TOXIC MARROW FAILURE AFTER TREATMENT OF CARCINOMA WITH CYTOTOXIC DRUGS

BY

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Dissatisfaction with the results of surgical treatment in cancer, combined with increasing success in the use of cytotoxic drugs, has led to the adoption of the latter form of treatment by an increasing number of surgeons in recent years. Great impetus was given to this movement by the report of Watson and Turner (1959), which showed that marked objective improvement was obtained in 30 out of 34 cases of breast cancer treated with thiotepa alone or with thiotepa and testosterone. These workers advocated a trial of surgery and chemotherapy for early breast cancers and described their preliminary results.

A similar trial was begun at the West London Hospital by Mr. Grant Batchelor. Eleven cases of carcinoma of the breast have been treated by a course of testosterone and thiotepa after simple mastectomy or wedge excision of the primary carcinoma. At the time of writing three cases were in the ward, two having completed one course. Three cases were treated with mannometrine ("degranol") and testosterone when thiotepa was not available. With the exception of one case awaiting a second course, a favourable response has been obtained in all 17 cases to date.

While the final verdict on this form of treatment must await a five-year or even a ten-year follow-up, the disappearance of skin metastases, the complete clearing of pleural effusions, and the relief of pain in bone metastases, combined with a remarkable improvement in the sense of well-being in stage IV cases, has been most encouraging. In stage III cases fixed lymph nodes have melted away and in no stage has there been any evidence of recurrence at the site of excision of the growth or in the simple mastectomy scar.

The six pre-menopausal cases were also treated by oophorectomy. The treatment was well tolerated, and the only important side-effect encountered was toxic damage to the bone-marrow. It is with regard to the prevention and treatment of this grave complication, which is likely to arise in the treatment of any form of cancer with cytotoxic agents, that this paper has been written.

Toxic damage was encountered in five cases, all of which recovered. Such damage was evidenced by a fall in the white-cell count to below 3,000/c.mm., with a corresponding fall in the platelet count to 100,000/c.mm. or less. The haemoglobin fell to 60–70% of normal. Three of these cases had bone metastases, one had fixed axillary nodes, and one was classified as stage I but had extensive destruction of the breast.

Patients received 200 mg. of testosterone propionate intramuscularly daily for five days a week, for five weeks. Thiotepa (triethylene thiophosphoramide) 30 mg. intramuscularly was given on alternate days for a total of nine doses.

The white-cell and platelet counts were repeatedly checked. In only one case (No. 1 below) was the toxic

marrow damage accompanied by a serious complication—severe haemorrhage.

The clinical course and haematological changes in two cases are recorded in detail.

Case 1

On February 29, 1960, a wedge excision of a stage III carcinoma in the breast of a woman aged 65 was carried out. She was given a course of testosterone propionate and thiotepa, and the white-cell count fell to 4,400. The ninth dose was omitted, as experience had shown that a fall in the white-cell count below 4,500 should be treated with caution. Two days later it rose to 5,800, and the patient was discharged to the out-patient department.

Ten days later she was readmitted suffering from severe epistaxis followed by melaena. She was shocked, and was given 1 pint (570 ml.) of packed cells after the nasal bleeding had been arrested by packing. The haemoglobin was 53% (7.6 g./100 ml.), clotting-time 3 minutes, and bleeding-time over 15 minutes; the white cells numbered 800, and the platelet count was very low.

Next day 2 pints (1.14 l.) of fresh donor blood was given. A day later the nasal pack was removed, but four days after this the epistaxis recurred and the nose had to be repacked. A further pint (570 ml.) of fresh donor blood was given one week after admission.

The white-cell count had remained at 800 (polymorphs 30%), with platelets down to 98,000 and bleeding-time 5 minutes 20 seconds. Arrangements were then made with Dr. H. E. M. Kay, of the Royal Marsden Hospital, for an infusion of fresh foetal haemopoietic tissue (liver suspension), while the result of a final pre-infusion white-cell count was awaited. The latter showed a rise to 1,000. Accordingly the infusion of foetal cells was not given. The white-cell and platelet counts rose steadily to 5,600 (polymorphs 65%) and 198,000/c.mm. respectively. Haemoglobin was 67% (9.8 g./100 ml.). There was no recurrence of either epistaxis or melaena, and the patient was discharged.

A course of tetracycline was given throughout the second admission, and a pyrexia of 103° F. (39.4° C.) which developed three days after admission subsided completely six days later, immediately after the second transfusion with fresh donor blood. The patient complained of a transient sore throat, but no objective evidence of inflammation was seen, and the throat swab grew no pathogens on culture.

Case 2

In April, 1959, a woman aged 77 was treated by left simple mastectomy for a carcinoma involving the axillary and supraclavicular glands with brawny swelling of the arm. She was subsequently given a course of radiotherapy.

The tumour had been present for two years and had ulcerated through the skin six months before admission. She remained well until February, 1960, when she developed pain in the left buttock and thigh that made walking difficult. X-ray examination revealed metastases in the pelvis with fractures of the iliopectic and ischiopectic rami. Hard nodules were found in the mastectomy scar, and there was a hard fixed gland in the right axilla.

A course of testosterone and thiotepa was given, but as the white-cell count fell to 3,800 after the seventh dose the drug was discontinued. The white-cell count continued to fall, being 1,000 21 days later; but after a further 12 days it had risen to 4,800, with 155,000 platelets, and the patient was discharged. She was walking completely free from pain and was feeling well. She had suffered no ill consequences from the marked fall in her white-cell count.

Discussion

These cases show one feature in common—a delayed but pronounced fall in the white-cell and platelet counts with a slow spontaneous recovery. The

remarkable fall in the white-cell count which gradually occurred over a period of three weeks in Case 2 emphasizes the importance of caution in dosage when the white-cell count falls below 4,500, while the unexpected delayed fall in Case 1 indicates the importance of weekly white-cell and platelet counts for the first few weeks after the cessation of treatment. These counts may be carried out in the out-patient department.

Experience suggests that, with careful dosage and control by regular haematological investigations, severe degrees of marrow damage can be avoided. The remarkable powers of recovery of the bone-marrow have been shown in all five cases of toxic damage in this series.

In the event of severe marrow damage, three possible lines of treatment are now available: (1) Repeated transfusions with fresh donor blood while awaiting spontaneous recovery of the bone-marrow. This procedure was successful in Case 1 and warns against too ready praise for the other lines of treatment which appear to be highly successful. Had the white-cell count in Case 1 remained low for 24 hours longer, great success would have been claimed for the graft of foetal cells planned. (2) Infusions of marrow from a donor. Homografts have been carried out successfully (Humble and Newton, 1958; Mathé *et al.*, 1959; Thomas *et al.*, 1959; Beilby *et al.*, 1960). Proved survival of the grafts was not longer than three to four months, except in the case reported by Beilby *et al.* in which the donor was a sister. In this case the donor cells were still present in a proportion of 40% in the blood nine months after infusion. Furthermore, this treatment carries the danger of "homograft disease" as described by Mathé and Bernard (1959). In view of this danger and the temporary nature of the grafts, they would be indicated only in very exceptional cases. (3) Infusions of foetal haemopoietic tissue as described by Bridges *et al.* (1960) employing liver and spleen suspensions prepared according to the method of Kay and Constandoulakis (1959).

Such infusions have been carried out successfully in a large number of cases (Kay, personal communication), but the grafts survive for less than a month. The tendency in the past has been to treat cases too hastily without awaiting spontaneous recovery in a damaged bone-marrow.

This method will probably increase in usefulness for selected cases with extremely severe marrow damage. Whether the benefit derived from adult and foetal homografts is due to the actual transplant of cells or to bone-marrow stimulants remains to be discovered.

Fresh donor blood may contain factors of great importance for haemopoiesis, as suggested by the improvement in Case 1.

Where it is desired to give a second course of cytotoxic agents, a strong case can be made for withdrawing the bone-marrow with a view to a possible subsequent autograft as described by Humble and Newton (1958) and Westbury *et al.* (1959).

Summary

Of the 17 cases of breast cancer treated with cytotoxic drugs and testosterone, five developed serious bone-marrow depression. Spontaneous recovery occurred in all cases, but one required repeated blood

transfusions for severe haemorrhage. The danger of a delayed fall in the white-cell count and the likelihood of spontaneous recovery are pointed out.

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A CASE OF TWIN ANENCEPHALIC PREGNANCY

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Malpas (1937) gave the incidence of anencephaly in the general population as 0.3% and the incidence of recurrency of the malformation as 2.6%. Martin (1849) recorded the occurrence of six anencephalic births in the reproductive history of one woman.

Anencephaly in a twin pregnancy is rare. Ru-Kan Lin and Plenk (1955) recorded seven cases of twin pregnancy in which only one foetus was affected. They also described fully a case of twin pregnancy in which both foetuses were affected, the diagnosis being made *ante partum* by radiological means: this appears to be the first case in which the diagnosis was so made. Cases of twin pregnancy in which both twins have been found to be anencephalic have also been described by Josephson and Waller (1933), Dunn and Salter (1944, personal communication of a case encountered by Mr. Wilson Clyne), and Toulouse and Dubois (1957).

The following case is therefore thought to be rare enough to be put on record.

Case Report

A primigravida aged 25 with no past history of serious illnesses and with a regular menstrual cycle, 4/28 days, had her last menstrual period on March 10, 1959. Movements were first felt on August 7, 1959. Her blood was group O rhesus-positive. The Wassermann and Kahn reactions were negative. She was first seen in the antenatal clinic when 13 weeks pregnant. The size of the uterus was found to be consistent with the period of gestation. Physical examination did not reveal any abnormality.

She was next seen at this hospital when 22 weeks pregnant and was noted to have definite hydramnios. Abdominal girth measured 32 in. (81.2 cm.) and no foetal heart was heard. When seen at the antenatal clinic one week later her