Prolonged Remission in Acute Leukaemia

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Acute leukaemia was formerly a rapidly fatal disease, but in the past decade treatment with corticosteroids and anti-metabolites has enabled life to be prolonged for many months and remissions can be obtained in the majority of cases, especially in children. Nevertheless survival for more than two years after diagnosis still remains exceptional, and the following two cases of unusually prolonged remission are worthy of record.

Case 1

A girl was admitted to hospital because of epistaxis in October 1956, when she was 5 years old. She had been pale and listless for a few months. There was nothing significant in her previous history. Both parents and her only sister were healthy. There was a history of diabetes mellitus on the paternal side.

FIG. 1.—Case 1. Photomicrographs of bone-marrow. $\times 235$ and $\times 500$.

On examination she was very pale. There were enlarged lymph nodes in the right posterior triangle of the neck and in both axillae and groins. The liver was 1 in. (2.5 cm.) and the spleen 3 in. (7.5 cm.) below the costal margin. No purpuric haemorrhages were present on the skin or mucous membranes.

The peripheral blood showed: haemoglobin 40%; white-cell count 13,000/c.mm. ("blast" cells 63%, eosinophil myelocytes 1%, neutrophils 10%, lymphocytes 20%, intermediate normoblasts 1%, late normoblasts 5%); platelets 41,000/c.mm. The bone-marrow (Fig. 1) was almost entirely occupied by blast cells, pro-lymphocytes, and lymphocytes, even the latter having a primitive appearance.

Treatment was started with prednisolone 100 mg. daily and methotrexate 2.5 mg. daily, and she was transfused with 2 pints (1,140 ml.) of blood. Within two weeks of starting treatment the blast cells disappeared from her peripheral blood and the platelets began to rise. Her progress was interrupted by the development of a suppurative thrombophlebitis at the transfusion site, but the infection remained localized and healed uneventfully. In the third week of treatment she developed diabetes mellitus characterized by excessive appetite and thirst, polyuria, and glycosuria. A random blood-sugar test showed 400 mg./100 ml. As the diabetes was attributed to corticosteroid therapy this was gradually withdrawn, and nine days later her blood sugar had returned to normal.

By the time of her discharge from hospital on 15 November 1956 her peripheral blood count was normal and the bone-marrow showed complete remission. Maintenance treatment with methotrexate 2.5 mg. daily was continued.

In March 1957, having been on continuous treatment for five months, she developed painful ulcers in the mouth. Methotrexate was discontinued, being replaced by mercaptopurine 50 mg. daily. After three months on this drug there was a fall in her haemoglobin, white-cell count, and platelets. Relapse was suspected, but the bone-marrow showed hypocellularity only. The dose of mercaptopurine was therefore reduced to 50 mg. on alternate days, and she remained on this up to the time of writing. Apart from an attack of chicken-pox, which followed an uneventful course, she has remained in excellent health and has grown normally. She has been in complete remission for eight years.

Case 2

A girl was referred to hospital in April 1958, when she was 9 years old, with a history of pallor and lassitude for five weeks following dental extractions. Apart from measles and mumps she had had no previous illnesses. The other four children in the family and both her parents were healthy.

On examination she had marked pallor of the skin and mucous membranes. The liver was palpable about 1½ in. (4 cm.) below the costal margin, and the spleen was just palpable; there were no enlarged lymph nodes. No purpuric haemorrhages were present and there was no bone tenderness. She had purulent otitis media on the right. Just before admission to hospital she had a brief generalized convulsion.

The peripheral blood showed a haemoglobin of 35%; white-cell count 3,500 (neutrophils 43%, lymphocytes 56%, monocytes 1%); platelets 226,000; reticulocytes 2%. The bone-marrow showed almost complete replacement by "blast" cells, probably lymphoblasts (Fig. 2).

On the basis of the bone-marrow findings a diagnosis of acute leukaemia was made. After blood transfusion treatment was started with mercaptopurine in a dosage of 150 mg. daily for 15 days, followed by 50 mg. daily. Penicillin and streptomycin were also given for the otitis. Eighteen days after starting treatment there was a sharp fall in the haemoglobin, white cells, and platelets. The bone-marrow now showed marked hypocellularity, the cells present being mainly lymphocytes, a few "blast" cells, and only scanty erythroid and myeloid precursors; the appearances suggested toxic depression. Mercaptopurine was stopped, and she was transfused and given triamcinolone 64 mg. daily. Over the next 10 days her haemoglobin, white cells, and platelets returned to normal. The triamcinolone was gradually withdrawn. On 15 July 1958 the bone-marrow showed complete remission, the appearances being normal except for slight reduction in cellularity. Mercaptopurine was restarted in a dosage of 50 mg. daily, and she remained on this up to the time of writing. Apart from occasional recurrences

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of the right otorrhoea she has remained perfectly well and her peripheral blood counts have been quite normal. She has been in complete remission for six and a half years.

FIG. 2.—Case 2. Photomicrographs of bone-marrow. $\times 235$ and $\times 500$.

Discussion

Survival Time

The mean survival time in untreated acute leukaemia was stated to be less than four months (Tivey, 1952), although 10% of cases survived for 11 months or more. Treatment with corticosteroids and antimetabolites has increased the survival time. Thus Lightwood *et al.* (1960) gave an average survival time of 13.3 months, Zuelzer and Flatz (1960) of 13 months, and Colebatch (1961) 14 months. From 1956 until 1963 70 cases of acute leukaemia were treated at Alder Hey Children's Hospital and six of the patients are still living. Excluding the survivors, the 50% survival time for the whole series was five and a half months. Twenty-one patients died within a month of diagnosis, some within a few days, and if these too are excluded the 50% survival time was 10 months. Among the patients who died the longest survival was three and a half years.

Zuelzer and Flatz (1960) reported 28 patients who had survived for more than 18 months and of whom 9 were still living and in remission at the time of the report. Three had survived for at least 36 months and one was still in remission at 87 months. In analysing their total series of 169 cases of acute leukaemia the only significant difference they could find between the long-term survivors and the others was that the former had more often presented with a white-cell count that was normal or low. They pointed out that even untreated cases with an initially low white-cell count tended to have a longer survival than those with a leucocytosis. The increased survival time in patients who presented with a normal or low white count has been reported by others (Haut *et al.*, 1959; Hyashi, 1959; Zuelzer and Flatz, 1960; Colebatch, 1961), although Thompson and Walker (1962) did not find this correlation in their series.

A few other exceptionally prolonged remissions have been reported. Dameshek and Mitus (1963) record a seven-year remission in an adult with acute leukaemia, the remission following a severe infection associated with a profound leucopenia. They also mention a child who had been in remission for nine and a half years following an almost fatal attack of chicken-pox. Fairbanks (1963) mentions three adults with remissions of from 2.3 to 5 years, and he refers to the patient of Frenkel and Meyers (1960) who had been in remission for five years at the time of their initial report and was alive and well after nine years' remission. He also refers to another patient of Meyers who had been in remission for five and a half years.

Roath *et al.* (1964) report a 14-year survival in a 5-year-old child treated with cortisone only, and they say that "she must be regarded as a true case of this disease which has been cured." Gasser (1964) reports three cases of paraneoplastic leukaemia and one case of promyelocytic leukaemia in children with prolonged remissions ranging from 5 to 12 years. All four children had been on maintenance therapy with either methotrexate or mercaptopurine, but two had stopped treatment after 4 and 10 years respectively.

Initial Diagnosis

Before accepting the occurrence of prolonged remission in acute leukaemia or the possibility of cure the initial diagnosis must be beyond doubt. A precise definition of the disease is difficult because of the many variable features, but the fundamental change is the presence of an increased number of primitive white cells in the bone-marrow. Wintrobe (1961) defines leukaemia as "a morbid condition of unknown aetiology and fatal termination which is characterized by widespread proliferation of leucocytes and their precursors in the tissues of the body. It is usually associated with qualitative and quantitative changes in the circulating white cells of the blood." According to Dameshek and Gunz (1958), "leukaemia may be defined as a generalized purposeless self-perpetuating abnormal proliferation (slow or rapid) of one of the leucocyte tissues, often associated with abnormal white blood cell counts and eventually leading to anaemia, thrombocytopenia, and death."

The first of the two cases reported above showed changes in the peripheral blood and bone-marrow which make the diagnosis beyond reasonable doubt. The initial marrow films have often been reviewed, and independent opinions by observers who were not informed of the subsequent course of events have agreed without question. In the second case the initial findings in the peripheral blood were those of anaemia with a relative lymphocytosis, but the bone-marrow showed almost complete replacement by blast cells, and, as Dameshek says: "The findings in the peripheral blood are of secondary importance . . . although they are usually a reflection of the blood-forming tissues; unfortunately the reflection is often an imperfect one and may indeed be misleading."

Prolonged Remissions

The cause of the prolonged remissions in these two cases, and in other reported cases, is not known, but certain features of their clinical course are of interest. The first patient developed transient diabetes during her initial treatment with corticosteroids. This is an unusual complication of steroid therapy in children. Although it has been suggested that children with a diabetic family history and of large birth weight are more susceptible to leukaemia (Stowens, 1960), if this were indeed the case it would be expected that large doses of corticosteroids would produce transient diabetes more

often, whereas this is the only instance in which it has occurred in my own patients, and Zuelzer (1960), with a much larger experience, has also seen only one case. It has been shown experimentally that glucagon produces significant slowing of tumour growth in DBA mice with lymphoma implants (Goranson *et al.* 1959), but a clinical trial of glucagon (combined with corticosteroids and antimetabolites) in a small group of leukaemic children, although producing moderate hyperglycaemia, has not had any marked effect on the course of the disease. Although two of the five patients so treated are still alive after more than two years, both have had at least one relapse. If glucagon, or perhaps hyperglycaemia *per se*, is a factor in promoting prolonged survival a further trial with larger doses for longer periods might produce a more definite answer.

The second patient resembled the long survivor of Dameshek and Mitus (1963) in that she developed a marked leucopenia during the course of treatment. It is possible that the original clone of leukaemic cells was more profoundly damaged by the mercaptopurine than the other haemopoietic tissues and that its recovery was delayed or perhaps indefinitely postponed. The goal of chemotherapy in malignant disease is the selective destruction of the abnormal cells without producing grave or fatal damage to normal cells. While it is not claimed that this is what has occurred in this patient, it is a possible explanation.

The initial dose of mercaptopurine received by this patient was higher than that usually recommended, but such a high starting dose has been used here since 1958, following the suggestion of Hyman *et al.* (1957). A review of all cases treated with mercaptopurine has not shown any real difference in survival, or in time of onset of remission, in those cases treated with the usual dose of 4.4 mg./kg./day as compared with the higher starting dose of 6.6 mg./kg./day, but neither has there been any increased incidence of toxic effects.

Both of these long survivors are still taking mercaptopurine, one of them having 50 mg. every other day, and the other 50 mg. every day. The treatment does not seem to have affected health or growth in any way. Both girls are developing secondary sexual characteristics although neither has yet menstruated. It is impossible to tell whether the continued treatment is doing any good, but it certainly does not appear to be doing any harm, and I am therefore reluctant to stop it.

Mere prolongation of life in a fatal disease is not necessarily a blessing to the patient or to his family. This applies especially if prolongation is accompanied by much suffering. In acute leukaemia, however, remission usually means the restoration of full health, all evidence of the underlying disease seeming to disappear. Such remissions are therefore well worth while achieving, and, even though they may only last a few months in most cases, the occasional long-term survival, as in those reported here, makes it even more important that every child who develops acute leukaemia should be treated. When the discovery of corticosteroids and folic-acid antagonists made remission a predictable event in

acute childhood leukaemia, the outlook for eventual control of the disease seemed bright (Dameshek, 1954). Although the hopes of that time have not yet been realized, further progress has been made both in the development of antileukaemic drugs and in the management of haemorrhage and infection, which are the usual causes of death. Enthusiastic treatment is fully justified in the hope that a cure will eventually be found.

Summary

This paper records two cases of unusually prolonged remission of acute leukaemia in children. The first patient, a 5-year-old girl, developed transient diabetes mellitus during her initial treatment with corticosteroids and has since been in complete remission for eight years. The second patient was a 9-year-old girl who developed toxic depression of the bone-marrow during treatment with mercaptopurine in a dosage of 150 mg./day (6.6 mg./kg./day). She has now been in complete remission for six and a half years.

The possible role of the transient diabetic state in producing the prolonged remission in the first patient is discussed and reference is made to a short but inconclusive trial of glucagon in the treatment of acute leukaemia.

In the second patient it is suggested that the toxic depression of the bone-marrow might have produced selective destruction of the original clone of leukaemic cells.

Both children have been on continuous maintenance therapy with mercaptopurine, and this does not appear to have interfered with growth, secondary sexual development, and resistance to infection.

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