phase, aggressive therapy can offer a clear advantage over the conventional approach.

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The Management of the Complications of Leukaemia

G. HAMILTON FAIRLEY, DM, FRCP, Physician,
St Bartholomew's and Royal Marsden Hospitals, London

The complications of leukaemia are well known, and consist of anaemia, severe infections, and haemorrhage due to the failure of the bone marrow to produce normal red cells, granulocytes, and platelets. In addition, the excessive production of uric acid may produce hyperuricaemia with gout, urinary calculi, and nephropathy. In recent years, the advent of very intensive chemotherapy, designed to eradicate all leukaemic cells from the body, has made these complications more frequent and more severe, and the management of patients, particularly with acute leukaemia, demands that special

facilities should be available if death from one or more of the complications is to be prevented.

Anaemia is the simplest to manage of all the complications, being readily

TABLE 1. The Mechanisms Affected in Different Diseases

Defence mechanism affected	Disease
Neutrophil granulocytes	Acute leukaemia
Cellular immunity	Hodgkin's disease
Humoral immunity	Malignant diseases of lymphocytes and plasma cells (i.e. chronic lymphocytic leukaemia, lymphosarcoma, myelomatosis, macroglobulinaemia)
Interferon	Chronic lymphocytic leukaemia

corrected by transfusion with fresh blood and presenting no therapeutic difficulties which are not well known.

Infections. It is important to recognise that infections may be caused by failure in any of the major defence mechanisms, and that different mechanisms may be affected in different diseases (Table 1).

Infections due to a deficiency in neutrophil granulocytes are common even in untreated acute leukaemia, but the use of powerful cytotoxic drugs, many of which further depress the number of circulating granulocytes, increases the risk of infection. Furthermore, some drugs, particularly the folic acid antagonist, methotrexate, also lead to ulceration of the buccal and pharyngeal mucosa which creates an additional portal of entry for infecting organisms. Fungal infections, particularly moniliasis of the mouth, pharynx, oesophagus, and elsewhere may be particularly troublesome in acute leukaemia, in addition to the common bacterial infections such as abscesses, cellutitis, pneumonia and septicaemia. Indeed, the therapeutic combination of prednisolone and broad spectrum antibiotics can almost be guaranteed to cause moniliasis, and it is our practice to give prophylactically both nystatin mouth washes and amphotericin lozenges. Similarly, if patients with leukaemia develop severe dysphagia, even without obvious oral moniliasis, this is almost always due to moniliasis, which can readily be seen on a barium swallow (Fig. 1). Not infrequently, the patient with acute leukaemia may obviously be suffering from an infection with a high fever but without a detectable source of infection; later it may become apparent that the patient has, for example, pneumonia. It is important to treat infections as early as possible and not to wait for the isolation of the pathogen involved. It is our practice to treat such cases immediately with a broad spectrum antibiotic once

specimens have been taken for bacterial examination. Sometimes no definite pathogen is isolated; at other times organisms are grown from the blood or sputum which in normal subjects would be non-pathogenic, and it is extremely

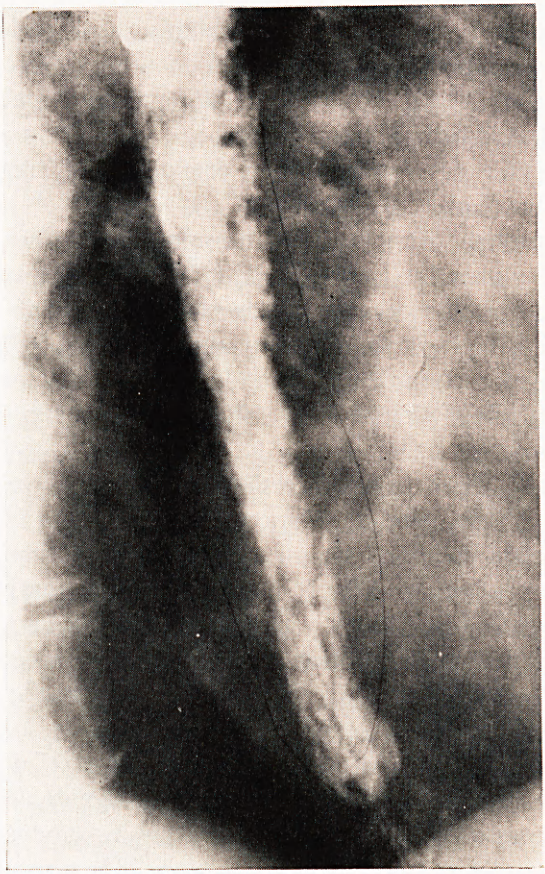


Fig. 1. Barium swallow in an adult patient with acute leukaemia showing extensive infection with monilia.

likely that so-called non-pathogenic organisms may be pathogenic in patients with granulocytopenia.

Cellular immunity is impaired in Hodgkin's disease more than in any other malignant disease, and may lead to unusual infections, such as miliary tuberculosis and cryptococcal meningitis as well as the more common infections, in particular herpes zoster, which may be severe and occasionally generalised. One of the problems in Hodgkin's disease is to decide whether

fever is due to infection or to the disease process itself. Only after infection has been excluded should the fever be attributed to the disease.

Humoral immunity is greatly impaired in the malignant diseases of lymphocytes and plasma cells (chronic lymphocytic leukaemia, lymphosarcoma, myelomatosis, and macroglobulinaemia), and this leads to recurrent bacterial infections, similar to those found in other cases of hypogammaglobulinaemia, particularly pneumonia, urinary tract infections, and recurrent boils. In addition, viral infections are common and in the case of chronic lymphocytic leukaemia reduced production of interferon may be a contributing factor (Lee *et al.*, 1966).

Not only are patients with impaired immune mechanisms more prone to infection, but once infection has occurred it is liable to be severe. This raises a very important question because it shows the danger of the introduction of living organisms, which would be harmless to normal subjects, into these patients. The obvious example is vaccination, which may lead to generalised vaccinia, particularly if the patients are receiving corticosteroids, and on occasions this may even be lethal.

The best method of preventing infections in leukaemia would be to correct the abnormality in the affected defence mechanism, but it is impossible to correct the defect in cellular immunity at the present time, because this is mediated by lymphocytes and the injection of homologous lymphocytes into patients with impaired immunity would lead to a graft versus host reaction. Similarly, there is no way of restoring the ability to form interferon. However, it is theoretically possible to treat both hypogammaglobulinaemia and neutrophil leucopenia. Shaw *et al.* (1960) and Fairley and Scott (1961) recorded patients in whom treatment with intramuscular injections of gamma globulin reduced both the number and severity of infections, but the treatment has the disadvantage that the injections are painful and need to be given once a week. To correct neutrophil leucopenia it is necessary to give 10^{11} granulocytes/m^2 body surface to raise the white blood count by more than 1,000mm^3 (Morse *et al.*, 1961). This would require between 20–40 pints of donor blood, a formidable undertaking. Some physicians have given the granulocytes from patients with chronic myeloid leukaemia with high white blood counts, but this has its disadvantages. For this reason cell separators are being developed (Freireich *et al.*, 1965), which enable the white cells to be removed from the blood while the red cells, platelets, and plasma are returned to the donor. These are still in the experimental stage, but the idea is more attractive than the alternative, which is to barrier the patient against pathogenic organisms, both exogenous and endogenous, from his own gut.

There are immense difficulties in preventing a patient becoming infected

by attempting to isolate him from all extraneous organisms, and to sterilise the gut to prevent endogenous infection. An elaborate reversed barrier nursing unit has been built in this country at The Royal Marsden Hospital under the direction of Dr Kay and Dr Thompson Hancock. This consists of single wards and plastic isolators which prevent the introduction of organisms, and elaborate precautions are taken to prevent infection from the medical and nursing staff (James *et al.*, 1967; Speers *et al.*, 1966). Despite attempts to sterilise the patient's gut using non-absorbed antibiotics such as neomycin, antifungal agents such as nystatin and amphotericin, and supplying only germ-free food, and to rid the skin of pathogenic organisms by using hexachlorophine, some patients may still develop fatal infections (Jameson and Kay, personal communication). The running of such a unit is a tremendous financial burden, which, in the future, will only be justified if it can be proved that intensive chemotherapy leads to a dramatic improvement in the prognosis of leukaemia.

Haemorrhage. This is usually due to thrombocytopenia which can be prevented by infusion of platelets, either in whole fresh blood if there is considerable blood loss, or in platelets concentrated from fresh donor blood by centrifugation. Tullis *et al.* (1959, 1968) have a technique for obtaining the platelets from the blood using a cell separator that enables the platelets to be collected from four pints of blood while the other elements are returned to the donor. Furthermore, Tullis *et al.* (1968) have devised a method of storing platelets obtained in this way at 4°C for periods of up to two years, which has the great advantage that, if a patient with thrombocytopenia is admitted as an emergency, platelets can be given at once, without the necessity of calling for donors to give fresh blood.

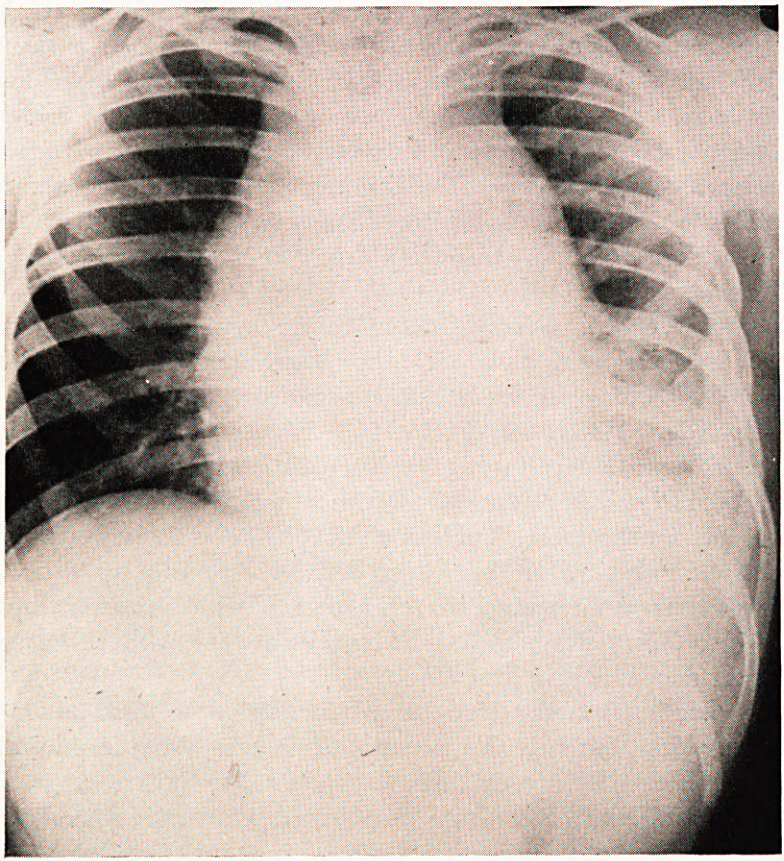
Not only is it important to give platelet transfusions to these patients with thrombocytopenia, but it is also essential to do everything to minimise the risk of haemorrhage. For example, intramuscular injections should be avoided if possible, and, following venepuncture, extra care should be taken to compress the vein at the puncture site for a long time to prevent the formation of a haematoma. Such a haematoma is uncomfortable for the patient and may increase the difficulty of subsequent venepunctures for diagnostic and therapeutic purposes.

Hyperuricaemia. Excessive uric acid production occurs in untreated patients with leukaemia, and treatment raises the level of serum uric acid even further. Hyperuricaemia may lead to the following complications:

(i) Secondary gout
(ii) Urinary calculi

(iii) Acute post renal obstruction by uric acid crystal aggregates
(iv) Acute uric acid nephropathy (uric acid precipitation in the renal tubules)

The problem of dealing with these complications has now been simplified by the use of allopurinol which reduces uric acid production by inhibiting



(a) before

Fig. 2. Chest radiographs of a boy aged twelve with acute lymphoblastic leukaemia.

the activity of the enzyme xanthine oxidase (Watts *et al.*, 1966). This drug should certainly be given to all patients with a raised serum uric acid before other treatment is given, and to those whose serum uric acid rises as a result of treatment. Indeed, allopurinol is so free from toxicity that there is an argument for giving it to all patients with leukaemia whenever treatment is liable to cause the sudden dissolution of a large number of malignant cells, providing

it is realised that this drug strongly potentiates the action of 6-mercaptopurine, as this compound is also detoxicated by xanthine oxidase. If allopurinol is given, the dose of 6-mercaptopurine should be only one-quarter of that usually given for the treatment of leukaemia.

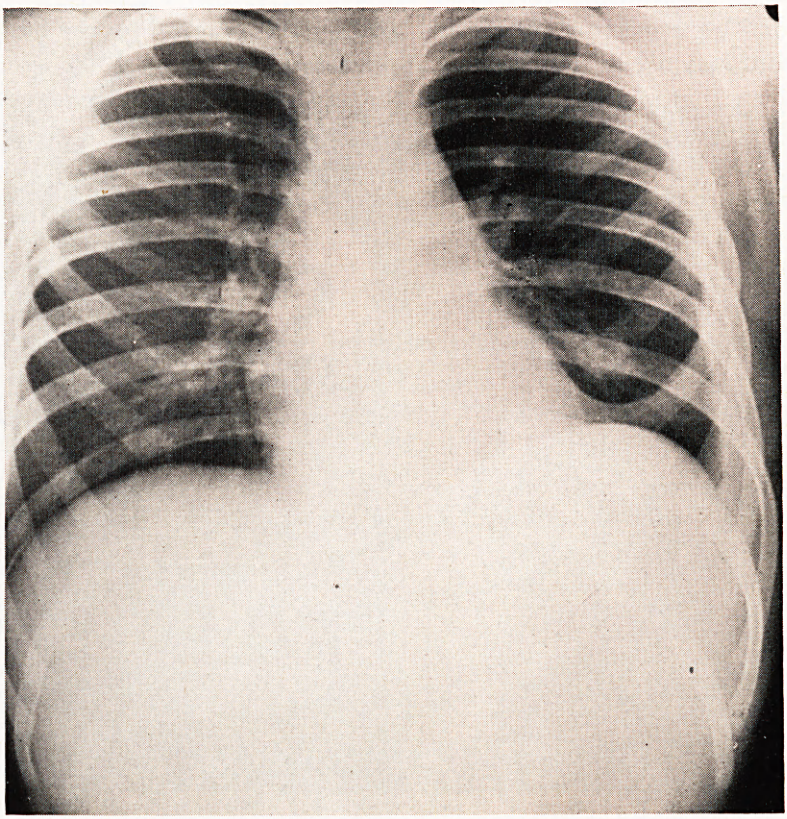


Fig. 2. *Cont'd.*
(b) one week after radiotherapy (dose 365 rads).

Finally, it is worth mentioning the management of some unusual manifestations of leukaemia, because, although they are not really complications, their anatomical distribution requires special attention. In acute lymphoblastic leukaemia large glandular masses, which are particularly common in the mediastinum in children, often respond dramatically to small doses of radiotherapy. In Fig. 2 the chest radiographs of a boy aged twelve with acute lymphoblastic leukaemia are shown; (*a*) before, and (*b*) one week after radiotherapy having been given in 365 rads. The response was rapid and

the relief of dyspnoea dramatic. Similarly, in acute leukaemia the pain from isolated bone lesions may be relieved quite rapidly by radiotherapy, and the complication of meningeal involvement can be quickly controlled by intrathecal methotrexate and radiotherapy to the skull and spinal canal. It is interesting that these complications frequently occur at a time when the blood and bone marrow are normal, and for this reason the true nature of the lesions may not be immediately appreciated.

It is clear that we have now reached the time when the aggressive treatment of leukaemia will be accepted as the best we have to offer, and this will increase rather than decrease the number of complications, making the management of this disease more complex, more time-consuming, and more demanding of all the hospital services.

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