physician will first identify or provide day-to-day care for such patients while they live in the community. This article gives an overview of certain aspects of normal host immunity, etiology and mechanisms in immunocompromisation, and outlines techniques for recognition and management of this special group of patients. (*Can Fam Physician* 1987; 33:349–359).

SOMMAIRE

On assiste à une augmentation du nombre de personnes présentant un déficit immunitaire, d'où l'importance pour les médecins de famille de bien comprendre leur état. Dans bien des cas, le médecin de famille commencera d'abord par identifier cette affection ou offrira des soins quotidiens à de tels patients lorsqu'ils sont encore dans la communauté. Cet article donne un aperçu de certains aspects de l'immunité chez l'hôte normal, de l'étiologie et des mécanismes de l'immunodéficience et esquisse les techniques permettant d'identifier et de traiter ce groupe particulier de patients.

Key words: immunocompromisation, immunodeficiency, normal host defences

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IMMUNITY is the property of resistance. As applied to humans in a world rife with hostile micro-organisms, this has usually meant resistance to infection, although it is now evident that immune defects are associated with neoplasia and atopy as well. *Immunocompromisation* can be taken broadly to apply to patients with *any* defect in their defences against infection. *Immunodeficiency* is applied here to patients affected by diseases or situations in which the immune system itself, including complement, phagocytes and lymphocytes, is impaired. The nature of this impairment can be primary (corresponding to diseases of congenital origin) or secondary (corresponding to a normal immune system's acquisition of an abnormality after birth). Understanding the immunocompromised state is fast becoming important to family physicians and at least two reasons for this come to mind.

An unremitting rise in the prevalence of the problem can be anticipated. This is largely a result of iatrogenesis (*e.g.*, new application of immunosuppressive therapy in malignancy, collagen vascular and autoimmune disease, and organ transplants), AIDS (16,000 new cases were expected in the United States in 1986[1]), an aging population, and improved survival and procreation among patients with rare, genetically governed, immunodeficiency diseases. In many instances it is, or will be, the family physician who first identifies the immunocompromised patient, or who provides onging day-to-day care for suppressed patients while they live in the community.

A second reason why family physicians need to be familiar with the immunocompromised state is that insight into all aspects of the problem will continue to mushroom, and with that exponential growth, distinct and effective directions in management will emerge. It is to be expected that these new approaches will often be applicable in the family physician's office. Current examples include the use of influenza and pneumococcal polysaccharide vaccine in appropriate situations and alternate-day use of steroids in chronic air-flow limitation.

Rudimentary knowledge of the immune response allows the FP to identify specific defects in components of this complex system. This paper therefore offers a brief review of normal host defences.

Normal Host Defences

A summary of the main defences against infection is given in Table 1,

and a schematic overview of the ontogeny of some of the important players in the immune response is given in Figure 1. Immune mechanisms are often described as specific or non-specific, but they act in concert.

Non-specific mechanism are characterized by lack of selectivity in both recognition and reaction to foreign agents; previous exposure to antigen does not alter the manner in which non-specific responses work. For example, intact skin serves as an effective inhibitor of a diverse variety of micro-organisms, mainly and simply because it is a mechanical barrier. Similarly, the bactericidal enzyme lysozyme, found in high concentration in certain secretions, is capable of disrupting the peptidoglycan cell-wall layer, primarily in gram-positive bacteria, in a non-adaptable unselective fashion.

The essence of a specific immune response is the lymphocyte, and its ability to recognize the presence of "non-self". This process involves binding between the lymphocyte or its product and the particular antigen, and subsequent selective activation of an effector event. Previous exposure to antigen can result in an adapted and improved response on later re-exposure, for example, the direct binding and neutralization of diphtheria exotoxin by immunoglobulin produced by activated B lymphocytes previously sensitized with vaccine.

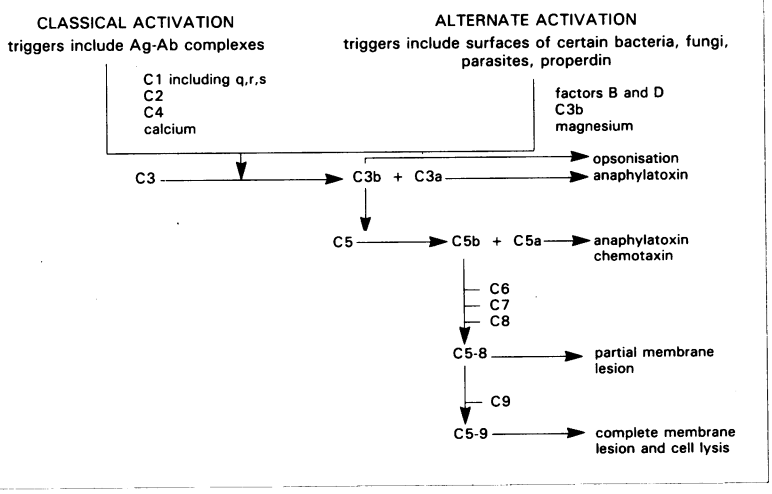
It is usually at the skin or other mucosal surfaces that first contact with potential pathogens is made. As a result, these surface barriers and the various, closely allied, non-specific defences are responsible for the majority of human-germ encounters that, from the human's perspective, are a success. If the micro-organism overcomes surface defences and enters underlying tissue, more sophisticated mechanisms can be brought to bear, including complement, phagocytes and lymphocytes.

Complement is a group of at least 18 serum proteins that, when activated, mediate several processes important to resistance. An abbreviation of the pathways of complement activation and its effects is given in Figure 2. The complement proteins circulate in an inactive state until triggered, leading to step-wise activation of each component by its predecessor. This cascade-like process is analogous to that of the coagulation and fibrinolytic systems, and serves to produce an amplified and rapid reaction to inciting stimuli. The most important step in complement activation is cleavage of C3 by C3-splitting enzymes produceable in two separate pathways called 'classical' and 'alternative'. The classical pathway can be turned on by antigen-antibody (IgM or IgG) complexes and staphylococcal protein A. The alternative pathway can be activated by components of surfaces of certain fungi, gram-negative bacteria, and parasites independent of antibody, C1, C2 or C4. Once formed, the C3-converting enzymes cleave C3 to C3b and C3a, with subsequent splitting of C5 to C5a and C5b. Further addition of components C6 to C9 to C5b creates a complex that, if fixed to the surface of a cell, can form holes within the membrane and kill the cell by means of lysis. This process of complement fixation is one important contribution made to host defence. In addition, several by-products formed during activation can facilitate other responses. C5a and C5, 6,7 assist in development of local inflammation at the site of invasion and are chemo-attractant for phagocytes. C3b can coat micro-organisms and then attach to phagocytes bearing C3b receptors, resulting in increased phagocytosis and destruction of the microbe. This is called 'opsonisation'. In resistance to infection, a normal complement system helps to defend against encapsulated gram-positive and gram-negative organisms such as *Streptococcus pneumoniae, Hemophilas influenzae, Klebsiella*, and *Neisseria* species.

Phagocytic cells include PMNs, monocytes, and the tissue derivitive of monocytes, macrophages; they assume an indispensable role in defence against infection. PMNs are often the first cellular element to encounter invading micro-organisms. In a complex manner, neutrophils are able to pass from the circulation, move to the pathogen, engulf and kill it. A variety of specific defects in these events, usually associated with appreciable morbidity, are described. In general, neutrophils defend against pyogenic, acute infection-producing, extracellular pathogens such as *Staphylococcus aureus, Klebsiella*, and coliforms. Macrophages have other important functions in addition to their phagocytic ability. Following ingestion and killing of micro-organisms, they can process and produce antigen derived from the phagocytosed cell on their surface to be recognized, in conjunction with gene products of the major histocompatability complex, by T lymphocytes. The lymphocytes may then effect other potent responses that are described below. Macrophages are also able to release substances that have a range of effects on the immune and inflammatory responses. An important example is interleukin 1 (Il-1) which is needed for T helper-cell activation.

Lymphocytes occupy the executive level in the immune corporate ladder. Two major types with distinct functional capabilities, sites of maturation, and surface membrane markers are recognized. B lymphocytes comprise about 5% – 10% of all circulating lymphocytes; they mature within the bone marrow. They are characterized by the

Figure 1: COMPLEMENT ACTIVATION

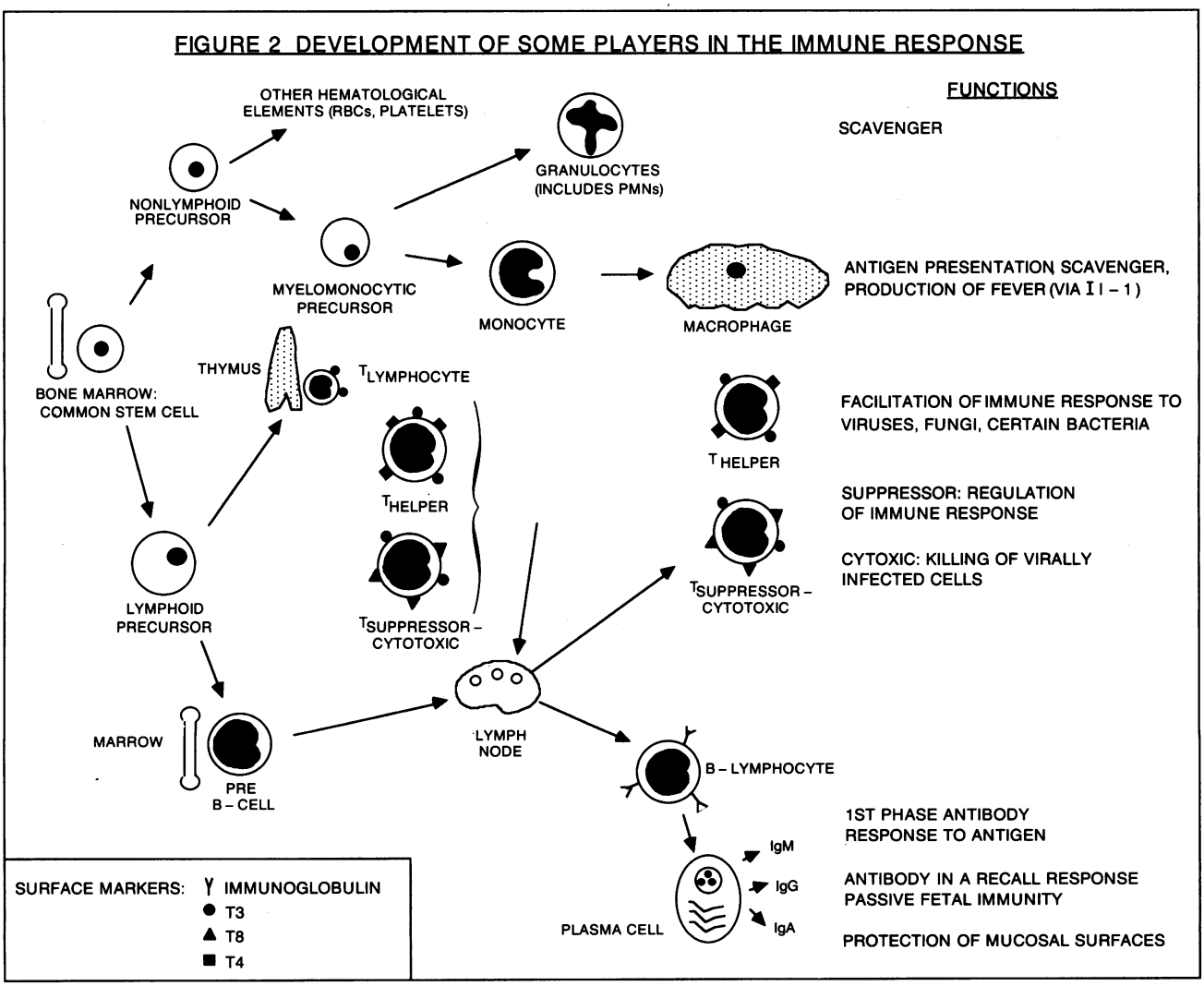


ability to produce immunoglobulin (antibody), either as a surface receptor (which is a property unique to B lymphocytes) or following antigen contact in the appropriate setting and differentiation into plasma cells which can then secrete antibody. The second major type is the T lymphocyte, which constitutes about 80%–90% of circulating lymphocytes and originates from stem cells that migrate to, and mature within, the thymus gland. Recently, monoclonal antibodies (groups of identical antibody produced by hybridizing normal B cells activated by a particular antigen with multiple myeloma cells) have been used to characterize T cell surface markers rapidly and precisely. T cells express marker to the monoclonal antibody OKT3.

B lymphocytes are able to respond to a huge number of different antigens. This quality of diversity of response predates Ag exposure and is a result of rearrangements within genes ultimately coding for the particular, and only, immunoglobulin made by that B cell or its plasma-cell derivative. Activation of resting B cells involves binding of Ag to the B cell having the closest-fitting immunoglobulin surface receptor and subsequent differentiation, which can be facilitated by soluble factors such as interleukin 1 and a T-cell product, B-cell stimulatory factor, and by direct interaction with subclasses of T lymphocytes, including T-helper cells. Antibody itself has a basic structure of two pairs of identical light (L) and heavy (H) polypeptide chains, with one end possessing two antigen-binding sites and the other, the means for particular effector functions. There are five classes of antibody (IgG, IgM, IgA, IgD, IgE) which differ in the composition of their heavy chains, the number of basic structures making them up (e.g., IgM: five; IgG: one; IgA: one or two) and effector functions. Antibodies convey "humoral" immunity and contribute to host defence in a variety of ways. IgG and IgM can fix complement, and can bind directly to, and neutralize, toxins, bacteria and viruses. IgG can enhance phagocytosis in a manner similar to C3b, by coating target structures and then binding to phagocyte surface receptors. IgG, by virtue of its small size, can cross the placenta and provide passive immunity to neonates while their own immune system matures. IgA, as the major immunoglobulin in secretions at mucosal surfaces, is important in neutralizing micro-organisms before they cross such surfaces. Antibody plays important roles in defence against encapsulated, aggressive organisms such as *Streptococcus pneumoniae, Hemophilus influenzae* and *Neisseria* species, and in limiting viremia.

T lymphocytes convey cell-mediated immunity (CMI). They perform a number of vital functions including immune-response regulation and direct killing of targetted cells. These functions can be ascribed to particular subsets of T cells identifiable by monoclonal antibodies. T-helper (T_H) cells facilitate immune responses and

FIGURE 2 DEVELOPMENT OF SOME PLAYERS IN THE IMMUNE RESPONSE



characteristically express receptor to the monoclonal antibody OKT4; about 60%–70% of circulating T cells possess this receptor. T_H cell activation requires their own ability to recognize and bind antigen found in close association with major histocompatability gene products on the surface of antigen-presenting cells (APC: e.g., macrophages) plus I1-1. Once activated, T_H cells produce a number of soluble factors that are called 'lymphokines' and, like I1-1, mediate immune responses elsewhere. The aforementioned B-cell stimulatory factor is one; others include interleukin 2 (which activates cytotoxic T cells), macrophage activating factor, and interferon. T_H cells can also activate T-suppressor (Ts) cells which check a number of B- and T-cell responses and thus circumvent an amok immune system.

Activated cytotoxic T cells (Tc) are able to recognize, combine with, and kill cells possessing surface foreign antigen. Recognition requires ascertainment of both the antigen and the class-1 gene products of the major histocompatability complex borne by most of our cells. Tc cells are important in elimination of cells infected by virus that express virally derived glycoproteins on their surface. Ts and Tc cells bear receptor to OKT8; OKT8-positive lymphocytes comprise about 30% of the circulating population. Delayed hypersensitivity skin testing (DHST) is also mediated through T lymphocytes by means of lymphokine release, and while cutaneous hyperactivity *per se* is not important in defence against infection, skin testing is a simple and useful office screen of cell-mediated immunocompetence. In general, CMI governs resistance to low-grade pathogens including fungi, viruses, parasites, and intracellular bacterial infection such as TB.

Etiologies and Mechanisms in Immunocompromised States

Table 2 summarizes most of the situations in which host defences are impaired. Many of the conditions and their effect on host resistance given in Table 2 are obvious enough, and so although intact mucous membranes, mechanical removal mechanisms and normal flora are extremely important in resistance to infection, we shall not discuss them further. Foreign bodies in the form of vascular and internal orthopedic prostheses may predispose to infection by limiting the phagocyte's ability to find and remove organisms taking haven on the prosthesis, either at the time of insertion or during subsequent bacteremic episodes. Tables 3 and 4 list some of the more common primary and secondary immunodeficiencies. Several general points are worth noting.

Primary immunodeficiencies are rare to exceedingly rare, and secondary immunodeficiences are common. Indeed, on a global scale, malnutrition probably accounts for the majority of all immunocompromisation. The most common primary immunodeficiency is selective IgA deficiency, with an approximate incidence of 0.1 percent;[2] severe combined immunodeficiency has an estimated frequency as low as one in 500,000 live births.[3] Congenital deficiencies of phagocytic function

Table 1: DEFENCES AGAINST INFECTION

Non-Specific

- Mechanical barriers:
  skin, mucous membranes, conjuntiva
- Mechanical removal:
  skin - desquamation of cells
  eyes - tears
  respiratory - coughing, sneezing, mucociliary transport
  urinary - urine flow
  gastrointestinal - gut peristalsis
- Competing normal flora of low pathogenicity on skin, gut, vagina.
- Chemical agents with bacteriostatic or bacterocidal properties:
  gastric acid, bile salts
  lactic acid, fatty acids (surface of skin)
  lysozyme (tears, saliva, mucous)
  interferons, properdin, c-reactive protein, α-l-antitrypsin
- Mediators of inflammation:
  complement, factor XII
  other chemotactic factors eg. kinins, leukotrienes
- Phagocytic cells:
  PMNs, monocytes, macrophages
  fixed tissue macrophages: eg. Kuppfer cells (liver), alveolar macrophages, microglia cells (CNS)

Specific

- Humoral immunity:
  B lymphocytes →plasma cells → antibody including IgM, IgG, IgA, IgE
- Cellular immunity
  T lymphocytes including T cell subsets: helper (H), suppressor(S), cytotoxic (C)

adapted from Durack D.T.
Clinical Aspects of Immunology
Blackwell Scientific Publications 1982

Table 2: IMMUNOCOMPROMISED STATES

- Interruption of mechanical barriers
  exfoliative skin diseases, thermal burns, penetrating wounds, intravenous lines, intravenous drug abusers
  urinary catheters
  endotracheal intubation or tracheostomy
- Impairment of mechanisms of mechanical removal

Respiratory:
  localized airway obstruction secondary to tumor or foreign body
  impaired mucociliary clearance eg. cystic fibrosis, cigarette smoking, influenza virus infection

Genitourinary:
  urinary obstruction and stasis for any reason

Gastrointestinal:
  bowel obstruction
  biliary duct obstruction
  post surgical blind loop

- Alteration of normal flora and selection of antibiotic resistant organisms secondary to chronic antibiotic therapy
- In-dwelling foreign bodies including intravascular and orthopedic prostheses
- Peripheral vascular disease with local immunocompromisation
- Impaired function of complement, phagocytes and/or lymphocytes

primary immunodeficiencies (table 3)
secondary immunodeficiencies (table 4)

and specific complement components appear to account for about 10% of primary immunodeficiencies.[4]

In general, primary immunodeficiencies are diseases of children, while secondary immunodeficiencies arise at any age, but have a greater tendency to occur in adult life. About 45% of primary immunodeficiencies are diagnosed in the first five years of life, and 60% by the age of 16.[4]

The classification of primary immunodeficiencies, given in Table 3, is not particularly satisfactory in that it is not complete (a number of very rare or poorly characterized primary immunodeficiencies are not included), and that delineation of separate categories of B- and T-cell dysfunction implies a lack of interaction between the two, which is not so. Also excluded are several chromosomal abnormalities associated with apparent immunodeficiency (e.g., Down Syndrome). Recent and more complete considerations of classification and etiopathogenesis in primary immunodeficiencies involving lymphocytes,[2, 3, 5] complement[6] and phagocytes[7] are available.

A number of conditions listed in Tables 3 and 4 deserve special mention because they are common, or because effective treatment exists; therefore early diagnosis may be beneficial.

Selective IgA deficiency is characterized by serum IgA levels of less than 0.1 mg/L (NR approximately 0.6–4.2 g/L), with normal IgM and overall normal IgG levels. Under normal circumstances, IgA is synthesized and released in proximity to mucosal surfaces and then transported to the exterior. In selective IgA deficiency there is an arrest of activation of IgA-bearing B lymphocytes to plasma cells. This may, in fact, not be restricted to IgA only, since deficiencies in IgE and subclasses of IgG are also reported in these patients.[8, 9] Certain drugs, most notably dilantin, are also capable of inducing isolated IgA deficiency. Absence of IgA within mucosal secretions can permit unhindered attachment of micro-organisms to the surface and subsequent infection, usually in the form of recurrent upper respiratory tract infections, including otitis media and sinusitis. IgA deficiency is also associated with normal health, asthma and allergy, including cow's milk intolerance and gluten enteropathy, and anti-IgA antibody, in up to 40% of patients with potential for significant transfusion reactions.[10]

In X-linked agammaglobulinemia maturation of B lymphocytes is frozen at a point within the precursor B-cell line, resulting in nearly complete inability to produce immunoglobulin of any type. Characteristically, serum immunoglobulins are all below the 95th percentile for age-matched controls; 'natural' antibodies such as isohemagglutinins A or B are also absent. Other features include an initial infection-free period of about six months, borne under the aegis of maternally acquired immunoglobulin, followed by recurrent, virulent pyogenic infections, including otitis media, sinusitis, pneumonia or meningitis; a positive family history in about one-quarter of maternal male relatives;[2] and failure to form specific antibody to tetanus and diphtheria toxoids. Although X-linked agammaglobulinemia is rare, effective and relatively simple treatment exists

Table 3: SELECTED PRIMARY IMMUNODEFICIENCIES

- Antibody, B Cell dysfunction predominant
  - X-linked agammaglobulinemia (Bruton, 1952)
  - common variable hypogammaglobulinemia
  - transient hypogammaglobulinemia of infancy
  - selective IgA deficiency
  - others
- T Cell dysfunction predominant
  - thymic dysplasia (DiGeorge, 1967)
  - purine nucleoside phosphorylase deficiency
  - chronic mucocutaneous candidiasis
- Combined B and T Cell dysfunction
  - severe combined immunodeficiences (SCID) including
    - autosomal recessive SCID with or without adenosine deaminase deficiency
    - X-linked SCID
    - others
  - Wiskott-Aldrich syndrome (eczema, thrombocytopenia, immunodeficiency)
  - Ataxia-telangiectasia syndrome (cerebellar ataxia, telangiectasias, ovarian dysgenesis, chromosomal instability)
- Phagocyte dysfunction
  - defects of neutrophil mobility
    - Chediak-Higashi syndrome
    - in association with hyper IgE including Job's syndrome
  - defects of neutrophil killing
    - chronic granulomatous disease
  - others
- Complement
  - homozygous C3 deficiency
  - C5, C6, C7, C8 deficiencies
  - others

Table 4: SELECTED SECONDARY IMMUNODEFICIENCIES

- Drugs eg. corticosteroids
  - azathioprine
  - cytotoxic agents
  - radiotherapy
- Diabetes Mellitus
- Infection eg. AIDS
  - influenza
  - miliary TB
- Alcoholism
- Chronic renal failure
- Hematological disease
  - neutropenia for any reason
  - lymphomas
  - multiple myeloma
- Splenectomy
- Protein-calorie malnutrition
- Protein-losing states
  - nephrotic syndrome
  - thermal burns
  - protein-losing enteropathies
- Collagen vascular disease
- Aging?

in the form of parenteral immune serum globulin (ISG).

Transient hypogammaglobulinemia of infancy (THI) has been defined as concentrations of one or more of IgG, IgM and/or IgA below the 95th percentile for age-matched controls in two or more determinations made in infancy, which return towards normal on remeasurement.[11] Ordinarily, there is a fall in immunoglobulin levels as maternally derived IgG is catabolized. This bottoms out between the third and sixth month of life and then begins to rise as the infant's own immune system becomes able to respond to antigenic stimuli. In THI, the decline lasts longer than normal; by two years of age however, immunoglobulin concentrations should be within appropriate age-matched ranges.[2] Unlike other congenital antibody deficiencies, natural antibody is present. Moreover, these patients are able to synthesize antibody to diphtheria and tetanus toxoid. The condition is rare and may or may not be associated with frequent infection; immune serum globulin is generally not indicated.[11]

An array of drugs are associated with an even greater array of suppressive effects on non-specific and specific immune responses. In many instances, these are in vitro observations; their translation into significant in vivo effects, in the form of increased infection not attributable to the underlying disease for which the drug is prescribed, is often difficult or impossible. For the family physician, corticosteroids are probably the most commonly encountered agents with clinically significant immunosuppressant properties. Steroids can alter and impair lymphocyte distribution and function,[12, 13] impair monocyte number and function,[14, 15] interfere with opsonisation,[16] alter phagocyte chemotaxis to sites of injury,[17] and blunt macrophage responsiveness to T-cell lymphokines.[17] Long-term use of high-dose steroids is associated with patterns of infection consistent with phagocytic (e.g., Staphylococci) and cellular-mediated dysfunction (fungi, viruses, mycobacteria).[17]

The relationship between diabetes mellitus, immunity and infection is complex. Defects in phagocyte chemotaxis in both type-I and type-II diabetes, and impaired lymphocyte activation in response to staphylococcal antigen have been observed.[18] Phagocyte function may be even more impaired during poor metabolic control with ketosis and hyperglycemia.[18] Complications of diabetes can be immunocompromising: autonomic neuropathy with impaired bladder emptying, peripheral vascular disease with reduced leukocyte availability and reduced oxygenation favoring anaerobic pathogens, and skin disruption by trophic ulceration are all examples. Clinical observation suggests that well-controlled, complication-free diabetics are at no greater risk of acquiring infection than non-diabetics;[19] however, once infection is established and diabetic control lost, eradication can be more difficult. Staphylococci and Candida are two commonly encountered pathogens in diabetes.

In AIDS, a retrovirus now called "Human Immunodeficiency Virus" infects and disrupts T_H lymphocytes. The ensuing impairment of CMI leads to overwhelming protozoal (e.g., *Pneumocystis, Toxoplasmosis*), fungal (e.g., *Candida, Cryptococcus*) and viral infections (e.g., *Herpes, CMV*). There is an absolute lymphopenia with reduction in the T-cell percentage to less than 30%. In addition, there is cutaneous anergy, the T_H to T_S cell ratio as determined by monoclonal antibodies is reduced to less than 0.5%, antibody response to antigens is reduced or absent despite hypergammaglobulinemia, and production of interleukin 2 is impaired.

Other infectious agents are also associated with impaired immune responses; examples include influenza viral respiratory tract infection with neutropenia and impaired phagocyte function, followed by secondary staphylococcal pneumonia, anergy in conjunction with measles and miliary TB, and congenital rubella.

A number of hematological processes are associated with impaired immune responses and infection. Neutropenia is the most common disorder of PMNs and is functionally defined when the absolute count is less than 1.5×10^9 per L. Causes include marrow replacement by leukemic, lymphomatous or solid tumour metastatic cells, aplastic anemia, and drugs, in either a relatively common predictable manner (e.g., cytotoxics such as cyclophosphamide) or an uncommon, unpredictable manner (e.g., phenothiazines, antibiotics, anticonvulsants). In general, the risk of infection does not become significant until counts fall below 1.0×10^9 per L. Staphylococci, gram-negative (*E coli, Klebsiella*) and systemic fungal infections are typical of the severely neutropenic patient. In multiple myeloma there is increased susceptibility to encapsulated bacterial infection (e.g., *Streptococcus pneumoniae*) resulting from impairment of normal serum immunoglobulin function. In Hodgkins lymphoma, cell-mediated immune dysfunction manifested by cutaneous anergy is paralleled by complicating infections such as Herpes zoster, cryptococcosis and Pneumocystis pneumonia.

Surgical or functional splenectomy conveys increased susceptability to infection by encapsulated bacteria such as *Streptococcus pneumoniae, Hemophilas influenzae* and *Neisseria meningitidis*. The precise mechanism(s) for this remain(s) unclear, but one possibility is through removal of the spleen's primary antibody response to antigen not dependent on T lymphocytes in inducing antibody formation, of which the capsular antigens of these organisms are examples. The risk appears highest in infants and children, and can be reduced by pneumococcal polysaccharide vaccine.

Protein-calorie malnutrition can lead to multiple abnormalities in the immune response. This condition may arise in chronically ill or hospitalized patients, alcoholics, the elderly and the destitute. Defects are observed in phagocytes (e.g., impaired migration and killing), T lymphocytes and CMI (e.g., T-cell lymphopenia and thymus gland involution, cutaneous anergy), immunoglobulins (e.g., reduced secretory IgA and reduced antibody response to antigen) and hypocomplementemia.[20] Susceptibility to pyogenic and viral illnesses including measles, CMV, Varicella and Herpes can ensue.[21]

Defences in the alcoholic host can be affected in a variety of ways, some of which probably result in increased severity and frequency of infection. Acute ethanol intoxication may impair glottis closure, with subsequent aspiration. Leukopenia may occur as a direct toxic effect of ethanol, as a feature of hypersplenism in cirrhosis with portal hypertension, or secondary to folate deficiency. Alcoholic cirrhosis and ascites are associated with spontaneous bacteremia and bacterial peritonitis.

Protein-losing states with hypogammaglobulinemia include thermal burns, the nephrotic syndrome, and protein-losing enteropathies. At least

in the cases of nephrotic syndrome[22] and burns, increased susceptibility to infection is seen. In the burned patient, infection is the usual cause of death following successful, initial resuscitation; other contributing factors are disruption of skin, hypocomplementemia and phagocyte dysfunction.

Chronic renal failure is associated with frequent and serious infection in conjunction with numerous in vivo and in vitro defects in CMI and phagocyte function.[23, 24] Other contributing factors to infection in these patients include procedures required in their care, such as urinary bladder catheterization, hemodialysis (vascular access infection and hepatitis B), and peritoneal dialysis (peritonitis).

The relationship between age *per se*, immune function and infection is unclear. Certain infections such as Herpes zoster, pneumococcal pneumonia, influenza, and tetanus are more frequent and/or more severe in the aged.[25, 17] Various abnormalities in immune parameters in apparently healthy elderly people are demonstrable; these include thymus involution and reduced maturation of T lymphocytes, impaired DH responses, increased auto-antibody formation, and increased incidence of monoclonal gammopathy.[25] However, it is difficult to link such immune defects directly with infections in the older patient because other conditions affecting non-specific or specific immune responses, and potentially accountable for the infection, are often present.

Apparent association has been made between several rheumatic diseases including SLE and RA, and infection. Contributing factors to this observation include immunosuppressive therapies for the disease (e.g., corticosteroids, azathioprine) and defects in non-specific defences as a result of complications of the disease, such as skin ulceration in RA. Underlying immune abnormalities can be demonstrated (e.g., SLE: hypocomplementemia and lymphopenia; RA: impaired function in PMNs obtained from synovial fluid), but it is not clear how significant a role these or other defects play by themselves in subsequent infection.

Recognition of the Immunocompromised Host

The tools to detect the majority of immunocompromised states lie behind the family physician's office door. These are, in descending order of importance, the clinical history, a small group of reasonably simple and available laboratory screening tests, and the physical exam.

The value of the history cannot be overemphasized. The critical questions are:

1. Is this patient immunocompromised and, if so, why?
2. Where does the problem lie with respect to non-specific, including phagocyte and complement, and/or specific immune defects?

With respect to question 1: infection is the hallmark of immunocompromisation. By this precept's inferred extreme, *any* infection must have occurred in an immunocompromised person, and while someday it may be possible, through more acute clinical and laboratory means, to predict surely an utterly healthy patient's next viral upper RTI and prevent it with timely intervention, it is impossible to do so today. Therefore, *significant* infection is the hallmark of immunocompromisation. Significant infection includes unusually recurrent, severe, unresponsive or exotic infectious episodes. Implicit to this condition is accurate characterization of the number and sites of infection, the need, or lack of need, for hospitalization, the microbiology through appropriate culture techniques, and the antibiotic(s) and other treatments employed.

It is difficult to be precise about 'usual' infectious events in children and adults and in this way, to delineate 'unusual' infections by exclusion. By way of examples, however, about one-third of children will have three or more episodes of acute otitis media in the first three years of life[26] and up to eight colds[27] per year, with recovery between each bout the rule. Adults have, on average, three viral URTIs per year.[28] Approximately 23,400 cases of streptococcal sore throat per 100,000 Canadians were reported in 1978;[29] and virtually no one with normal host defences contracts Pneumocystis pneumonia.

In the pediatric patient with unexplained failure to thrive, immunodeficiency should be a consideration. The history can also help to make the distinction between recurrent RTI (e.g., fever, productive cough) and allergy (e.g., seasonal pattern, nasal obstruction with mouth breathing, and the "allergic salute"), which often mimic one another.

Reasons why a patient might be immunocompromised can be quite obvious: for example, chronic renal failure, multiple myeloma or steroid therapy. Special attention in history taking should be given to drug use (including antibiotics, IV-drug abuse, and ETOH), nutrition, sexual practices, family history, co-existent allergy, and response to live-virus vaccines.

With regard to the second question: not only can infection herald immunocompromisation, but patterns of infection can suggest the site of the underlying immune defect (Table 5). Many of the associations listed in Table 5 reflect observations made of patients with primary immunodeficiencies and, more recently, with AIDS. In general, patients with phagocytic defects (primarily involving neutrophils) are predisposed to invasive fungal disease, and sinopulmonary and skin infections by Staphylococci and gram-negative rods. Patients with deficiencies in antibody or certain complement components are prone to sinopulmonary, middle ear, and meningeal infections by encapsulated, virulent organisms such as *Streptococcus pneumoniae* or *Hemophilas influenzae*. Patients with impaired cellular immunity are subject to a wide range of normally low-grade viral, protozoal, fungal and bacterial infections involving a variety of organ systems.

In primary immunodeficiency diseases, some other points relevant to natural history may distinguish antibody from cell-mediated defects. In general, and taking X-linked agammaglobulinemia as the archetype, recurrent sinopulmonary infection, potential survival into early adulthood, and lymphoid tissue hypoplasia suggest antibody deficiency while, using SCID as the example, failure to thrive, fatal inability to handle live vaccines, and death in infancy or early childhood are features of cell-mediated immune deficiency.[3]

Table 6 lists useful screening tests for immunodeficiency. These tests are available to most FPs either within their own office or through commercial or public health laboratories. It is best to test when the patient is infection free, since acute infection itself can induce abnormalities in the results of such investigations.

The CBC and differential provides absolute neutrophil and lymphocyte counts, which are of obvious value. The complement hemolytic 50% (CH_{50}) screens the overall integrity of

classical and terminal pathways, based on the amount of serum needed to lyse a suspension of sheep erythrocytes. A normal value (approximately 100–200 units per ml) excludes homozygous component deficiencies within these sequences; a value of 0 strongly suggests it. In the presence of a profoundly low CH_{50}, C_3 and C_4 concentrations can help to isolate the defect within the terminal activation sequence (normal C_3 and C_4) or at C_3. It is important to remember that many acquired conditions, some of which have already been mentioned, can lead to depletion of complement components either through consumption or inadequate production.

Quantification of serum IgM, IgG and IgA can provide useful diagnostic information in patients over two years of age if one or more Ig concentrations is below (IgA deficiency or X-linked agammaglobulinemia) or above (e.g., multiple myeloma: monoclonal; AIDS: polyclonal) normal ranges. It is essential that normal ranges be taken from local age-matched controls because Ig concentration will vary with age and environment. The usefulnes of Ig concentrations in infants under two years is limited because the range of normal values is wide. Neither low nor normal immunoglobulin concentrations, respectively, guarantee or exclude a diagnosis of primary immunodeficiency. In the former, consideration should be given to conditions leading to secondary hypogammaglobulinemia, such as excess protein loss, while in the latter, antibody response to antigenic stimulation should be tested if the clinical history or other points strongly suggest humoral defects.

Antibody responses can be determined to A and B antigens on red blood cells; to antigens to which exposure is the rule in the majority of the population; or in response to active immunization, using non-live vaccines. Isohemagglutinin A and/or B titres should be 1:16 by two years of age in all patients except those with type AB blood.[30] In patients previously immunized with one or more of diphtheria, pertussis, or tetanus, antibody titres can be determined to these agents: an intact humoral response at the time of immunization should result in development of specific antibody. In remotely or non-immunized individuals, non-viable vaccine such as tetanus toxoid or typhoid antigens H and O can be given in the usual manner and antibody titre measured three weeks after injection. In the case of typhoid H and O agglutinins, post-exposure titres less than 1:40 to both are abnormal.

T-cell function is screened through absolute lymphocyte count and DHST. In DHST a battery of six or more common antigens is given intradermally, and the sites are checked for induration 48 to 72 hours later. More than 90% of adults show a positive reaction (>5 mm of induration) to one or more of *Candida albicans*, trichophyton, tetanus toxoid, mumps, streptokinase-streptodornase, and diphtheria toxoid. Failure to do so means anergy and suggests impaired T-cell function; some clinical situations associated with anergy have already been mentioned, but, to reiterate, the major categories are concurrent infection, including AIDS; immune-mediated diseases such

Table 5: ORGANISMS ASSOCIATED WITH PARTICULAR DEFECTS IN HOST DEFENSE

- Complement deficiency
  - C3 — **Streptococcus pneumoniae**, **Hemophilas influenzae**
  - C5, C6, C7, C8 — disseminated **Neisseria meningitidis**
- Phagocytic defects
  - **Staphylococci**
  - **Enterobacteriaceae**
  - **Klebsiella**
  - systemic **Candida**
  - **Aspergillus**
- B lymphocyte and antibody deficiences
  - **Streptococcus pneumoniae**
  - **Hemophilas influenzae**
  - **Neisseria meningitidis**
  - **Giardia lamblia**
- Cellular defects
  - **viral** — **CMV**, **Herpes simplex I and II**, **Varicella-zoster**
  - **bacterial** — **Listeria**, **Legionella**, **Mycobacteria**, **Salmonella**
  - fungal — **Cryptococcus neoformans**, **Histoplasma**, **Coccidioides**
  - protozoal — **Pneumocystis carinii**, **Toxoplasma gondii**

Table 6: SCREENING TESTS IN SUSPECTED IMMUNODEFICIENCY

- CBC and differential for absolute neutrophil and lymphocyte count
- CH50
  - C3
  - C4
- delayed hypersensitivity skin testing battery
- quantitative serum immunoglobulins (IgM, IgG, IgA) isohemagglutinin A and B titres (measures IgM)
- antibody to previous immunization, or response following vaccination to non-live agents (eg. typhoid H + O agglutinins)

as lupus; drugs, neoplasia and certain primary immunodeficiencies. In the face of an anergic test battery, repeat testing using a higher dose of antigen is suggested. Whether repeat skin testing delivers sufficient antigenic stimulus to convert a negative to a positive response remains unclear.[30] Some pitfalls in DHST include measurement of erythema (mediated by antibody, not T-cell products) rather than induration; injection of antigen subcutaneously rather than intradermally, leading to dilution of injectate and falsely negative results; and its limited use in infants less than one year old, through lack of antecedent antigen exposure and sensitization.

Two other simple tests, not listed yet of potential value in suspected immunocompromisation, are the chest X-ray, which can reveal evidence of recurrent pulmonary infection, as well as show thymus gland size in infants (reduced in SCID), and a fasting blood-sugar test to exclude diabetes mellitus. A variety of other investigations may be useful in diagnosis in the numerous other problems of non-specific immune defences and secondary immunodeficiencies; in most cases, these tests should be suggested by the patient's history and physical exam.

More complex investigations, available at specialized centres, of function and quantities of complement, phagocytes, and B and T cells may be indicated if a screening test is abnormal, if the clinical picture strongly suggests immunodeficiency despite normal screening, or if the patient is less than two years old; in this last instance, as has been mentioned, routine immune assessment has limitations.

In some instances the physical findings suggest a diagnosis: for example, Kaposi's sarcoma in a young man or lymphadenopathy in Hodgkin's disease. Very often, however, the findings are non-specific, disclosing evidence of previous infection, but of little else. An important point to remember is the immunodeficient patient's possible inability to generate an inflammatory response and, with that, masking of physical changes normally associated with infectious processes.

Particular mention should be made of diagnosis of AIDS in view of its anticipated increase. AIDS is a clinical syndrome defined by diagnosis of opportunistic infection or neoplasia (e.g., Kaposi's sarcoma in patients less than 60 years old) characteristic of impaired CMI, in a patient not immunosuppressed for other reasons. The various immunological abnormalities, some of which have been noted, are not specific to the syndrome and therefore must always be interpreted in relation to the clinical situation. A summary of some important points in the diagnosis is given in Table 7.

Aspects of Management in Immunocompromised Hosts

Several self-evident, but important, points can be made about management of the immunocompromised host. Avoid infection through proper hygiene and dental care and minimization of contact with active, contagious, infectious disease. Avoid, minimize or reverse, whenever possible, factors and diseases contributing to the immunocompromised state such as urinary catheters, prolonged bed rest, chronic daily steroid use, poorly controlled DM, and poor nutrition. When treating an immunocompromised patient, maintain a high index of suspicion for infection, and, given the choice, treat early (including hospitalization) rather than late, in light of greater potential for severe infection if left untreated. As always, antimicrobial choice is based on appropriate cultures and sensitivities obtained prior to treatment, with selection of the least toxic, narrowest-spectrum antibiotic. In some settings, more esoteric and fastidious organisms requiring special handling may need to be considered: for example, *Mycobacterium avium* pulmonary, urinary or gastrointestinal infections in AIDS. In such cases the local microbiology laboratory may be able to offer assistance.

There are three issues surrounding vaccination and the immunocompromised host. The first and most important of these has been alluded to, *viz* live, attenuated vaccines are contra-indicated in suspected or confirmed severe primary and secondary immunodeficiencies. These include BCG and vaccines for poliomyelitis, measles, rubella, and mumps. The second issue has also been noted, namely the potential use of non-live vaccines in evaluating antibody response in suspected immunodeficiency states. The third issue is the use of vaccination in various clinical situations to augment specific immunocompetency and thus allay subsequent infection; included here are pneumococcal, influenza, tetanus and meningococcal vaccines.

Current recommendations for pneumococcal vaccination include asplenia, Hodgkin's disease, chronic CV and pulmonary disease, alcoholism, cirrhosis, renal failure, multiple myeloma, other conditions associated with immunosuppression and CSF leaks.[31] The use of this vaccine in healthy adults over 65 years is problematic, largely because proof from randomized controlled trials is not available. Nevertheless, the Centers for Disease Control, Atlanta, recommends the vaccine's use in these patients.[31] In elective splenectomy, pneumococcal vaccine should be given pre-operatively, if it has not been given before, to ensure maximum antibody response.

Annual influenza vaccination is recommended in patients with chronic CV or pulmonary disease, chronic metabolic disease including DM, renal failure, anemia, immunosuppression, residents of nursing homes and chronic-care facilities, and healthy individuals over 65 years of age.[32]

Although it is recommended that tetanus toxoid booster shots be given every 10 years, about one-half of patients 60 years or older have inadequate protective antibody levels.[33] Tetanus is most common and serious in the elderly; individuals who have not received a tetanus toxoid booster shot within the preceding 10 years should receive at least two doses of toxoid over 1 month.[33]

Meningococcal vaccination is recommended in patients over two years of age with terminal complement-component deficiencies and in asplenia.[34]

It is difficult to make definitive all-encompassing comment on continuous antibiotic prophylaxis in immunocompromisation. The potential benefit of use (prevention of rapid overwhelming infection) is balanced by risk (resistant organism infection and toxicity). Occasionally clear-cut support for specific antibiotic prophylaxis in a specific setting exists in the form of a randomized controlled trial[35, 36] but more often, such data is not available. It is rational not to use antibiotics in a chronic prophylatic fashion unless there is acceptable evidence that benefit outweighs risk.

Blood transfusion should be considered carefully in immunodeficiency. A possible scenario for the FP is transfusion in IgA deficiency: because of potential anti-IgA antibody in these pa-

tients, blood should be from an IgA-deficient donor or contain multiple washed red cells. In patients with possible or confirmed cell-mediated immunodeficiency, graft rather than host disease from donor lymphocytes can occur unless precautions are taken, such as irradiation of the donor cells.

Finally, there is an assortment of potentially or clearly valuable treatments in some immunodeficiency states. Replacement of gammaglobulin can be effective in patients with primary humoral immunodeficiency. It can be given by IM or IV injection monthly. It cannot correct deficiency of IgA at mucosal surfaces and therefore, in addition to the potential for formation of anti-IgA antibody, is not indicated in selective IgA deficiency. Bone-marrow transplantation is emerging as the treatment of choice in SCID. Granulocyte transfusion may be helpful in granulocytopenia with septicemia. To date, there is no specific treatment for AIDS, despite extensive ongoing research. ◉

References

1. Peterman RA, Curren JW. Sexual transmission of human immunodeficiency. *JAMA* 1986; 256(16):2222–6.

Table 7: DIAGNOSIS OF AIDS

History

- Risk Factors: homo- or bisexuality or heterosexual contact with someone at high risk for AIDS
  exposure to blood or blood products
  parenteral drug use
  offspring of a woman at high risk for AIDS
- Past history of disease associated with AIDS[37 38]
  Opportunistic infection *eg. Pneumocystis* pneumonia
  malignancy *eg.* Kaposi's sarcoma
- Symptoms:

General	- weight loss, fatigue, fever, night sweats
GI	- recurrent oral ulceration, dysphagia, persistent diarrhea, persistent rectal fissures
RESP	- persistent, nonproductive cough, progressive dyspnea
Skin	- changing skin lesions, mucocutaneous ulceration
Neur	- headache, changes in mental status, focal deficits

- Absence of immunosuppression for other reasons.

Physical Exam

Skin	- Kaposi's and herpetic lesions, folliculitis, seborrhea
G.I.	- Oral candidiasis, rectal fissures, oral leukoplakia
Lymphoreticular	- Lymphadenopathy, hepatosplenomegaly
Resp	- adventitious breath sounds
Neur	- abnormal mental status - fundi: exudates, papilledema - focal CNS abnormalities - signs of peripheral neuropathy, meningitis

Laboratory: Suspected Case

- HIV antibody
- CBC, differential
- quantitative immunoglobulins
- T cell subset analysis (T_4, T_8)
- others - DHST battery
  - Hepatitis B serology

2. Rosen FS, Cooper M, Wedgewood R. The primary immunodeficiencies. *N Engl J Med* 1984; 311(4):235–42, 311(5): 300–10.

3. Buckley RH. Immunodeficiency. *J Allerg Clin Immun* 1983; 72(6):627–40.

4. Graziano FM, Bell CL. The normal immune response and what can go wrong. *Med Clin North Am* 1985; 69(3):439–52.

5. WHO Scientific Group on Immunodeficiency. Primary immunodeficiency disease. *Clin Immun Immunopath* 1983; 28:450–75.

6. Whaley K. Laboratory investigation of complement disorders. *Clin Immun Allerg* 1985; 5(3):407–21.

7. Klempner MS, Wolff S. The neutrophil in host defence: congenital acquired and drug-induced abnormalities. In: Grieco MH, ed. *Infections in the abnormal host*. New York: Yorke Medical Books, 1980.

8. Oxelius A, Laurell AB, Lindquist B, et al. IgA subclasses in selective IgA deficiency: importance of IgG2-IgA deficiency. *N Engl J Med* 1981; 304:1496–7.

9. Polmer SH, Waldmann TA, Balestra ST, et al. IgE immunologic deficiency disease. *J Clin Invest* 1972; 51:326–30.

10. Amman AJ, Hong R. Selective IgA deficiency: presentation of 30 cases and review of the literature. *Med* 1971; 50: 223–6.

11. Tiller T, Buckley RH. Transient hypogammaglobulinemia of infancy: review of the literature, clinical and immunological features of 11 new cases, longterm follow-up. *J Pediatr* 1978; 92:347–53.

12. Fauci AS, Dale DC. The effect of in vivo hydrocortisone on subpopulations of human lymphocytes. *J Clin Invest* 1974; 53:240.

13. Thong YH, Hensen SA, Vincent MM, et al. Effect of hydrocortisone on in vitro cellular immunity to viruses in man. *Clin Immunol Immunopath* 1975; 55:22.

14. Fauci AS, Dale DC. Alternate day prednisone therapy and human lymphocyte subpopulations. *J Clin Invest* 1975; 55:22.

15. Rinehart JJ, Sagone AL, Balcerzak SP, et al. Effects of corticosteroid therapy on human monocyte function. *N Engl J Med* 1975; 292:236.

16. Schreiber AD, Parson J, McDermott P, et al. Effect of corticosteroids on the human monocyte IgE and complement receptors. *J Clin Invest* 1975; 56:1189.

17. Pinching AJ. Secondary immunodeficiency. *Clin Immun Allerg* 1985; 5(3): 469–90.

18. Gocke TM. Diabetes mellitus. In: Grieco MH, ed. *Infection in the abnormal host*. New York: Yorke Medical Books, 1980.

19. Infection and Diabetes (editorial). *Br Med J* 1974; 3:76.

20. Keusch GT. Effects of malnutrition and metabolic sequelae of infection. In: Grieco MH, ed. *Infection in the abnormal*

host. New York: Yorke Medical Books, 1980.

21. Oleske JM, Minnefor AB. Viral and chlamydial infections. In: Grieco MH, ed. *Infections in the abnormal host*. New York: Yorke Medical Books, 1980.

22. Rubin HM, Blau EB, Michaels RH. Hemophilus and pneumococcal peritonitis in children with the nephrotic syndrome. *Pediatr* 1975; 56:598.

23. Morrison G, Greheb M, Earley Le. Chronic renal failure. In: Seldin DWl, Geibisch G, ed. *The kidney: physiology and pathophysiology*. New York: Raven Press, 1985.

24. Axelrod JL. Uremia and organ transplantation. In: Grieco MH, ed. *Infections in the abnormal host*. New York: Yorke Medical Books, 1980.

25. Busby J, Caranosos GJ. Immune function, autoimmunity, and selective immunoprophylaxis in the aged. *Med Clin North Am* 1985; 69(3):465–74.

26. Klein JO, Teele DW, Tosuer B. Epidemiology of otitis media in children. *Ann Otol Rhin Laryng* 1980; 89(suppl. 68) 5–6.

27. Stiehm ER. Immunodeficiency disorders—general considerations. In: Stiehm ER, Fulginiti VA, eds. *Immunological disorders in infants and children*. Toronto: W.B. Saunders, 1980.

28. Feigin RD, Cherry JD, eds. *Textbook of pediatrics infectious diseases*. Toronto: W.B. Saunders, 1980.

29. Statistics Canada. *Annual report of notifiable diseases*. Ottawa: Statistics Canada, Health Division, 1978.

30. Katz P. Clinical and laboratory evaluation of the immune system. *Med Clin North Am* 1985; 69(3):453–64.

31. Immunization Practices Advisory Committee, Centers for Disease Control. Update: pneumococcal polyaccharide vaccine usage—United States. *Ann Int Med* 1984; 101:348–50.

32. Centers for Disease Control. Prevention and control of influenza. *MMWR* 1985; 34(19):262–75.

33. Ruben FL, Nagel J, Fireman P. Antitoxin responses in the elderly to tetanus-diptheria immunization. *Am J Epidemiol* 1978; 108(2):145–9.

34. Centers for Disease Control. Meningococcal vaccines. *MMWR* 1985; 34(18): 225–9.

35. Hughes WT, Kuhn S, Chaudhury S, et al. Successful chemoprophylaxis of pneumocytsis carinii pneumonitis. *N Engl J Med* 1977; 297:1419–26.

36. Stamm WE. Prevention of urinary tract infections. *Am J Med* 1984; 76(5A):148.

37. Centers for Disease Control. Update on AIDS—United States. *MMWR* 1982; 31: 507–14.

38. Centers for Disease Control. A revision of the case definition of AIDS for national reporting—United States. *MMWR* 1985; 34:373–5.