is much more common in immunosuppressed patients (Doll & Kinlen, 1970). Fifty-two primary malignant neoplasms have been reported in patients on cytotoxic immunosuppressive therapy following organ transplantation (Schneck & Penn, 1971; Table 3). An

TABLE 3. Malignant tumours arising in organ-homograft recipients reported to the Denver Registry (Schneck & Penn, 1971)

Epithelial tumours	28
Mesenchymal tumours	24
Leiomyosarcoma	2
Lymphomas unclassified, Kaposi's sarcomas	22 (11 involving the brain)
Total	52

increased frequency of malignant disease of the lymphoreticular system is particularly significant and it has been estimated that for 'reticulum cell sarcoma' this represents a greater than 50-fold increase in incidence over subjects who are not immunosuppressed. Unfortunately, the term 'reticulum cell

TABLE 4. The increased incidence of lymphomas in patients with immunological deficiency diseases (Doll & Kinlen, 1970)

	Ataxia- telangiectasia	Wiscott Aldrich syndrome	Chediak Higashi syndrome
No. of cases	200	90	50
No. malignant disease (usually of lympho- reticular system)	14	11	11

sarcoma' refers to a miscellaneous group of undifferentiated tumours which may represent rather different malignant diseases.

An increased incidence of lymphomas has also been observed in three congenital immunological

deficiency diseases, namely, ataxia-telangiectasia, the Wiscott-Aldrich and Chediak-Higashi syndromes (Table 4). The evidence that malignant disease is increased in patients who are immunosuppressed must be viewed with a certain amount of circumspection. The malignant diseases described have usually involved the lymphoreticular system and this is affected directly by the cytotoxic immunosuppressive treatment and in the congenital abnormalities of this system.

References

- ALLISON, A.C. (1970) Potentiation of viral carcinogenesis by immunosuppression. *British Medical Journal*, **4**, 419.
- CASAZZA, A.R., DUVAL, C.P. & CARBONE, P.P. (1966) Summary of infectious complications occurring in patients with Hodgkin's disease. *Cancer Research*, **26**, 1290.
- CONE, L. & UHR, J.W. (1964) Immunological deficiency disorders associated with chronic lymphocytic leukaemia and multiple myeloma. *Journal of Clinical Investigation*, **43**, 2241.
- CROWTHER, D., BATEMAN, C.J.T., VARTAN, C.P., WHITEHOUSE, J.M.A., MALPAS, J.S., HAMILTON FAIRLEY, G. & BODLEY SCOTT, R. (1970) Combination chemotherapy using L-asparaginase, daunorubicin and cytosine arabinoside in adults with acute myelogenous leukaemia. *British Medical Journal*, **4**, 513.
- DOLL, R. & KINLEN, L. (1970) Immunosurveillance and cancer: epidemiological evidence. *British Medical Journal*, **4**, 420.
- GOFFINET, D.R., GLATSTEIN, E.J. & MERIGAN, T.C. (1972) *Annals of Internal Medicine* (in press).
- MILLER, D.G. (1962) Patterns of immunological deficiency in lymphomas and leukaemias. *Annals of Internal Medicine*, **57**, 703.
- MORSE, E.E., BRONSON, W., CARBONE, P.P. & FREIREICH, E.J. (1961) Effectiveness of granulocyte transfusion from donors with chronic myelocytic leukaemia to patients with leucopenia. *Clinical Research*, **9**, 332.
- SCHNECK, S.A. & PENN, I. (1971) De-novo brain tumours in renal transplant recipients. *Lancet*, **i**, 983.
- SOKAL, J.E. & FIRAT, D. (1965) Varicella-zoster infection in Hodgkin's disease. *American Journal of Medicine*, **39**, 452.

Infection associated with immunosuppressive therapy

M. H. LESSOF
M.D., F.R.C.P.

Professor of Medicine, Guy's Hospital, London, S.E.1

RESISTANCE to infection depends on a number of things. It depends on the integrity of the skin and mucous membranes. It also depends on the function of polymorphonuclear leucocytes, macrophages, lymphocytes, antibodies, the complement system, and interferon. A disturbance in the response to infection may result from a failure of any of these factors, and immunosuppressive drugs can interfere at a number of different points.

Because of the complexity of the immune response it is helpful to analyse some of the congenital immune deficiency states in order to observe what happens when any one part of the immune system fails to function. In general terms, not only may the more common pathogenic organisms then cause infections, but organisms which are usually regarded as non-pathogenic may become invasive. Despite such presenting features as diarrhoea and wasting,

there are cases in which no pathogenic organism may be isolated from the stool. Inflammatory reactions in general are impaired, and an accompaniment of the failing immune system may be the development of autoimmune reactions. Polyarthritides resembling rheumatoid arthritis, dermatomyositis and haemolytic anaemia are all seen in infants suffering from immune-deficiency states (reviewed by Lessof & Russell, 1971). When lymphocytes are deficient, as in inherited lymphopenia, the infant appears to be particularly prone to intracellular infections with viruses or fungi. Tuberculosis and pneumocystis carinii infections may also occur when there is a deficiency in cellular immunity. When antibodies are deficient, as in agammaglobulinaemia, bacterial infections tend to occur more frequently, with pneumonia, pyelonephritis, septicaemia or skin abscesses.

There are a number of comparable situations in adults. This becomes apparent not only when adults are treated with recognized immunosuppressive therapy, but also during treatment with a variety of drugs which interfere with cell metabolism. Examples of these are the cytotoxic drugs used in cancer chemotherapy or the antibiotics (such as chloramphenicol) which are prescribed because of their ability to interfere with bacterial metabolism but may, incidentally, interfere with lymphocyte function and antibody production in the host.

During any treatment which interferes with the host response, infections may occur with bizarre organisms. These infections may be multiple, and Stinson *et al.* (1971) found forty-seven separate organisms in fifteen patients receiving immunosuppressive drugs for the purpose of cardiac transplantation (see Table 1). The presence of local tissue damage may increase the susceptibility to infection as has been noted in the animal studies of Pearce (1942) and might be inferred from the results of the

TABLE 1. Forty-seven infections in fifteen cardiac transplant patients receiving immunosuppressive drugs (data of Stinson *et al.*, 1971)

Twenty-five bacterial	
Gm -ve	19
Gm +ve	6
Eleven viral	
Cytomegalovirus	9
H. simplex	1
Hepatitis	1
Seven fungal	
<i>Aspergillus</i>	5
<i>Candida</i>	1
<i>Rhizopus</i>	1
Four protozoal	
<i>Pneumocystis</i>	2
<i>Toxoplasma</i>	1
<i>Trichomonas</i>	1

aortic valve homograft operations reported by Davies *et al.* (1968). As an accompaniment of such infections, there may be evidence of auto-immune reactions, but Davies *et al.* showed that anti-heart antibodies may arise after cardiac surgery, regardless of whether infection is detected or not. Infection, by itself, is a potent factor in leading to auto-antibody formation. Antiglobulin 'rheumatoid' factors, anti-nuclear factor and cryoglobulins are all seen in infectious mononucleosis (Kaplan, 1968) or may be seen in bacterial endocarditis (Messner *et al.*, 1968; Dreyfuss & Librach, 1952). Auto-antibodies are also well known to occur in syphilis, and antiglobulins have also been reported in leprosy, trypanosomiasis and kala-azar (Houba & Allison, 1966) as well as in infectious hepatitis, tuberculosis, and even after vaccination (Aho, Somer & Salo, 1967).

It is notable that the antemortem diagnosis of some of the infections occurring in immunosuppressed patients may be extremely difficult. This also applies to other conditions, such as acute leukaemia in which the response to infection may be impaired even before immunosuppressive or cytotoxic drugs are given. Of fourteen cases of visceral candidiasis reported by Preisler, Hasenclever & Henderson (1971) only seven showed a rise in agglutinating antibody titre (see Table 2). Of the remaining seven, who showed no rise

TABLE 2. Antibody studies and blood cultures in the diagnosis of visceral candidiasis (fourteen cases—data of Preisler *et al.*, 1971)

Agglutinating antibody titre	Patients (no.)	Positive blood cultures (no.)	Precipitating antibodies (no.)
Rise	7	2	6
No rise	7	3	0

in antibody titre, only three had a positive blood culture. There remained four patients who had only clinical, rather than laboratory evidence of visceral candida infection before death. In these circumstances the diagnosis cannot always be made. The almost universal presence of *Candida* in the mouth in such cases can make the diagnosis of visceral involvement even more difficult.

In summary, the infections which supervene in patients who are receiving immunosuppressive drugs are influenced by the effects of these drugs on antibody production and lymphocyte function. They are also influenced by the underlying disease for which this treatment is given, especially in tumours which involve the lymphoid system or affect the production of polymorphonuclear leucocytes. When multiple infections occur the immunological responses may be overwhelmed, and the diagnosis of such conditions as visceral candidiasis need not always require a

positive blood culture or evidence of an antibody response. As in other infective conditions, auto-antibody reactions are also seen.

References

- AHO, K., SOMER, T. & SALO, O.P. (1967) Rheumatoid factors and immuno-conglutinin responses following various vaccinations. *Proceedings of the Society of Experimental Biology and Medicine*, **124**, 229.
- DAVIES, H., MISSEN, G.A.K., BLANDFORD, G., ROBERTS, C.I., LESSOF, M.H. & ROSS, D.N. (1968) Homograft replacement of the aortic valve. A clinical and pathology study. *American Journal of Cardiology*, **22**, 195.
- DREYFUSS, F. & LIBRACH, G. (1952) Cold precipitable serum globulins ('cold fractions', 'cryoglobulins') in subacute bacterial endocarditis. *Journal of Laboratory and Clinical Medicine*, **40**, 489.
- HOUBA, V. & ALLISON, A.C. (1966) M. antiglobulins (rheumatoid factor-like globulins) and other gamma-globulins in relation to tropical parasitic infections. *Lancet*, **i**, 848.
- KAPLAN, M.H. (1968) Cryoglobulinaemia in infectious mononucleosis. *Journal of Laboratory and Clinical Medicine*, **71**, 754.
- LESSOF, M.H. & RUSSELL, A.S. (1971) Immunity, autoimmunity and immunosuppression. In: *Progress in Clinical Medicine* (Ed. by R. Daley and H. Miller), 6th edn. Churchill Livingstone, Edinburgh and London.
- MESSNER, P., LAXDAL, T., QUIE, P.G. & WILLIAMS, J.C. (1968) Rheumatoid factors in S.B.E. *Annals of Internal Medicine*, **68**, 746.
- PEARCE, J.M. (1942) Susceptibility of the heart of the rabbit to specific infection in viral disease. *Archives of Pathology*, **34**, 319.
- PREISLER, H.D., HASENCLEVER, H.F. & HENDERSON, E.S. (1971) Anticandida antibodies in patients with acute leukemia. A prospective study. *American Journal of Medicine*, **51**, 352.
- STINSON, E.B., GRIEPP, R.B., DONG, E. & SHUMWAY, N.E. (1971) Results of human heart transplantation at Stanford University. *Transplantation Proceedings*, **3**, 337.