BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 9 1955

THE TREATMENT OF ACUTE LEUKAEMIA*

BY

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The last decade has seen the focus of haematological interest shift to the problem of acute leukaemia. This disease has been forced upon the clinicians' attention by its steadily mounting frequency; while the research workers have found it a convenient field for the study of chemotherapy in cancer, and as a result of their exertions it has become possible for the first time to influence its course.

The aim of this paper is to review the methods of treatment at present available and to discuss their application and value in the light of experience gained in the past six years.

The Present Series

In this period 121 patients with acute leukaemia have been under treatment. The composition of the series is set out in the Table. The majority of children with this disease are under the care of paediatricians; thus the series must contain a disproportionate number of adults and cannot give an exact indication of the age incidence in the general population.

Composition of the Cases of Acute Leukaemia

	Male	Female
Acute myeloblastic leukaemia:		
"Classical" type	26	32
Erythromyelosis	1	3
Acute lymphoblastic leukaemia:		
"Classical" type	12	6
Pure medullary type	7	3
Sternberg type	6	1
Acute monocytic leukaemia	11	8
Acute erythraemia (di Guglielmo)	4	1
Total all types	67	54

The difficulties of cytological classification, and in particular of distinguishing the myeloblast from the lymphoblast, are familiar and inescapable. Nevertheless the figures (see Fig.) show the generally accepted age incidence of the three cytological types of acute leukaemia: myeloblastic, affecting all ages indifferently; lymphoblastic, predominantly children; and monocytic, the middle-aged. Five examples of di Guglielmo's acute erythraemia are included, and four of erythromyelosis are grouped with the myeloblastic leukaemias. Prognosis, in respect of remission, depends largely upon the cytological type of the disease, and classification is thus no longer the sterile academic exercise it once seemed.

*A paper read at a meeting of the physicians of the South-east Metropolitan Region, April 30, 1955.

Nevertheless there is a practical value in their differentiation, because the patients in whom the proliferative process is at first restricted to the bone marrow have a greater liability to remission than those with extramedullary infiltrations, and, *per contra*, the chances of remission are remote in the Sternberg variety, where the disease is primarily limited to one group of nodes and only later becomes systematized. In this respect the classical form occupies a position intermediate between the two.

The present series illustrates these points. It includes 10 patients, varying in age between 3 and 78 years, with the pure medullary type, and in each some degree of remission was noted. In one it was entirely spontaneous; in five it followed blood transfusion; and in four it was the result of specific treatment. The anti-thesis is provided by 7 patients, aged 4 to 20 years, with the Sternberg type, in none of whom was any improvement observed.

Treatment

The treatment of acute leukaemia includes measures designed to relieve symptoms resulting from anaemia, infection, and the haemorrhagic state, as well as attempts, which may be termed "specific," to restrain the leukaemic process.

Control of the Leukaemic Process: (1) Blood Transfusion

Spontaneous remissions have been noted in 4 to 10% of children with acute leukaemia (Diamond, 1951; Southam *et al.*, 1951). A review of recorded examples showed that they often followed blood transfusion (Dreyfus, 1948). The use of exsanguination-transfusion derived from this observation, and remissions were reported in 33% of 60 patients so treated (Bessis and Dausset, 1950). The initial inference that a plasma maturation factor was responsible has not been supported by later observations, and it has been suggested that any improvement should be attributed to liberation of cortisone following transfusion shock (Bessis, 1954).

This specific effect of transfusion has been stressed again recently by a report of remissions thus induced in 34% of 41 adults with acute leukaemia (Hayhoe and Whitby, 1955); a much higher figure, it should be noted, than would be expected from the use of cortisone. In the present series 46 patients were treated by blood transfusion alone, and in 9 (19.5%) significant remission followed. Exsanguination-transfusion was undertaken only in three; two died within a few days, and although the third survived for four months the course of the disease did not appear to be altered. The difficulties and dangers of the method have led most workers to discard it.

(2) Antimetabolites

An antimetabolite obstructs the operation of an enzyme system by displacing its related metabolite, and its effects are similar to those resulting from a deficiency of the metabolite itself. The first of these substances to be used in the treatment of acute leukaemia were the folic acid antagonists (Farber *et al.*, 1948), following the observation that the leukaemic process had been accelerated by giving a folic acid conjugate. The biologically active derivative of folic acid, citrovorum factor, is essential for normal haemopoiesis, and some theoretical basis for its deficiency exerting a selective depressant effect upon leukaemic proliferations is afforded by the finding that its concentration in leukaemic cells is five times that in normal leucocytes (Swendseid *et al.*, 1951).

The two folic acid antagonists in common use are aminopterin (4-aminopteroylglutamic acid) and amethopterin (4-amino-N10-methylpteroylglutamic acid). The daily oral dose of the first is 0.5 to 1 mg. for children and up to 3 mg. for adults, and of the second 2.5 to 5 mg. and up to 10 mg. respectively. Treatment may have to continue for as long as eight weeks before remission is procured. Toxic effects may appear within a few days or not for months; the earliest is buccal ulceration, followed by diarrhoea, vomiting, and sometimes gastro-intestinal haemorrhage.

Many reports of the value of the folic acid antagonists have been published. In adults remission is rare, being noted occasionally in lymphoblastic, seldom in myeloblastic, and hardly ever in monocytic leukaemia. In children the results are more hopeful; in an analysis of published series, 68% of 425 cases showed significant improvement (Fountain, 1954). In another report 37% of 119 children responded by complete remission (Burchenal, 1952). In lymphoblastic leukaemia the rate is as high as 60%; in myeloblastic less than 10%. The duration of remission varies from two weeks to two years, the mean lying between two and three months. Second remissions may occur, but thereafter the disease usually becomes resistant to these drugs.

Folic acid antagonists have not been used extensively in the present series: partial remission was obtained in two of three children with myeloblastic leukaemia, and in two of six with lymphoblastic leukaemia. One of two adults with monocytic leukaemia had a short incomplete remission.

The second group of antimetabolites are the purine antagonists, the theoretical rationale being their presumed interference with nucleic acid metabolism. The first shown to have antileukaemic activity was 2:6-diaminopurine (Burchenal *et al.*, 1951), but it was soon supplanted by the more effective 6-mercaptopurine (Burchenal *et al.*, 1953; Fountain, 1955). This drug, given by mouth in a daily dose of 2.5 mg. per kg. body weight, is virtually without toxic side-effects. Treatment is continued for four weeks unless remission occurs sooner. The results are similar to those obtained with folic acid antagonists. In the first report (Burchenal *et al.*, 1953) 15 complete and 10 partial remissions were recorded in treating 43 children, while 4 of 10 adults showed significant improvement. Remission is induced far more readily in lymphoblastic than in the other types of leukaemia. Leukaemia resistant to folic acid antagonists may respond to 6-mercaptopurine. In this series 10 patients have received 6-mercaptopurine:—Myeloblastic leukaemia: 4 adults, no improvements; 1 child, good remission. Lymphoblastic leukaemia: 1 adult, good remission; 2 children, 1 moderate remission. Monocytic leukaemia: 2 adults, no remission.

(3) Steroid Hormones

Cortisone was shown to inhibit the growth of transplanted lymphosarcoma in mice in 1944 (Heilman and Kendall, 1944), but the first reports of its action in human leukaemia were not until 1950 (Pearson *et al.*, 1950; Farber *et al.*, 1950), when satisfactory remissions were claimed in 80 of 175 children and in 14 of 60 adults. An analysis of published series shows that of 425 cases treated with cortisone or corticotrophin (A.C.T.H.), there was complete remission in 29% and partial in 24% (Fessas *et al.*, 1954). In a small group of 47 cases complete remission was reported in 18 of 22 children and in 3 of 9 adults with lymphoblastic and partial in 2 of 15 patients with myeloblastic leukaemia. Remission occurs more rapidly than with antimetabolites, but is of shorter duration and less complete.

The daily dose of cortisone required in acute leukaemia is 200 to 300 mg. by mouth in adults, and up to 200 mg. in children. Corticotrophin is given by intramuscular injection every six hours, in daily doses of 100 mg. for children, or 200 mg. for adults, or by intravenous infusion in children in quantities of 25 to 40 mg. in 8–12 hours.

In the present series 23 patients have received cortisone or corticotrophin:—Myeloblastic: 6 adults (1 complete, 1 partial remission); 4 children (1 complete, 2 partial remissions). Lymphoblastic: 5 adults (3 complete remissions); 5 children (2 complete, 1 partial remission). Monocytic: 3 adults (no remissions).

Symptomatic Treatment

Relief of Anaemia.—The cause of anaemia in acute leukaemia is obscure: haemorrhage must contribute its share; evidence of exaggerated blood destruction is lacking; and defective formation is usually accepted as its basis, although recent studies with radioiron do not support this view (Schapira *et al.*, 1954). Whatever the cause of the anaemia, blood transfusion is the only effective means of relief. Its place in treatment has already been discussed: it may be used in the hope of inducing remission or with the less ambitious aim of maintaining a reasonable haemoglobin level. When an attempt is being made to obtain remission by "specific" treatment, a haemoglobin level of 50 to 60% should be maintained. Transfusion should never be prescribed *faute de mieux*, but should be a purposive measure undertaken in the knowledge that it is impossible to deny a patient repeated transfusions after he has experienced the benefit that one confers.

Control of Infection.—General and local infections are common in acute leukaemia, and antibiotics should be prescribed in conformity with established general principles. Their prophylactic use is to be deprecated, and it should be noted that fever in this disease does not of necessity indicate a secondary infection. Intramuscular injections in the leukaemic patient commonly cause haemorrhage into

the tissues; thus drugs should, when possible, be given orally. Mouth-washes help to relieve the misery of leukaemic stomatitis. Hydrogen peroxide (1.5%) or a saturated solution of sodium perborate is useful, and citric acid (1 to 1.25%) twice daily for two consecutive days has been recommended (Hayhoe and Whitby, 1955).

Control of the Haemorrhagic State.—Anaemia and infection are both susceptible of treatment, but the liability of the leukaemic patient to bleed still defies control. This tendency bears a general, but not a precise, relation to the level of the platelet count; other factors have been suspected, but have hitherto eluded detection. The importance of the haemorrhagic state is shown by the present series: post-mortem examination was made in 41 cases; in 17 (41%) haemorrhage appeared to be the immediate cause of death, and in 12 (29%) it was intracranial. Platelet transfusion is perhaps the logical method of treatment (Stefanini and Dameshek, 1953), but technical difficulties prevent its general use at present. Recent reports suggest that intravenous injection of a chloroform extract of acetone-washed brain may be of value (Hayhoe and Whitby, 1955). At present, transfusion of fresh blood is the only measure likely to allay the tendency to bleed, and its results are inconsistent. Local application of thrombin solution, after careful toilet, is often effective in controlling haemorrhage from the gums.

Prognosis

The outcome of acute leukaemia remains fatal; the only prognostic question to be answered is whether remission will occur. This, it has been shown, is more probable in children under the age of 12 years and in the lymphoblastic variety, particularly of the pure medullary type.

The influence of "specific" treatment on the mean length of survival is difficult to assess. Transfusion and the antibiotics are said to have prolonged the lives of children with the lymphoblastic form from 5.6 to 8.9 months (Bierman *et al.*, 1950). In the present series, of 81 patients treated with blood transfusion and antibiotics the mean length of survival from the first symptoms was 20.2 weeks, and in 34 who also received specific treatment, 20 weeks; in 17 children under 12 years without specific treatment the mean survival was 19.9 weeks, and of 9 with specific treatment 26.8 weeks.

The variable length of survival in acute leukaemia probably deprives these figures of any significance.

Discussion

It is often suggested that considerations of humanity should limit the treatment of acute leukaemia to relief of distress and forbid officious attempts to induce remissions which can never be more than ephemeral. Every physician must answer these questions for himself. It is certain, however, that therapeutic nihilism demoralizes the patient, his relatives, and sometimes the medical attendant; moreover, it ensures that no advance in treatment will ever be made. In this paper it is assumed that efforts to procure remission are desirable.

Management varies with the age of the patient, with the cytological and clinical type of the disease, and with the severity of the illness.

In a child, when high fever and haemorrhagic state indicate rapidly advancing disease, a start should be made with cortisone by mouth or with corticotrophin by intravenous drip. Antimetabolites may be used concurrently, but are better reserved for the first signs of relapse. If the child's condition suggests that he is likely to survive more than three weeks, antimetabolites should be given preference. It is advisable to use 6-mercaptopurine rather than a folic acid antagonist, because its toxic effects are negligible; a change should be made to the second if the disease proves resistant to the first. By employing the various "specific" measures in sequence, changing from one to the next as resistance develops, repeated remissions may be induced in favourable cases. Maintenance treatment, once remis-

sion is achieved, has not proved satisfactory, and "specific" drugs are best withheld until the onset of relapse is evident. The first sign of this event is an increase in primitive cells in the bone marrow, but most workers prefer to await changes in the peripheral blood rather than subject children to repeated bone-marrow puncture.

In adults, 6-mercaptopurine should be given a trial if the patient's general condition is satisfactory. It may be combined with or followed by cortisone. The alternative is to watch the effect of blood transfusion alone for a period of two or three weeks; in 15 to 20% of patients it will induce a satisfactory remission. In lymphoblastic and myeloblastic leukaemia cortisone should be given if it becomes apparent that neither blood transfusion nor 6-mercaptopurine is likely to be effective. Monocytic leukaemia is resistant to cortisone, but occasional cases respond to 6-mercaptopurine. The folic acid antagonists have no place in the treatment of acute leukaemia in adults.

Conclusion

The therapeutic position in acute leukaemia has been reviewed. The results of treatment afford no grounds for optimism, but they do show that in some instances and for short spells the leukaemic process can be checked or even reversed. From this observation we must draw hope that a means of controlling this tragic disease will one day be vouchsafed to us.

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The Professional Classes Aid Council, of which Lord Moran is president, began the financial year on April 1, 1954, with a deficit of about £1,000, but ended it on March 31, 1955, with a surplus of £1,115, states the council's 34th annual report. This achievement was made possible by a £944 increase in donations and subscriptions; a £583 increase in dividends from invested legacies; and by the £1,656 17s. 3d. response to Lord Moran's wireless appeal. As the B.B.C. will not consider application for a further broadcast for three years, this last sum was divided between the budgets for the current and two succeeding years. In spite of restricted expenditure, 266 families were helped; 76 were new cases. The total number of applications was 471. Of the 205 refused, the great majority were helped to find alternative sources of relief, often from the relevant professional funds. Yearly grants were made to 69 people who, through age or ill-health, will never be self-supporting again; temporary help, often a single gift, was given to the total of £1,531 10s. 1d.; and education grants were made to 110 children and 42 students.