Infection of immunosuppressed patients

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I hope it is no longer old-fashioned to consider the immune system as being primarily concerned with defence against infection by micro-organisms. I intend to deal with the types of immunodeficiency listed in Table 1, except for the first two categories, and with particular emphasis on the commonest that we encounter—general immunodeficiency due to metabolic and nutritional abnormalities and drug-induced depression of immune activity. We must consider the types of organism concerned, the consequence of an infection during a state of immune suppression, the few specific associations that exist between a particular state of depression and a particular organism, problems in the diagnosis of infection, its prevention, and, very briefly, treatment.

Table 1 *Types of immunodeficiency*

(1)	Genetic restriction
(2)	Specific tolerance
(3)	Immaturity
(4)	Selective humoral deficiencies
(5)	Selective cellular deficiencies
(6)	Combined states—natural
	—drug-induced
(7)	General states —malnutrition, malabsorption, metabolic disorders, trauma, burns, etc.

But first a point of definition: the word infection is used to mean both the act of acquiring a pathogenic organism by the body and also, rightly or wrongly, the train of events that may occur then, or perhaps much later, as a result of that acquisition. The distinction is important since in immunosuppressed subjects many of the 'infections' are really reactiva-

tions. A glance at a table of organisms illustrates the point (Table 2). On the left are organisms—viruses, bacteria, protozoa, or fungi—which are almost universal infectors but rarely cause disease in normal subjects. On the right are organisms that are rarely encountered—at least in Britain—but universally cause serious disease. Between the two come the commoner pathogens. The organisms on the right we may perhaps neglect. If an immunosuppressed patient gets bitten by a rabid dog we have a serious problem on our hands, but luckily a rare one. What concerns us are reactivations of latent infection or reinfection by ubiquitous organisms, but equally important are primary infections by some of the organisms in the middle, since suppression is likely to affect primary immune responses more than secondary ones. For example, the commonest cause of death in remission for a child with acute lymphoblastic leukaemia are varicella and measles. One of the incidental benefits of the eradication of smallpox is that patients with chronic lymphatic leukaemia will no longer suffer the occasional disaster of progressive vaccinia. The other important aspect of primary infections is that they are largely preventable whereas most reactivations are not.

Table 3 shows some of the factors that determine whether an infection occurs and the form it takes. Some of these are obvious, such as concomitant tissue damage; others, such as microbial competition, are putative but probably important; and others are considered in more detail below.

Table 4 shows some of the consequences of infection in the immunosuppressed—firstly, an over-

Table 2 *Examples of infecting organisms in immunosuppressed patients*

	Universal 'non-pathogens'	Common	Occasional	Rare lethal
Viruses	JC H. simplex	CMV Zoster—Varicella —Measles—	Vaccinia	Rabies B virus
Bacteria	Lactobacilli Bacteroides	Coliforms Pneumococci	Shigella Salmonella	<i>P. pestis</i>
Fungi	Cryptococcus Candida	Aspergillus	Coccidioidomycetes	
Protozoa	Pneumocystis	Toxoplasma	<i>P. falciparum</i>	

Table 3 *Determinants of infection in immunosuppressed patients*

(1) Chance acquisition—primary responses usually more severely affected than secondary responses
(2) Type of immune deficit—splenectomy, IgM deficiency, post-radiation, T cell depletion, etc.
(3) Local factors—tissue damage, etc.
(4) Circumstances of original infection—quality and location of infecting agent
(5) Microbial competition

Table 4 *Consequences of infection in immunosuppressed patients*

	Consequences
(1) Fulminant infections	Septicaemia, etc.
(2) Non-reactive disease	Tuberculosis, hepatitis, 'silent' acute abdomen
(3) Chronic carrier and excretor state	CMV, hepatitis, respiratory viruses
(4) Immunopathology	Atopy, immune complex disease, autoimmunity, ? G v H
(5) CNS dissemination	PML, measles, etc.

whelming proliferation of the organism, especially as a septicaemia and especially when the front-line components of immunity, polymorphs and/or IgM, are lacking. Along with an absent immune response there may be no inflammatory response—that is, non-reactive disease which is either acute or, in the case of a relatively slow organism such as the tubercle bacillus, rather more prolonged. Most non-reactive states are fatal but in the case of viruses the lack of an immune reaction or its suppression may actually protect the individual from cellular damage at the cost of becoming a chronic carrier and excretor of the virus, as happens in the experimental example of lymphocytic choriomeningitis of mice (Lehmann-Grube, 1972).

In man the massive proliferations of hepatitis B virus or cytomegalovirus (CMV) which can occur in renal transplant and similar patients are more familiar. What is less well-known, and is as yet insufficiently investigated, is the prolonged carriage of respiratory viruses such as measles in malnourished or drug-immunosuppressed children (Dossator *et al.*, 1977; Wesley *et al.*, 1978). If they continue to excrete the virus there may be serious consequences in wards and clinics where other immunosuppressed children may be concentrated, especially as the classical signs of infection may be absent so that the condition remains undiagnosed (Gardner, 1978).

One must also realise that there is a vicious circle of infection in these susceptible patients. A defective immune system that can react almost normally to a single new agent may be overwhelmed by a double infection especially when, as in the case of measles,

there is a strong immunosuppressive effect of the first infection.

When instead of total non-reactivity (which is relatively rare) there is some part of the normal immune response—perhaps, for example, antibody-formation—then there may be pathological consequences—immune complex disease, for example; or atopy if it is a question of the type of antibody produced, IgE rather than G or A; or autoimmunity for which one mechanism might be that the failure of a defective initial response leads to a prolonged production of cross-reacting antibody. In this complex subject some associations are well-documented—for example, the lupus-like syndrome and haemolytic anaemia of the NZB mouse, or the occurrence of arthritis, lupus-like disease, and autoantibodies in patients with immunoglobulin deficiency or in carriers of the gene for chronic granulomatous disease—but the exact chain of cause and effect is not always clear (Soothill, 1976; Schaller, 1975).

Finally, the failure of an immune response may allow access or proliferation of viruses in the central nervous system. The JC Papova virus, for example, may or may not enter the CNS in normal subjects, but only with severe immunosuppression does it proliferate to cause progressive multifocal leucoencephalopathy, while 'inclusion-body' measles encephalitis—to be distinguished from acute measles encephalitis and subacute sclerosing panencephalitis (SSPE)—is known only in association with drug treatment (Kay, 1978).

There are a very few close associations between particular forms of immunodeficiency and particular infections, and some of these are listed in Table 5.

Table 5 *Specific associations*

Form of immunodeficiency	Associated infection
Splenectomy	Septicaemia (pneumococcal)
IgM deficiency	Septicaemia (meningococcal)
IgE and IgA deficiency	Respiratory bacterial infections
IgG deficiency	CNS ECHO-virus infection
Neutropenia	Bacterial infections
T-cell reduction?	Zoster
Corticosteroids	Candida infection
Multiple drug immunosuppression	Pneumocystis
C6 and 8 deficiency	Neisseria infection

References: ECHO-virus infections (Wilfert *et al.*, 1977); pneumocystis infection (Hughes *et al.*, 1975); Neisseria infections (*Lancet*, 1978).

The lack of a spleen has been studied in some detail. Apparently there is deficient antibody production in the primary response and a failure to transfer from IgM to IgG antibody formation after repeated antigenic stimulation (Sullivan *et al.*, 1978). In general the pattern of immune reactions is so complex, with

interactions between the different cell populations and compensating mechanisms to remedy any single defect, that we should regard any degree or mode of suppression as a predisposition to any sort of infection.

What, in brief, can be done (Table 6)? Obviously isolation and hygiene can be invaluable in preventing primary infections. A few simple inexpensive measures such as the use of a side-ward and hand-washing can give some protection to a patient with myelosuppression—for example, acute myeloid leukaemia—for the time that he requires it. Avoidance of the main sources of respiratory pathogens should be attempted, especially for children with acute lymphatic leukaemia, but where contact occurs passive immunisation is needed. Ideally, perhaps, immunoglobulin could be given routinely if there were adequate supplies. There is a place for active immunisation, especially with pneumococcal vaccines (*Lancet*, 1978), and perhaps with other organisms if the killed vaccines are effective.

Table 6 *Prevention of infection in immunosuppressed patients*

Isolation and hygiene
Passive immunisation—Vig, measles Ig, etc.
? Active immunisation—killed vaccines, pneumococcal, etc.
Antibiotics—postsplenectomy, gut regimens, co-trimoxazole, etc.

Antibiotic prophylaxis is certainly worthwhile in some circumstances—penicillin to guard against pneumococcal infection, co-trimoxazole for *Pneumocystis* infection, and a non-absorbable antibiotic regimen during short periods of neutropenia as in acute myeloid leukaemia.

Of the greatest practical importance is the diagnosis of infections in the immunosuppressed patient. This may be a difficult matter for reasons given in Table 7. The usual signs of infection may be absent and for similar reasons diagnostic tests may fail. On the other hand, the organisms may be unusually prolific and in the long run antibody-production seldom fails completely except in congenital states. Inaccessibility of organisms, the doubtful significance of low-grade pathogens, and multiple infections all help to compound the problems.

Table 7 *Difficulties in diagnosis of infection*

- (1) Absent signs of infection. No polymorphs, no pus. Inflammatory reactions suppressed.
- (2) Organisms inaccessible—pneumocystis, candida.
- (3) Negative serology. Infection occurs because of failure to make antibodies.
- (4) Doubtful pathogenicity. Should positive cultures of *Staph. albus*, etc., be treated?
- (5) Multiple infections.

When it comes to treatment (Table 8), awareness of what may be happening and prompt, blind antibiotic treatment may be life-saving. A septicæmia regimen is essential. We have used gentamicin plus carbenicillin for the past 10 years whenever a neutropenic patient has had a temperature of 101°F (38.3°C) once or 100°F (37.8°C) twice in four hours, and I know of nothing better. (The results of blood-culture may, of course, indicate the need for a change.) Generalised candida infection is so difficult to diagnose that blind therapy must often be used, and the same applies sometimes to *Pneumocystis* pneumonia.

Table 8 *Treatment of infection in immunosuppressed patients*

Antibiotics (septicæmia regimen)
? Antibodies
Platelets and granulocytes
Transfer factor
Interferon

Immunoglobulin is often given—for example, for varicella—but is of doubtful benefit, and the introduction of an antibody bolus could precipitate an Arthus-type reaction. Probably this is only a theoretical risk. I know of no actual evidence that giving immunoglobulins is harmful.

Granulocytes are obviously useful whenever neutropenia is severe. They are especially valuable for local infection—for example, a perianal abscess or pneumonia—while platelets may often have to be given in large quantities since they may be consumed in areas of cell damage and inflammation. Remarkable results have been claimed for transfer factor in rare cases of some congenital immunodeficiencies (Kohler *et al.*, 1974) or congenital CMV infection (Thomas *et al.*, 1977), while interferon has still to be tried on a scale that will allow its evaluation.

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