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MEDULLARY APLASIA IN CHRONIC MYELOID LEUKAEMIA DURING BUSULPHAN THERAPY

BY

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Busulphan (1:4-dimethanesulphonyloxybutane; "myleran") is now well established as an effective and relatively safe agent in the control of chronic myeloid leukaemia. Haddow and Timmis (1953) first noted the strong depressant action exerted by this compound on myelopoiesis, and many clinical trials in leukaemic and neoplastic states have since been reported (Galton, 1953; Bollag, 1953; Wilkinson, 1953; Hansen, 1954; Wagner, 1954; Petrakis *et al.*, 1954; Galton and Till, 1955; Haut *et al.*, 1955; Bernard *et al.*, 1955; Kurrle, 1955; Louis *et al.*, 1956; Blackburn *et al.*, 1956; Frost and Jackson, 1956; Greig, 1956; Hyman and Gellhorn, 1956). From the results of these trials it is clear that busulphan has a remarkably specific action against the myeloid cell series, and is capable of bringing into good remission over 80% of patients suffering from chronic myeloid leukaemia. It is inactive in acute leukaemia, in chronic lymphatic leukaemia, and in neoplastic conditions, including the lymphomas.

Patients treated with busulphan are singularly free from the unpleasant side-effects which would result from simultaneous attack on rapidly dividing normal tissues, such as the skin or the gastro-intestinal mucosa. Only two important toxic reactions have been recorded in the considerable literature that has now accumulated on busulphan therapy in chronic myeloid leukaemia. One is a progressive myeloid depression—an exaggeration of the desired therapeutic response—leading to marrow aplasia. The other is renal failure due to hyperuricaemia caused by very rapid breakdown of granulocytes. It would be misleading to give the impression that either of these two reactions occurs often, but, despite their rarity, both are serious enough to warrant close attention, particularly when suggestions for the routine use of busulphan are being put forward and the drug is being increasingly prescribed by general physicians. The development of hyperuricaemia can be avoided, as Hyman and Gellhorn (1956) suggest, by adjusting dosage to prevent too sharp a fall in leucocyte count, and by

forcing fluid intake to 3 to 4 litres daily during the danger period. It would also seem reasonable to maintain an alkaline urine. In our own restricted experience of 12 cases this problem has not arisen, but we have encountered two cases of marrow aplasia while using dosages within a range generally regarded as orthodox.

In the present report we give details of the toxic reactions in these two patients, and make some general observations on precautions in the routine use of busulphan.

Case 1

A woman aged 30 was admitted to hospital in February, 1955, having complained of abdominal swelling for six months, frequency of micturition and dysuria irregularly for four months, and aching in legs and back and nocturnal sweating for two months. She was found to have massive enlargement of the spleen, which extended across the midline and 25 cm. below the xiphisternum. The blood count showed a typical picture of chronic myeloid leukaemia, with haemoglobin 9 g. per 100 ml. and total leucocytes 700,000 per c.mm., with 300,000 granulocyte precursors per c.mm. She was treated with mercaptopurine, and an initial course of 150 mg. daily was given for 18 days. After an interval of a month, a second course of this drug was given for seven days. The effect of this treatment on the peripheral blood count is shown in Fig. 1; the leucocyte and platelet counts showed on each of the two occasions a response during the period of administration, with continued increasing effect for about two weeks after the drug was stopped, and then rapid relapse.

Because of the erratic response to mercaptopurine, busulphan was started on April 14 at a dosage of 4 mg. daily. After 72 days on this dose the response with respect to the haemoglobin level, leucocyte count, splenomegaly, and general clinical state was unimpressive, and the dose was increased to 10 mg. daily for the next 28 days. The response was dramatic, the haemoglobin rose steadily from 9.9 to 12.6 g. per 100 ml., the leucocytes fell from 230,000 to 70,000 per c.mm., and the spleen was greatly reduced in size. The dose was then decreased to 8 mg. daily and treatment continued for 58 days. By that time the patient had become symptom-free, the spleen tip could only just be felt on deep inspiration, the haemoglobin level was 12.4 g. per 100 ml., the leucocytes numbered 6,000 per c.mm. with a normal differential count, and the platelet count was 200,000 per c.mm. Because the response to the initial daily dose of 4 mg. of busulphan had been slight a maintenance dose of 4 mg. daily was then started.

FIG. 1.—Case 1. Haematological response to treatment.

During the ensuing few weeks the patient noticed a few bruises, but at her next attendance 26 days later there were many fine scattered petechial haemorrhages on the legs, occasional bruises on the trunk and limbs, and an ulcer below the tip of the tongue. The spleen and liver were both palpable 2 cm. below the costal margins. The haemoglobin had fallen to 10.1 g. per 100 ml., the leucocyte count to 3,200 per c.mm., and the platelets to 50,000 per c.mm. Busulphan was stopped, but improvement during the next 18 days was confined to diminution of purpura. Mouth ulceration was now more severe, with sublingual ulcers, an ulcer $\frac{1}{2}$ in. (6 mm.) in diameter inside the lower lip with a necrotic slough, and gross fetor oris. There was no further increase in the size of liver or spleen. A blood count at this time (November 1) showed peripheral pancytopenia, with haemoglobin 6.2 g. per 100 ml., leucocytes 2,900 per c.mm., and platelets 30,000 per c.mm., and the patient was readmitted to hospital for transfusion and steroid therapy.

A marrow aspirate obtained on November 16 was found to be hypoplastic. Despite frequent transfusions and the use of cortisone in high doses the pancytopenia was not relieved, but persisted, with only minor fluctuations in the level of leucocytes and platelets, until death occurred two months later, on January 14, 1956. Haemorrhagic features had become particularly prominent during the terminal stages, and gastro-intestinal bleeding, epistaxes, haematuria, and various ecchymoses developed. Platelets were fewer than 10,000 per c.mm. for the last six weeks of life. The general pattern of haematological response to transfusion and the ineffectiveness of this therapy and also of cortisone are shown in Fig. 1.

Case 2

A woman aged 67 was admitted to hospital in January, 1954, with typical chronic myeloid leukaemia. She had been increasingly unwell since April, 1953, with muscular pains in the legs, backache, lassitude, constipation, and abdominal swelling. Her spleen extended across the midline and almost to the pelvic brim, and the liver edge was palpable 5 cm. below the left costal margin. Examination of the peripheral blood showed haemoglobin 10.8 g. per 100 ml. and leucocytes 230,000 per c.mm., with 46% granulocyte precursors. Platelets numbered 300,000 per c.mm. Treatment was started with 1 g. of urethane three times a day, and was continued for two months before it had to be stopped because of increasingly severe nausea. During this time the leucocyte count fell to 40,000 per c.mm. and the haemoglobin level rose to 13 g. per 100 ml. The spleen had become smaller and the general clinical state was much improved. During the next six months a gradual deterioration in the blood count took place, but the patient felt well and was symptom-free. Bone and muscle pains then began to recur, and both the splenic size and the peripheral blood picture were found to have reverted to the pretreatment position. Therapy was started again, this time with mercaptopurine (100 mg. daily). Response to mercaptopurine was rapid, but lasted only a few weeks after the drug had been stopped, and several short courses of treatment were therefore given during the succeeding 10 months.

Because of the fluctuating haematological findings, shown in Fig. 2, and the unstable clinical course on mercaptopurine therapy, treatment with busulphan was started on July 14, 1955, in a dosage of 4 mg. daily. The response was very good, with a steady rise in haemoglobin and fall in leucocyte count, and a reduction in spleen and liver size, so that after 104 days the haemoglobin had reached 13.4 g. per 100 ml., the leucocytes numbered 8,200 per c.mm., with no granulocyte precursors present, platelets

were 200,000 per c.mm., and neither liver nor spleen could be felt. At this stage the dosage of busulphan was reduced to 2 mg. daily.

One month later the leucocyte count had fallen to 3,750 per c.mm., while the haemoglobin had dropped to 11.2 g. per 100 ml. and platelets had decreased sharply to about 10,000 per c.mm. There were no specific complaints or fresh physical signs, and, in particular, no sore throat or purpura. Busulphan was stopped, but pancytopenia became increasingly severe, and four weeks later, on December 23, there were scattered petechiae and well-marked bruises on the limbs and the blood count showed haemoglobin 6 g. per 100 ml., leucocytes 1,600 per c.mm., and platelets fewer than 10,000 per c.mm. The patient was admitted to hospital and treated with transfusions of fresh blood and courses of cortisone, corticotrophin, and prednisone. For a period of four months there was no sign of returning haemopoietic activity, the haemoglobin level fluctuating in accordance with transfusions, the white cells varying between 350 and 3,000 per c.mm., with relatively few polymorphs, and the platelets remaining fewer than 10,000 per c.mm.

The first clear evidence of commencing recovery appeared on May 3, 1956, when the expected fall in haemoglobin level during the week after a transfusion did not take place and reticulocytes rose to 2.9%. The reticulocytosis persisted between 3 and 7% for the next two months, and during this time the blood findings all showed clear improvement. Steroid therapy was stopped on June 5 and subsequent progress was uninterrupted. Complete remission, both clinical and haematological, of aplastic and leukaemic processes took place, and has persisted to the time of writing (June, 1957). Details of the haematological progress and therapy are charted in Fig. 2.

Discussion

A number of different schemes of treatment, using a fairly wide range of dosage, have now been reported in the literature on busulphan therapy in chronic myeloid leukaemia. Galton and Till (1955), recording the results of treatment of 31 cases during a five-year period, recalled that their initial short intensive dosage scheme, in which 100–150 mg. were given in one to six days, was stopped because three patients developed severe marrow depression and one died. Subsequently a more conservative plan of therapy was used, with doses rarely exceeding 4 mg. daily. Treatment was stopped "when clinical and haematological improvement

FIG. 2.—Case 2. Haematological response to treatment.

seemed to justify it, or when the leucocyte count was thought to be falling too steeply." In general they have aimed to maintain the leucocyte count between 10,000 and 20,000 per c.mm., and no further cases showing signs of toxicity were encountered.

Greig (1956) used a similar initial dosage of 4 mg. daily, but continued treatment at this level until "the blood count showed no further evidence of improvement." The leucocyte count was brought to "normal levels," and maintenance therapy continued at a dose between 1 and 2 mg. daily. Marrow aplasia occurred in only 1 of 34 cases in his series, and that in a patient who had inadvertently received a double dosage rate for 45 days (8 mg. daily). Recovery took place when busulphan therapy was stopped. Greig noted that in two patients who were thrombocytopenic at the start of treatment the effect of busulphan was to aggravate this feature, and the drug had to be stopped.

A more precise plan of therapy which appears equally safe and allows more rapid remission to be produced has been used by Hyman and Gellhorn (1956). They gave initial doses of 10 mg. daily and followed the peripheral leucocyte count every two to three days until it reached 25% of the original level. Therapy was then discontinued until the leucocyte fall stopped. Further treatment was given if necessary to bring the white-cell level to within the normal range of 6,000–10,000 per c.mm. If initial response was unsatisfactory, doses of as much as 20 mg. daily were given until a suitable rate of fall was achieved. An even more aggressive routine plan of therapy has been used by Dameshek (1957), who gave initial doses of 8–16 mg. daily until the leucocyte count reached 5,000–6,000 per c.mm. The drug was then stopped, and while the white-cell count sometimes continued to fall to 2,000–3,000 cells per c.mm. Dameshek has encountered no deleterious effects from this procedure in a series of 34 cases, apart from two temporary cases of thrombocytopenia. Maintenance with doses of the order of 2–4 mg. daily may be well tolerated and lead to prolonged remission, but unexpected bone-marrow failure has developed suddenly in a few patients so treated (Haut *et al.*, 1955; Storti and Pederzini, 1955, Case VIII).

Clearly, the administration of large doses of busulphan is frequently associated with the development of aplastic states (Wilkinson, 1953; Galton and Till, 1955; and Storti and Pederzini, 1955). In the majority of cases high dosage rates are now used only in patients who have proved resistant to more conservative schemes of treatment, and then only with very close haematological supervision. The dosage employed by Dameshek appears to be too close to the toxicity level to be safely used without very frequent blood counts, and, although in his experience undue marrow depression has not occurred, the advantages of such intensive therapy for routine use would seem to be outweighed by the risks.

It is theoretically desirable to maintain the white-cell count between 5,000 and 10,000 cells per c.mm., and Hyman and Gellhorn emphasize that in their experience the best results of treatment with busulphan are obtained when the leucocyte level has been reduced to below 10,000 cells per c.mm. In practice, however, this ideal is difficult to achieve. Although the response to busulphan may remain uniform for long periods, a change in sensitivity to the drug may occur in either direction. If treatment is stopped the white-cell count may continue to fall to an unpredictable and varying extent.

The two cases reported here did not receive intensive courses of treatment. After the leucocyte count had been reduced to the 5,000–10,000 cells per c.mm. range, by doses of 8 mg. daily in Case 1 and 4 mg. a day in Case 2, maintenance therapy of 4 and 2 mg. per day respectively was given. Both patients developed progressive marrow aplasia during the next four weeks.

Recommendations for Routine Use

The initial conservative dosage of 4 mg. daily used by Galton and Till seems the most advisable regimen for the

treatment of chronic myeloid leukaemia on an out-patient basis when blood counts and physical examination can be carried out at fortnightly to monthly intervals. Treatment should be stopped temporarily when the leucocyte count has fallen to between 10,000 and 20,000 per c.mm., and recommenced at a lower level when the white cells have begun to increase. By this means a very gradual reduction to between 5,000 and 15,000 cells per c.mm. may be effected with little risk of too severe a fall. Higher dosage busulphan therapy in the occasional resistant patient is probably best carried out in hospital unless very frequent visits for blood counts can be made, since a sudden rapid fall may occur even in an initially resistant patient.

The average sensitive patient presenting a high peripheral leucocyte count may be given an initial dose of 10 mg. a day when blood examinations at intervals of two to three days can be undertaken. This may be done, for example, in cases where treatment is begun in hospital. The busulphan should be stopped when the white count has fallen to about 25% of the initial level, as recommended by Hyman and Gellhorn, unless the fall is very precipitous, in which case the drug should be stopped when the count has been roughly halved. When the leucocyte level has stopped falling, treatment may be started again with smaller doses, and an attempt made to reduce the level cautiously to about 10,000 cells per c.mm.

When the early stages of therapy have brought about a satisfactory fall in leucocyte count, improvement in haemoglobin level and in physical condition usually follows rapidly, and a decision must then be made about maintenance treatment. In our view it would be unwise to continue giving busulphan, even in doses as low as 0.5 to 2 mg. daily, to any patient whose leucocyte count is below 8,000 per c.mm. When the white-cell level is between 10,000 and 20,000 per c.mm., and even more so if it is higher, benefit is likely to result from continued therapy. In general the aim should be to adjust dosage so that the count is kept between 10,000 and 20,000 cells per c.mm. Because of the change in sensitivity which has already been mentioned, it is unsafe to leave a patient on treatment without blood examination for more than four weeks.

The onset of purpura or a sharp fall in platelet level at any stage of treatment should lead to prompt cessation of therapy.

Summary

Details are given of two patients with chronic myeloid leukaemia who developed bone-marrow failure while on busulphan therapy. In one case the aplastic state proved irreversible, but in the other recovery occurred.

The literature on toxic reactions to busulphan is reviewed. Initial doses of 4–10 mg. a day are recommended, since more intensive treatment carries a high risk of marrow failure. Careful control of dosage in accordance with the rate of fall of the peripheral leucocyte count is essential. Opinions vary concerning the most satisfactory indications for stopping treatment and the relative advantages of maintenance therapy and intermittent courses in long-term management. The best remissions have generally been achieved when the white-cell count has been reduced to 5,000–10,000 cells per c.mm. by the initial course of busulphan, but the two cases here reported illustrate the risk of continuing treatment, even in very low doses, when the count is at these levels.

Dosage schemes and methods of management which should minimize the risk of marrow failure are suggested for use in patients treated initially in hospital or able to attend frequently for blood counts and also for those who can attend less often as out-patients. We think it unwise to continue giving busulphan in any circum-

stances to a patient whose leucocyte count is below 8,000 per c.mm. or to one who manifests purpura or a sharp fall in platelet level.

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RUBELLA ENCEPHALITIS

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Since the classical description by Bénard (1921) of 13 cases of encephalitis occurring amongst 291 hospital patients with rubella, there has been considerable interest in this and other not uncommon complications of the latter. Steen and Torp (1956) reported 88 definite cases of rubella encephalitis from the literature, and added a further three cases of their own. Most of the reported cases have occurred during epidemics of rubella.

The neurological symptoms most often occur one to six days after the onset of the exanthem. They are characteristically brief in duration, with complete recovery in most cases. Usually encephalitic, myelitic, or meningitic signs are elicited either singly or in combination. Death can occur (it occurred in 20% of the cases reviewed by Schleisner *et al.*, 1955). More rarely, permanent sequelae are encountered.

Cases of rubella complicated by neurological involvement do not seem to differ in any way from cases not so affected. Further, there is no relationship between the severity of the initial illness and the occurrence of neurological complications (Barraclough, 1937).

Case 1

A girl aged 6 years was admitted to hospital during a mild epidemic of rubella with a history of onset of headache and drowsiness seven days previously. Next day she developed a generalized maculopapular rash diagnosed by the family physician as rubella. A younger sister aged 3 had developed rubella one week previously, and, although drowsy at the time of the rash, rapidly recovered as the rash faded.

As the exanthem subsided, the patient's drowsiness increased, and the persistence of this together with the severe headache resulted in her being confined to bed. Three days before admission she noticed the gradual onset of "giddiness," which became worse whenever she attempted to sit up in bed. This in turn became progressively worse, until on the day of admission vomiting occurred whenever the "giddiness" was severe. There had been no convulsions or loss

of consciousness, and no diplopia, speech disturbance, or dysphagia. The child had previously suffered from measles, mumps, chicken-pox, and infantile eczema.

Neurological examination revealed an afebrile, intelligent, co-operative girl who continually lapsed into a drowsy state when not engaged in conversation. There was no evidence of cranial nerve involvement and ophthalmoscopic examination was normal. Abnormal findings included mild bilateral horizontal nystagmus and intention tremor. The tendon reflexes were all brisk, but the plantar responses were flexor. Kernig's sign was negative. She had gross ataxia with vertigo when erect, the ataxia being most pronounced when the eyes were closed. There was a tendency to walk on a wide base. The only other positive finding on examination was pharyngitis with fetor. A provisional diagnosis of rubella encephalitis was made and symptomatic treatment given.

Investigations.—Mantoux reaction 1:1,000 negative. Throat swab—no pathogens. X-ray examination of skull and chest normal. E.S.R., 32 mm. in one hour. Lumbar puncture on admission: clear colourless fluid; pressure 70 mm. water; cells, less than one leucocyte/c.mm.; chloride, 125 mEq/litre; protein, 20 mg./100 ml.; Pandey reaction negative; W.R. negative; glucose, 29 mg./100 ml. (probably unreliable, as the specimen was left in the refrigerator overnight without preservative); Hb, 12.7 g./100 ml.; W.B.C., 10,000/c.mm. (55% neutrophils, 40% lymphocytes, 5% monocytes).

Four days after admission the E.S.R. was 16 mm. in one hour; W.B.C., 6,000/c.mm. (30% neutrophils, 60% lymphocytes, 5% monocytes, 5% eosinophils). Lumbar puncture 11 days after admission: cells, 3 leucocytes/c.mm.; chlorides, 117 mEq/l.; glucose, 60 mg./100 ml.; protein, 60 mg./100 ml.; Pandey reaction negative.

The drowsiness and vomiting continued for a further three days, but the vertigo and ataxia lasted another day. From this time onward, recovery was rapid and the patient was discharged 15 days after admission with no residual disability. Two weeks later she started at school again, having made an apparently full recovery.

Case 2

A girl aged 8½ years, the youngest of three children, was admitted to hospital with a history that seven days previously she had had fever and rash. The rash, which faded in two days, was diagnosed by the family physician as rubella. She was well in herself at the time and remained so until the morning of the day of admission, when she awoke with headache and anorexia, and was "off colour" all day. That evening she vomited and had a generalized convulsion which lasted 1½ hours and left her stuporous. She had previously had measles and whooping-cough, but no convulsions.

The mother and two other children were well. The father had had a temporary "influenza"-like illness with fever, headache, sweating, and generalized muscular pains one week before.

On neurological examination the temperature was 99.6° F. (37.6° C.) and pulse 36. The patient was semiconscious, very restless and uncooperative, and showed no recognition of her surroundings. The pupils were equal and reacted to light. Cranial nerve palsies were not present. There was moderate nuchal rigidity, with a positive Kernig's sign. Tendon reflexes were all present but brisk, the plantar responses uncertain. The only other positive finding was an inflamed throat. Her weight was 70% of normal for her age. A diagnosis of rubella meningo-encephalitis was made and she was kept sedated with intramuscular phenobarbitone.

By next morning she was fully conscious but still rather drowsy. She was not confused but had some retrograde amnesia. She was now afebrile and had had no further convulsions. She remained well subsequently and was discharged one week after admission, having phenobarbitone ½ gr. (32 mg.) b.d. When seen three weeks later she was very well and the phenobarbitone was discontinued.