REFRESHER COURSE FOR GENERAL PRACTITIONERS**LEUKAEMIA—II. TREATMENT**

BY

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The nature, and, indeed, the institution, of treatment are greatly influenced by the acuteness of the disease, by the urgency of symptoms, and to some extent by the haematological type. Symptomless types, especially in the elderly, are better left untreated. And equally, in the final phases of the acute disease, there is little to be gained by prolonging a miserable existence for a few days by a massive blood transfusion. At the outset the practitioner himself should fully appreciate that no cure is known. Treatment which is designed to relieve symptoms and prolong efficiency has no material effect in prolonging life. Nevertheless, the relief of distress arising from anaemia, or of pain from pressure on other organs or from traction by an enlarged spleen, may greatly increase comfort and efficiency. Rest in bed is essential whenever there are fever, infarcts of the spleen, signs of cardiac failure, haemorrhage, or other generalized symptoms, but otherwise patients should be encouraged to lead a normal life on a full diet. Indeed, the maintenance of morale is one of the important points in treatment, and how much or how little of the inexorable end-result of the disease should be communicated to the patient or the relatives is a matter for judgment in each case.

Spectacular features, such as the high leucocyte count found in the chronic type which may be quickly reduced from hundreds of thousands to tens (or less) of thousands, may provide a suitable prop for morale, especially if associated with improvement in general well-being. On the other hand, these effects may be a double-edged weapon, since the count usually rises as a prelude to a relapse, and the patient who has been informed, even to the point of keeping a graph, is apt to become pessimistic unless his philosophy is such that he has been able to be told the whole truth.

Acute Leukaemias

The acute forms of the disease, with fever, toxæmia, haemorrhagic symptoms, and distressing stomatitis, are rarely amenable to any form of treatment designed to restrain or control the leukaemic process. Spontaneous remissions may suddenly and unexpectedly occur, and these are often attributed to whatever treatment has been instituted, as indeed they may well be. But, since such remissions seem to occur quite frequently without (or in spite of) treatment, one sometimes wonders whether unpleasant procedures, such as exchange transfusion, are worth the discomfort and apprehension they cause or, often, the effect that they may or may not temporarily accomplish. Such remissions, spontaneous or otherwise, are most common with the acute lymphoblastic type of leukaemia in children, and there is some evidence that massive transfusion, or exchange transfusion, may positively induce a remission (sometimes of months' duration and, therefore, of value) so strikingly that glands disappear and even the marrow almost reverts to normal.

Transfusion, on account of its dramatic significance, sometimes brings comfort to distressed parents, especially if they themselves can be used as donors. In the majority of acute cases, however, the most to be expected from any form of treatment is a temporary and fleeting remission, and such has been claimed to follow blood transfusion especially, with or without aminopterin or urethane. The same results are obtained with A.C.T.H. and cortisone, which in early days were thought to have striking beneficial effects in leukaemia, especially in the acute forms of the disease. Extensive trials have now shown that, whereas a proportion of cases of acute or subacute lymphoblastic leukaemia in children may exhibit a rapid remission when treated with either A.C.T.H. or cortisone, the result is unfortunately of only short duration and is rarely repeatable. These results, though disappointing, are significant and illuminating, since these substances are neither destructive nor antimetabolic and so differ fundamentally from almost all other forms of treatment used for the purpose of controlling the leukaemic process. Thus, even though neither A.C.T.H. nor cortisone effects cure or control of the disease, their mere action opens up new and promising lines for therapeutic research which have a physiological basis and may eventually reveal an endocrine control (or lack of control) in leukaemia itself.

Irradiation is contraindicated in any form of acute leukaemia, and most of those with experience have the impression that it stimulates the disease. The monocytic type of leukaemia, which is generally acute or subacute, is very little influenced by treatment. The distressing condition of the mouth, in which spirochaetes are often abundant, is unaffected by arsenic paint or the injection of neoarsphenamine or most of the commonly used astringent mouth-washes. One of the best preparations for removing the sloughs and cleaning the gums is a mouth-wash consisting of 40 gr. of citric acid to 1 oz. of water (1 g. to 10 ml.) diluted to at least one part in seven with water before use. The dilution which can be tolerated has to be found by trial in each case. The wash should not be used for more than three days on end without an interval of two or three days.

Chronic Leukaemia

In the chronic form of leukaemia attention is again directed towards the relief of symptoms. Many cases are, however, suitable for the institution of treatment designed to restrain or control the leukaemic process, particularly when leukaemic infiltration has caused painful or troublesome pressure symptoms or led to the gross enlargement of organs such as the spleen or lymph nodes.

Anaemia may not be prominent at the outset, but inevitably develops during the course of the disease. The anaemia is ordinarily intractable and is unaffected unless the leukaemic process is controlled, in which case

spontaneous improvement occurs. Neither iron nor liver is significantly effective, but both are usually prescribed, and some benefit occasionally follows the use of the rather unpalatable proteolysed liver preparations. Transfusion may be required, but its effect is usually short-lived unless other measures have exerted some control over the leukaemic process itself. The dramatic remissions which may follow massive transfusion in the acute disease (see above) are not usually obtained.

There is little doubt that *arsenic*, an old-fashioned remedy, has an important place in the treatment of the disease, particularly in relieving troublesome symptoms arising from leukaemic infiltration. Arsenic in appropriate dose will control fever, reduce the leucocyte count, reduce the size of the spleen, *relieve pruritus and itching*, and improve anaemia. By carefully regulating the dose of arsenic, remissions, especially in the chronic myeloid type of the disease, may sometimes be sustained for long periods. Five minims (0.3 ml.) of Fowler's solution may be given three times a day, increasing by 1 min. (0.06 ml.) daily until signs of arsenical intoxication appear, whereupon administration should be stopped for four or five days and then be resumed at a lower dosage. Arsenic, which is never given concurrently with irradiation or other antimitotic measures but may be used in the intervals between such treatment, is probably the best form of treatment for *pregnant women*, for whom irradiation is unsuitable.

The distressing symptom of priapism is very difficult to relieve, and, unless x-ray applications are effective, surgical measures, involving incision and evacuation of the contents of the corpora cavernosa, are the only means of treatment.

The Leukaemic Process

Treatment which is designed to restrain or control the leukaemic process is based on the fact that mitosis in a dividing cell is inhibited or prevented by physical factors such as ionizing radiations and by certain antimitotic drugs. Ionizing radiations may be derived from x rays, radium, or radioactive isotopes of phosphorus (which is selectively absorbed by bone) or sodium (which is generally distributed). Antimitotic drugs include arsenic (see above), colchicine, urethane, nitrogen-mustard derivatives, and pterins or folic-acid antagonists. By temporarily limiting the degree of leukaemic hyperplasia or leukaemic infiltration, secondary features, such as anaemia, or pressure symptoms are often improved. Treatment needs to be carefully controlled by regular haematological examinations in order that the antimitotic process may not proceed to the length of causing agranulocytosis, severe thrombocytopenia, and aplastic anaemia. The choice in respect of these various antimitotic measures is guided sometimes by fashion, sometimes by availability, sometimes by the patient's tolerance to a particular treatment, and sometimes by specificity, whereby a particular form of leukaemia appears to respond better to one than another.

As to fashion, in a disease in which the prognosis is inevitably fatal and which may appear suddenly and unexpectedly in the dearly loved only child of a family, irrespective of wealth or social status, it is inevitable that, like the Athenians, there should always be a searching after "some new thing." At a certain level of society there will be a demand for the very latest treatment, such as may be found to be fully documented

or at least optimistically described in some lay publications, which know that advances in medicine are news, long before they have been either properly tested or confidently advocated in the medical press. It is as well to keep pace with such fashions, since a display of knowledge about them and even their employment may be one of the ways in which the morale of the household may be maintained.

Irradiation

Irradiation is an effective form of treatment in the chronic myeloid and lymphatic forms of the disease, but may not be available within easy distance. Irradiation is not used in acute and subacute forms or in the monocytic type (which, in fact, is usually acute), and is rarely advisable when the blood picture is aleukaemic. In many the treatment produces the miserable state of irradiation sickness, and in others profound depression, so that endurance of the disease (which, indeed, may be symptomless) is preferred to endurance of the treatment. Irradiation sickness may sometimes be controlled with pyridoxine hydrochloride (vitamin B₆), which can be given either intravenously (25–50 mg.) at the onset of sickness or in a dose of 75–100 mg. by mouth three times daily before meals. A high carbohydrate diet is also said to help, as well as other members of the vitamin-B complex, including nicotinic acid and thiamin. The best preventive, however, is said to be "dramamine" in doses of 100 mg. one-half to one hour before treatment, and repeated one and a half and four and a half hours afterwards.

The technique of irradiation treatment is highly specialized and extremely variable according to the views of different radiotherapists. Some give a general irradiation of the whole body, others irradiate the skeleton, others the spleen or vital organs which, symptomatically, appear to be infiltrated. No more than the principles of treatment can be understood by the expert, but it is important to know the general principles employed by the radiotherapist in order to give a rational explanation to the patient of reactions or results. Many experts regulate the amount of irradiation by means of the leucocyte count, which is usually reduced to 20,000 per c.mm. or less. Others regulate the radiotherapeutic treatment by the general condition and by the red-cell count rather than by the size of the spleen and the leucocyte count. In many ways the general condition is the best guide; a patient may feel fit and well with a leucocyte count of hundreds of thousands, a large spleen, and a haemoglobin value of 90%, whereas he is ill and may feel desperately so with a leucocyte count that has been reduced to the normal limits, a spleen that has been reduced beyond the point where it can be felt, and a haemoglobin of 50 to 60%.

Irradiation may also be applied by means of radioactive isotopes, more especially phosphorus (P³²), which has a half-life of 14.3 days. The results are in general comparable with those obtained with x rays, but the method has a grave and incalculable disadvantage, in that the variation in individual susceptibility is great. Some tolerate large amounts; others rapidly develop thrombocytopenia, haemorrhagic symptoms, or severe anaemia or agranulocytosis, or all, with even minimal doses. Freedom from irradiation sickness is one practical advantage which patients who have previously had x-ray therapy greatly appreciate. In general, there is now a tendency to discard the use of radiophosphorus

and to use conventional x-ray therapy as being somewhat safer in its effect, more predictable in its results, and attended by less hazards to the patient, even though it may cause some sickness or discomfort in the course of treatment.

Antimitotic Drugs

The alternatives to irradiation are the antimitotic drugs, urethane, which is given by the mouth, and modifications of nitrogen mustard, which are administered intravenously. The general effect of urethane is similar to that obtained by treatment with x rays—namely, a fall in total leucocyte count and a reduction in primitive cells, so that the haematological pattern returns to normal. At the same time the spleen and lymph nodes are reduced in size, whilst accompanying anaemia may be greatly improved. The great advantage of urethane is the ease of administration and the relative infrequency of unpleasant effects as compared with x rays. However, a proportion of patients manifest intolerance by anorexia, nausea, vomiting, and, less commonly, by diarrhoea and drowsiness. Not all subjects react favourably, and treatment needs to be carefully controlled by regular blood counts, since thrombocytopenia, agranulocytosis, and even aplastic anaemia are readily produced by overdosage. The inhibiting haematological effects continue for some time after the withdrawal of the drug. In my own experience, urethane has given the best results in chronic myeloid leukaemia and, save for a few cases of intolerance and a few of failure, is as effective and less misery-making than x rays. The drug is also reasonably effective in chronic lymphatic leukaemia, but is valueless in any of the forms of acute leukaemia. The usual dose of urethane is 0.5–1 g. three or four times a day, administered by mouth. Treatment is continued until the leucocyte count falls to about 50,000 per c.mm., whereupon the dose is reduced to 0.5–1 g. for the whole day; the treatment is stopped when the count reaches 20,000 per c.mm. Maintenance treatment can be prescribed once the early signs of relapse appear.

Synthetic modifications of mustard gas, the nitrogen mustards, have the same effect as the original material—namely, to cause aplasia of the haemopoietic system—and they have been used for the treatment of various neoplastic conditions, including leukaemia. The two compounds most used are the *bis* and *tris* nitrogen mustards, and of these the *bis* form is the less toxic. The drug is not suitable for the acute leukaemias, and does not appear to be more effective than x rays in the chronic forms of the disease, though some improvement has occasionally been found in cases resistant to irradiation. The results are extremely variable and irregular, but the chronic myeloid type responds most consistently and somewhat better than the chronic lymphatic forms. The dosage is 0.1 mg. per kg. of body weight administered intravenously, daily or every second day for one to seven days. Untoward effects include pain, inflammation, and, sometimes, thrombosis at the site of injection, with tissue necrosis if leakage or extravasation occurs. At the same time, within an hour of injection there are usually systemic symptoms such as anorexia, nausea, vomiting, headache, and vertigo. If dosage is excessive or not properly controlled agranulocytosis, thrombocytopenia, and aplastic anaemia readily occur. There can be little doubt that this form of treatment, for which much was hoped, is unpleasant, not without danger, and no more effective than irradiation.

Folic Acid Antagonists

The discovery of the effect of folic acid on haemopoiesis led to the trial of folic acid antagonists in the leukaemias. These *pterins*, of which aminopterin has proved the most satisfactory, are of considerable theoretical interest, since they open up a potential line of treatment affecting cell metabolism rather than cell destruction. However, it must be admitted that, in general, the results of treatment have been to produce haematological rather than clinical improvement—a criticism which unfortunately applies equally to all forms of treatment designed to control the activity of the leukaemic process. With aminopterin the toxic manifestations may be severe, and even fatal; these include severe and refractory stomatitis, agranulocytosis, enteritis, aplasia of the bone marrow, haemorrhagic symptoms, and loss of hair.

One of the difficulties of treatment is the immense variation in the clinical picture, the presentation, the symptoms, and the general features of the disease from case to case, so that what suits one case may be quite unsuitable for another. On the whole, the condition has to be treated symptomatically, and there is little point in treatment for treatment's sake when the case is symptomatic, as treatment does not appear to prolong life.

On the other hand, when the form of the disease is radiosensitive—and in this respect lymphosarcoma can usually be included—much can be accomplished in the way of improving comfort and efficiency by reducing the size of a tumour or an affected organ, thereby relieving symptoms caused by pressure, traction, or obstruction.

A DIAGNOSTIC UNIT FOR PRACTITIONERS AND ITS FIRST FIVE YEARS' WORK*

BY

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This paper describes a small diagnostic unit for general practitioners which has been built up in London during five years since the war, a unit with its own pathological laboratory and full-time pathological technician, with an x-ray department and radiographer working on the spot. The work of this unit has been carefully supervised by a consulting pathologist and by a consulting radiologist. It has been in the nature of an experiment, and will be described as such, step by step, just as it developed from its very small beginnings. This experiment has not been connected with the National Health Service; but I hope that its results will prove worth recording, without any suggestion or implication that it should be copied exactly elsewhere. General practices differ enormously, nowhere more so than in the centre of a large city; and what is convenient and satisfactory for one is unlikely to suit another. It is not my intention to criticize any other type of family practice. Quite enough criticism of general practice has been heard recently. I shall try to put forward something positive—a description of an experiment which is being tried,

*A paper read before the General Practice Section of the Royal Society of Medicine on April 18, 1951.