When properly indicated parenteral iron is an irreplaceable remedy, but it should be reserved for cases of iron deficiency in which oral iron has failed. Such failure may be the result of poor intestinal tolerance, to malabsorption, or to the patient's inability to sustain oral treatment for an adequate time. There are also situations, such as late pregnancy, in which the efficiency of intestinal absorption is in doubt and time does not permit an adequate trial of oral therapy, when parenteral iron may be justified.

Intravenous or Intramuscular?

The intramuscular route for parenteral iron has obvious practical advantages in ease of administration, and while general toxic reactions to intramuscular iron-dextran are known, they appear to be uncommon.

Of greater importance are two observations which are perhaps connected. Firstly, the relatively high proportion of iron remaining at the site of injection, and therefore not available for haemoglobin synthesis, variously estimated at from 10 to 20% of the injected dose. Secondly, the carcinogenic action demonstrated in mice and rats presents at the moment an unknown hazard for man. In experiments still in progress I have so far found one sarcoma at the site of injection after six months of weekly iron-dextrin by subcutaneous injection in mice. It is likely, therefore, that iron-dextrin will prove to be of the same order of carcinogenicity as iron-dextran in experimental animals, and thus does not commend itself to intramuscular use.

The intravenous route has the merit of encouraging careful attention to the indications for parenteral iron. In the presence of iron deficiency, the high utilization for haemoglobin synthesis ensures that no undue excess of iron is deposited at any site. The main disadvantages have been the risk of severe local inflammation and general toxic reactions which seem to have been minimized with iron-dextrin at the 100-mg. dose level.

Summary

The response to treatment with intravenous iron-dextrin in 51 cases of iron-deficiency anaemias, including 26 in pregnancy, is described. A satisfactory haematological response was obtained in 49 of these cases, with a mean utilization of iron for haemoglobin synthesis in the non-pregnant group of 0.44 g. Hb % per 100 mg. of iron (1% Hb increase for 33 mg. of iron). In the pregnant group, apparent utilization was 0.33 g. Hb % per 100 mg. of iron (1% Hb increase for 41 mg. of iron).

With doses of 100 mg. of iron clinical toxicity was infrequent and mild in degree. There was no instance of thrombophlebitis or pain along the vein used for injection. No general reactions occurred among the pregnancy anaemias.

Indications for, and the administration of, parenteral iron are discussed.

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CYCLOPHOSPHAMIDE IN ADVANCED BREAST CANCER

A CLINICAL AND HAEMATOLOGICAL APPRAISAL

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Nitrogen mustard was introduced into the treatment of cancer in 1946, and its derivatives and allied compounds, the alkylating agents, still maintain a leading place in cancer chemotherapy. Their effect on the cell is both cytotoxic and nucleotoxic, vital enzymes in the synthesis of protein being blocked. The cytostatic activity of these compounds is probably due to the reactivity of the chloroethyl group attached to the nitrogen atom, and most of them are associated with high toxicity in the body.

In the development of these compounds, attempts have been made to widen the toxic-therapeutic ratio, and modifications of the basic compound have decreased the toxicity. Thus in nitrogen mustard oxide ("nitromin") and mannomustine ("degranol") there is a delayed activity of the functional group, and therefore a lower toxicity. The concomitant therapeutic results are, however, not outstanding. The ethylenimine compounds—for example, tretamine (triethylene melamine), thiotepa (triethylene thiophosphoramidate) and the ethylene-iminoquinone (E.39)—are very active cytotoxic agents but are at the same time very toxic to all elements of haemopoietic tissue. Watson and Turner (1959) suggested a possible modification of thiotepa toxicity by concomitant administration of androgens.

On the other hand, the haemopoietic toxicity of the group has indicated therapeutic usages. Thus, busulphan ("myleran") has a specific depressant effect on granulocytes, and is useful in the treatment of myeloid leukaemia. Again, chlorambucil ("leukeran") has a more specific effect on the lymphocytic series, and is useful in the treatment of lymphatic leukaemia and lymphosarcoma.

In 1957 a new nitrogen mustard derivative, cyclophosphamide ("endoxan"), was synthesized, and is claimed to be characterized by thrombocyte- and erythrocyte-sparing properties. This compound, possessing a cyclic phosphoramidate ester group, shows a remarkable contrast between a good curative effect on experimental tumours *in vivo* and a lack of effect *in vitro*, suggesting that it is converted to the active form only after entering the body (Brock and Wilmanns, 1958).

Clinical Report

Beginning in November, 1959, 43 patients with advanced cancer were treated by cyclophosphamide, using the intermittent massive-dose technique (Coggins *et al.*, 1959). The series included 27 cases of mammary carcinoma with measurable soft-tissue lesions.

Mammary carcinoma was specially selected for this study because, of all the solid tumours, cancers of the breast, ovary, and bronchus have in the past shown the most definite sensitivity to the administration of alkylating agents. In addition, skin manifestations are easily measured and evaluated in their response to chemotherapy. Available reports show no clinical trial of any dimensions using cyclophosphamide in breast carcinoma. The largest trials reported to date are those of Coggins *et al.* (1959), 10 cases (5 evaluable); Shnider *et al.* (1960), 13 cases; and Bergsagel and Levin (1960), 12 cases (6 evaluable).

The massive-dose technique of cyclophosphamide administration was chosen because, according to Brock and Wilmanns (1958), the therapeutic index of this compound for several experimental tumours in the rat favours its short-term administration. This index, which determines the possibility of permanent cure, is the ratio between the smallest lethal dose (LD₅) and the safe curative dose (CD₉₅). Its selection was further indicated by the observation of groups like Rundles *et al.* (1960) that patients on small maintenance dosage become cumulatively intolerant of its side-effects.

It is of interest that the tumour recovery rate of mammary carcinoma to x-ray irradiation favours short-term rather than long-term fractionation, and the action of the alkylating agents is in many ways radiomimetic. Finally, the platelet-sparing action of cyclophosphamide, suggested by the experimental reports, is confused in many clinical reports, as the compound has been used in fractionated dosage on patients with bone-marrow infiltration or damage. Used in a uniform series, the massive-dose technique, in our opinion, shows more clearly than a fractionated technique the platelet-sparing effect of cyclophosphamide.

Material

A series of 27 patients with *measurable* soft-tissue lesions from advanced breast carcinoma was observed. All showed progressive lesions. Each patient was given a single dose of 45–50 mg./kg. body weight of cyclophosphamide intravenously if there was no clinical evidence of liver or osseous metastases. In nine cases

where such metastases were present in addition to soft-tissue lesions the dose was reduced to 30–35 mg./kg. body weight. (The lower limit of each dose was given when the patient was thought to be overweight relative to her height and build.)

Anti-nausea drugs were given for at least 12 hours before and 12 hours after intravenous cyclophosphamide. In 10 cases where fluoxymesterone had been given for at least two months previously with no sign of control of advancing disease the androgen was continued, in an attempt to assess a possible effect in controlling haemopoietic depression. Pantothenic, nicotinic, or folic acid was given in a further six cases, with the same aim. None of these agents appeared to make any difference to the proportion of cases showing leucopenia, thrombocytopenia, vomiting, or alopecia.

Small-dose maintenance therapy of cyclophosphamide was not given, but a second massive dose was administered after six to eight weeks, at about two-thirds of the previous dosage, if transient response was noted and the patient's general condition was good.

Toxic Effects

Vomiting was noted in 21 of the 27 cases in spite of anti-nausea drugs. It was of a fairly severe nature in 13 of the 21 cases. Its onset was at 6–10 hours in the majority, and lasted about four to six hours. Dizziness immediately after the injection was noted in three cases, temporary sterile cystitis in one case, and diarrhoea in one case. In two cases with associated bone metastases aching in bones was noted at 24 hours after the injection.

Alopecia was the most troublesome side-effect. The hair began to fall out at about three to four weeks in all cases observed for that period of time. It progressed to 80% alopecia or more in 10 out of 23 cases, to 25–75% in eight cases, and to less than 20% in five cases. It is of interest that, according to Shnider *et al.* (1960), the incidence of alopecia is 45% for weekly doses over 15 mg./kg. but only 6% for lower fractions. Alopecia was maximal at two months, and hair began to grow again at three months in all cases surviving. A second massive dose within two months caused no further alopecia, but in one case, where a third dose was given after five months, a further loss of hair occurred.

Effect on Haemopoiesis

In the chemotherapy of solid malignant tumours to date, a degree of damage to haemopoietic tissue has been accepted as a justifiable risk. The line separating good clinical response from severe marrow damage is, however, fine, and granulopenia, lymphopenia, gross anaemia, and thrombocytopenia are regularly encountered. Whereas the first three of these can be counteracted by the use of haematinics, blood transfusions, and antibiotic cover, the last has sometimes led, in our experience, to intractable haemorrhages. These cannot be controlled by the use of A.C.T.H., cortisone, vitamin K, vitamin B₁₂, vitamin C, folic acid, stilboestrol, testosterone, or any other of the measures recommended, except repeated whole-blood transfusions.

Haemoglobin, leucocyte (total and differential), and thrombocyte estimations were carried out in this series two or three times weekly. The white-cell count fell to below 1,000/c.mm. in 11 out of the 15 surviving cases given 45–50 mg./kg. (Fig. 1). This fall occurred

in a very predictable manner between the seventh and thirteenth days, and in all cases began to recover within a few days, and returned to normal in the fourth week. Of the cases given 30–35 mg./kg. because of the likelihood of a damaged marrow, again the white-cell count fell below 1,000/c.mm. in 10 out of 14 cases (Fig. 2). Recovery in these cases may have been a little slower, but again was complete within four weeks of the injection. Of the 29 observations, 12 showed a minimum white-cell level below 500/c.mm., but since counts were not carried out daily this would be a conservative estimate. Antibiotics were not given during the period of leucopenia and no intercurrent infection manifested.

There is a relative lymphopenia in the first week after the injection, and a relative granulopenia in the second and third weeks, by which time the lymphocyte level had almost recovered. There is an average fall of 10% in the haemoglobin level.

The platelet count remained practically unchanged in 13 out of the 29 cases graphed (Figs. 3 and 4). In eight cases there was a slight reduction in its level (100,000–150,000), in two there was a moderate reduction (50,000–100,000), and in only four of the 29 was there

a marked reduction in the level (below 50,000). This is in contrast with the marked fall in white-cell count to below 1,000/c.mm. seen in 21 of the 29 cases. The lowest platelet levels were recorded between the seventh and thirteenth days, as for the leucocyte levels.

Comparison with Thiotepa

It was thought to be of interest to compare the haematological effects with those of short intensive thiotepa administration. In Figs. 5 and 6 are depicted the fall in white-cell count and platelet levels in nine patients with soft-tissue metastases from breast carcinoma given a short course of thiotepa. Between 2 and 3 mg./kg. was given in 8–14 days. Androgens were given concomitantly in all cases (Watson and Turner, 1959), in the form of fluoxymesterone 30 mg. daily, as suggested by Holden and Sundstrup (1959). Whereas the lowest levels in the leucocyte count in the thiotepa series occurred after the twenty-fifth day, and persisted for 14 days (Fig. 5), in the case of cyclophosphamide the low levels occurred after the seventh day, and persisted for only seven days (Figs. 1 and 2). At corresponding time periods the platelet level in the thiotepa series was greatly depressed in the majority (Fig. 6), but in the cyclophosphamide series there was much less depression (Figs. 3 and 4).

FIG. 1.—White-cell count in 15 patients with breast cancer with no evidence of osseous or hepatic metastases. Single dose of 45–50 mg. of cyclophosphamide per kg. body weight. (⊗ = Concomitant androgens.) Lowest W.C.C. >1,000 in four cases and <1,000 in 11 cases.

FIG. 2.—White-cell count in seven patients with osseous or hepatic metastases, and seven patients receiving second massive dose of cyclophosphamide six to eight weeks after first. Both groups received single dose of 30–35 mg. of cyclophosphamide per kg. (⊗ = Second group.) Lowest W.C.C. >1,000 in four cases and <1,000 in 10 cases.

FIG. 3.—Blood-platelet levels in 15 patients with no evidence of osseous or hepatic metastases. Single dose of 45–50 mg. of cyclophosphamide per kg. (⊗ = Concomitant androgens.) Unchanged in six cases, slight reduction in four cases, moderate reduction in two, and marked reduction in one case.

FIG. 4.—Blood-platelet levels in seven patients with osseous or hepatic metastases, and seven patients receiving second massive dose of cyclophosphamide six to eight weeks after first. Both groups received single dose of 30–35 mg. of cyclophosphamide per kg. (⊗ = Second group.) Unchanged in seven cases, slight reduction in four, and marked reduction in three.

The difference between the two drugs in the time-lag between administration and the maximum haemopoietic depression can be explained in two possible ways. Firstly, that the effect of thiotepea on the marrow is delayed. This is unlikely in view of the rapid fixing in the tissues that occurs after intravenous thiotepea administration (Mellett and Woods, 1960). The alternative explanation is that the damage exerted by the agents occurs immediately after the injection, and therefore injures only one stage of developing cell in the marrow (Nissen-Meyer and Höst, 1960). In the case of cyclophosphamide, the vulnerable stage is about two weeks older than the stage vulnerable to thiotepea; therefore the depression in the blood picture appears two weeks earlier. Nissen-Meyer and Höst suggest that the older megakaryocyte may be less vulnerable to cyclophosphamide than the granulocyte, possibly because of lesser enzyme activity. The damage to the marrow is thus more transient, and repeated heavy dosage is possible at intervals of three to four weeks.

Clinical Response

Of the 27 patients under review, three died of metastases within nine days and one was lost to follow-up. Three other cases are excluded from assessment because concomitant steroid therapy was given at the same time as cyclophosphamide.

There was objective tumour regression of growth in 7 of the 20 evaluable cases. In addition, three cases

FIG. 5.—White-cell count in nine cases with breast carcinoma given thiotepea 2–3 mg./kg. in 8–14 days. (Concomitant androgens in all cases.) O = Osseous or hepatic metastases present.

FIG. 6.—Blood-platelet level in nine cases with breast carcinoma given thiotepea 2–3 mg./kg. in 8–14 days. (Concomitant androgens in all cases.) O = Osseous or hepatic metastases present.

showed transient regression of growth, confirmed clinically by two observers. In 10 cases no regression of growth was seen.

Eight patients had bone metastases, the response of which was evaluable in four. Of these, three noted definite relief from pain.

Both subjective and objective control were limited to approximately two months in all cases. New metastases or a recurrence of activity appeared at that time. A second dose was given to the seven cases responding, but control was achieved for a further similar period in only three of them.

Summary

27 cases of advanced breast cancer, with measurable soft-tissue metastases, were treated by a single massive dose of cyclophosphamide. Dosage was 45–50 mg./kg. body weight if the marrow was thought to be intact.

Objective regression was seen in 7 out of 20 assessable cases. In a further three cases transient changes were noted, of a degree which was not demonstrable in a photograph. In only one case could the response be described as excellent, and in all cases control lasted for a maximum of two months only. In half the cases where the dose was repeated a further short benefit was obtained.

With this dose regime there is a remarkably predictable depression in the leucocyte level in the second week after injection. A relatively less depressing effect on the platelet level distinguishes cyclophosphamide from the other alkylating agents in general use, and a possible explanation is discussed. Graphs of the haemopoietic depression after a short course of thiotepea are shown to illustrate this point.

Alopecia developed in all cases surviving one month or more. This is a very real disadvantage of the massive-dose technique, and will discourage its extensive use, unless greater prolongation of remissions can justify it.

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The number of "foreign body" cases [submitted for testing by the public] appears to be increasing, possibly because higher standards of hygiene are now demanded by the public. Mould was confirmed in sausages, apple pie, and lemon barley water, and a fragment of glass in a jar of mincemeat. A can of strawberries contained brush bristles and had been overheated, thus reducing this delicate fruit to a "mush." Granulated sugar contained a number of human hairs, and some shelled peanuts were obviously from the bottom of a sack, as husks, dirt, and sacking fibres were present in abundance. Four specimens of bread contained sooty matter, machinery grease, a branny pellet, and a feather fragment respectively. (*Report for the First Quarter, 1961, City of Birmingham Analyst.*)