Infection associated with immunosuppressive therapy*

D. CROWTHER

M.A., Ph.D., M.B., M.R.C.P.

Physician to the Imperial Cancer Research Fund, Department of Medical Oncology,
St Bartholomew's Hospital, London E.C.1

ACQUIRED immune-deficiency states occur in a number of malignant diseases, particularly when the disease is advanced. The nature and severity of the immune deficiency varies with the type of tumour (Table 1). Patients with Hodgkin's disease are particularly liable to develop depression of cell-mediated immunity and patients with early disease may be affected. The impairment is much greater in Hodgkin's disease than in any other neoplasm of the lymphoreticular system.

TABLE 1. Immunosuppression in human malignant disease

	Malignant diseases of lymphocytes and plasma cells	Hodgkin's disease and histiocytic lymphoma
Cellular immunity	Usually normal	Impaired
Primary antibody response	Impaired	Impaired
Secondary antibody response	Impaired	Usually normal
Immunoglobulin levels	Usually low	Usually normal

Malignant diseases of the lymphoreticular system

Impaired immunity in patients with Hodgkin's disease results in an increased incidence of infection. Bacterial, viral, fungal and parasitic infections are increased in incidence and severity (Casazza *et al.*, 1966). The infections involved are often caused by opportunist organisms which rarely cause trouble in patients with normal immune mechanisms. Organisms such as the *Herpes zoster*/varicella virus or *Candida* which normally cause mild infections, can be fatal in immunosuppressed patients with Hodgkin's disease. In the years when tuberculosis was more prevalent there was a significant association between Hodgkin's disease and the development of tuberculosis. Cryptococcosis, a rare infection in normal subjects, has an increased incidence in patients with Hodgkin's disease and often runs a virulent course. As with tuberculosis, there is some evidence to suggest that immunity to the cryptococcus is largely cell-bound.

* Lecture to the Association for the Study of Infectious Disease, December 1971. To be published in the *Proceedings of the Royal Society of Medicine* (1972).

Herpes zoster infection is a common complication in patients with Hodgkin's disease. Recurrent exacerbations may occur and the infection may become disseminated and fatal. Pooled human gamma-globulin has been helpful in treating such infections and may prevent dissemination of local zoster infections (Sokal & Firat, 1965). Treatment with idoxuridine and more recently with cytosine arabinoside has been followed by rapid resolution of infection. Most lesions clear spontaneously, however, and the role of gamma-globulin and antiviral chemotherapy remains to be clarified. Reports have been anecdotal and in the absence of controlled trials it is uncertain whether such treatment is effective or not.

The most comprehensive survey of *H. zoster* infections in patients with Hodgkin's disease has been made by investigators at the Stanford Medical Centre (Goffinet *et al.*, 1972). The data in Table 2 are derived from their paper. Ninety-one out of a total of 592 patients with Hodgkin's disease suffered from this infection during the course of their disease, whereas only thirty-eight of 538 patients with other lymphomas developed this complication during the same period (1959-69). The maximum incidence occurred during the last 2 years of the analysis and it was suggested that newer forms of treatment

TABLE 2. The relationship between the incidence of shingles and the treatment of Hodgkin's disease (Stanford Medical Center; Goffinet *et al.*, 1972)

	Number patients	Number with shingles	Percent
Hodgkin's disease (HD)	592	91	15.4
Other malignancies	538	38	7.1
HD without splenectomy, no combination chemotherapy	418	51	12.2
HD without splenectomy with combination chemotherapy	24	7	29
HD with splenectomy without combination chemotherapy	122	28	23
HD with splenectomy with combination chemotherapy	28	5	18

involving splenectomy and combination chemotherapy were, in part, responsible for the increased incidence. Twenty-two percent of 150 patients with Hodgkin's disease who had their spleens removed developed symptoms of *Herpes zoster* infection, whereas only 13.1% of 442 patients without splenectomy suffered this complication. The two groups were fairly comparable since splenectomy was routine for at least 100 consecutive patients in this series. The incidence during combination chemotherapy was 23% and symptoms usually occurred within the first 6 months of chemotherapy. Following radiotherapy, the site usually involved the irradiated area, and nearly all infections occurred within 1 year of radiotherapy. In general, the occurrence of shingles did not indicate a poorer prognosis, but if the involved site was outside the irradiated area, recurrent disease seemed more likely within 1 year.

In contrast with Hodgkin's disease, cellular immunity is relatively intact in patients with lymphoid malignancies such as chronic lymphocytic leukaemia, although sensitization to new antigens such as 2,4-dinitro-fluorobenzene may be impaired (Cone & Uhr, 1964). Antibody production is frequently impaired in these diseases. Miller (1962) reported serum electrophoretic determinations of gamma-globulin in 325 patients with lymphomas and leukaemias. A reduction in gamma-globulin levels occurred in 35.6% of patients with chronic lymphocytic leukaemia, whereas only 2.9% of patients with Hodgkin's disease had similar reductions. Bacterial infections are particularly common in patients with chronic lymphocytic leukaemia and are related to the hypogamma-globulin. Recurrent bacterial pneumonia with common organisms may lead to serious sequelae in these patients. As in Hodgkin's disease, *Herpes zoster* infection occurs with increased frequency and vaccination with live vaccinia virus has led to disseminated infection and death. The use of corticosteroids and cytotoxic chemotherapy in these conditions frequently adds to the effect of the immune deficiency associated with the disease itself.

Acute leukaemia

The risk of infection in patients with acute leukaemia is very great. The deficiency in neutrophil granulocytes and monocytes is usually pronounced even in untreated acute leukaemia, but the use of modern intensive cytotoxic chemotherapy further depresses the number of circulating granulocytes and increases the incidence of infection. Ulceration of mucosal membranes provides an additional portal of entry for infectious agents. Fungal infections such as moniliasis of the mouth and pharynx are so common that prophylactic local amphotericin B or nystatin is routine in our patients with acute myelogenous leukaemia (AML) in the early stages of treatment.

In nearly all patients dying with AML, infection is a leading cause of death. Twenty-three out of forty patients with AML recently treated at St Bartholomew's Hospital achieved a complete remission using intensive intermittent chemotherapy (Crowther *et al.*, 1970). Of the remaining seventeen patients, twelve died of infection during the first 4 weeks of treatment. Effective supportive treatment would therefore be expected to be of value in increasing the remission rate in this disease. Prevention of infection is difficult since many of the infections are endogenous in origin. Protected environments are expensive and involve the provision of air, food, and nursing care to patients in 'sealed' rooms. Psychological problems are common, nursing is difficult, the food is somewhat unpalatable and contact with the doctors is reduced. Carefully controlled trials are essential to analyse the problems involved. There is some evidence that prophylactic antibiotics, which reduce the number of pathogenic organisms in the gut, have decreased the number of new infections in patients under treatment. The antibiotics used included vancomycin, gentamicin and nystatin as oral preparations and were well-tolerated. As yet, there is no good evidence that the use of protected environments has added to the effect of good nursing care, cleanliness and prophylactic antibiotics. The value of protected environments appears to be marginal at present and may well diminish as treatment improves. To correct a neutrophil leucopenia it is necessary to give 10^{11} granulocytes/m² body surface to raise the blood count by more than 1000/mm³ (Morse *et al.*, 1961). This is difficult using normal donors and the use of leucocytes from patients with chronic granulocytic leukaemia is attended by the risks of transfusing malignant cells. At an anecdotal level, granulocyte transfusions have resulted in a recovery from infection but controlled trials have not yet been carried out.

Immune deficiency and the development of malignant disease

In experimental animals immune-deficiency states induced by thymectomy, corticosteroids, anti-lymphocytic globulin or immune suppressive cytotoxic drugs increase the incidence of malignant lymphomas. It is of interest to note in this context that all the tumours so far found in mice receiving long-term immunosuppression have been leukaemia, lymphomas, osteosarcomas, mammary tumours, or polyoma-induced tumours of the salivary glands. In all these cases there is good reason to suspect that a virus is concerned in the aetiology (Allison, 1970). Evidence is increasing that immunosuppression in man may be accompanied by the development of malignant disease.

Malignant disease of the lymphoreticular system

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,