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TOTAL THORACIC SUPERVOLTAGE IRRADIATION FOLLOWED BY THE INTRAVENOUS INFUSION OF STORED AUTOGENOUS MARROW

BY

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The inevitable result of large-volume high-dosage radiotherapy is damage to bone marrow and a subsequent lowering of the circulating blood elements. This factor, combined with the adverse constitutional effects on the patient, has undoubtedly prevented the full exploitation of radiation in the disseminated radiosensitive tumours.

Many workers have described the severe and sometimes permanently damaging effects to marrow that can follow from a dosage of radiation well below that used by the radiotherapist in the treatment of cancer. Stewart (1958), in a study of 126 patients with ankylosing spondylitis, comments that 2,000 r may render the bone marrow hypoplastic for years and that after 4,000 r there is no recovery in 50% even after several years. This substantiates the observation of Humble (1948), who has shown the profound effect on cellularity which can accrue from moderate dosage radiotherapy (Table I).

Kurnick *et al.* (1958) described the use of stored autogenous marrow to combat the haemopoietic depression which followed multiportal techniques when giving 400 kV *x*-ray therapy to approximately 2,000 r tissue dose over a total period of two months in a patient with a disseminated testicular tumour. They were able on two quite distinct occasions to restore to more normal limits severely depressed peripheral blood-cell counts. A further patient with renal carcinoma was given 700 r centre dose to the torso in 10 days, presumably at the same kilovoltage as the first patient. Here no benefit followed the bone-marrow infusion. Both their patients died—the first four months after the initial marrow infusion, and the second 10 days after the injection of bone marrow. This valuable work demonstrated clearly the ability of the body to reaccept stored autogenous marrow even though the therapeutic effect of the radiation was disappointing.

TABLE I.—*Effect of Direct X-irradiation on Sternal Marrow After 2,000 r in 22 Days*

	Before Irradiation	After Irradiation
Total nucleated count	56,000 per c.mm.	9,200 per c.mm.
Myeloblasts	0·4%	0·0%
Promyelocytes	1·8%	0·0%
Myelocytes, neutrophil	11·2%	0·2%
Metamyelocytes ,,	0·0%	0·2%
Polymorphs, ,,	41·0%	72·4%
Myelocytes, eosinophil	2·4%	0·0%
Polymorphs, ,,	1·8%	0·6%
Myelocytes, basophil	0·2%	0·0%
Polymorphs, ,,	0·0%	1·2%
Proerythroblasts	0·2%	0·0%
Normoblasts, early	3·6%	0·0%
,, intermediate	11·0%	0·0%
,, late	3·4%	0·0%
Lymphocytes	19·6%	12·4%
Monocytes	2·8%	12·4%
Plasma cells	0·4%	0·6%
Reticulum cells	0·0%	0·0%
Macrophages	0·0%	0·0%
Megakaryocytes	0·2%	0·0%
Myeloid/erythroblast ratio	3 23 : 1	—

Note the almost complete aplasia of the second specimen.

It was decided to treat the entire thorax of selected patients with multiple pulmonary metastases by means of the 2 MeV Van de Graaff generator. This apparatus has certain advantages, as described below, when compared with more conventional machines. It was anticipated that the treatment of such large volumes of tissue, apart from the haematological effects, must inevitably result in considerable constitutional disturbance with much nausea, vomiting, and distress. Therefore it was decided to shorten the overall treatment time in an attempt to obtain a uniform dose of 3,000 r in two weeks. This programme has now been carried out in two cases. Somewhat to our surprise, it was found that one (Case 2) of the two patients tolerated this course of treatment with virtually no constitutional disturbance whatsoever. This does not, of course, refer to the haematological response which is mentioned in the description of the individual cases.

Case 1

A woman aged 22 was referred to Sir Stanford Cade on February 13, 1957, with pain in the right wrist of three or four weeks' duration. She was found to have a highly vascular bone lesion at the lower end of the right ulna, which on clinical and radiographic grounds was thought to be an osteogenic sarcoma. In view of the vascularity, biopsy was not done. Treatment was given by means of 2 MeV *x* rays from February 19 to April 15 to a maximum tumour dose of 7,000 r. This resulted in complete relief of pain and marked recalcification of the tumour. The patient remained well until she attended the hospital on September 10, 1958, complaining of dyspnoea and loss of

2 stone (12.7 kg.) in weight. Radiographs of the chest at this time showed the presence of multiple metastases in the left lung, with the appearance of a large effusion on the right side with a considerable deposit above it. The right ulna itself remained entirely symptomless and good recalcification was seen to have taken place.

On September 22 a light general anaesthetic was given and marrow was aspirated from both iliac crests and the sternum, approximately 1.1×10^9 cells being obtained. This was frozen and stored at $-79°$ C. as described below.

On September 23 treatment to the entire thorax was begun.

Details of Radiotherapy

September 23 to October 7, 1958. Period of treatment, 2 weeks: 2 MeV *x* rays. F.S.D. 122 cm. Two opposing fields, each 25×30 cm. approx.

First five days with 2 MeV *x* rays	Skin dose	= 1,199 r
	Maximum tumour dose	= 1,102 r
	Minimum tumour dose	= 946 r
Next four days with 2 MeV *x* rays	Skin dose	= 2,399 r
	Maximum tumour dose	= 2,202 r
	Minimum tumour dose	= 1,890 r

Picker *x*-ray set 250 kV *x* rays. H.V.L. 3.4 mm. Cu. F.S.D. 75 cm. Two opposing fields, each 25×30 cm.

Final 2 days 250 kV *x* rays	Skin dose	= 2,999 r	Final total dose in röntgens
	Maximum tumour dose	= 2,708 r	
	Minimum tumour dose	= 2,250 r	

These are equivalent to absorbed doses:

Total skin dose	= 2,920 rads
Maximum total soft tissue dose	= 2,637 rads; maximum total "average bone dose"=2,533 rads
Minimum total soft tissue dose	= 2,191 rads; minimum total "average bone dose"=2,083 rads
Estimated integral dose	= 39.4 megagram-röntgens.

Five days after the start of *x*-ray therapy the patient complained of generalized pain in the chest, both anteriorly and posteriorly, characterized by tenderness of the ribs and sternum and accompanied by rise in temperature and pulse rate. Within three days the pain had gone, but it returned on the day of completing treatment. On this occasion she was obviously distressed and unwell, and by the next day was cyanosed. On October 9 her stored marrow was thawed and infused intravenously, the whole procedure taking one and a half hours. Over the next two days the general condition improved markedly and she was discharged from hospital on October 22. Two days before, during, and after the *x*-ray therapy the following medicaments were prescribed daily: prednisone 20 mg. and vitamin K 100 mg. daily, and perphenazine 4 mg. t.d.s.

Haematological Findings.—Fig. 1 shows that after the marrow infusion there was an immediate rise in the total circulating white cells. This rise is not readily accounted for on a basis of marrow repopulation, nor was it merely due to cessation of *x*-ray therapy. The most readily acceptable explanation lies in postulating a non-cellular humoral factor in the marrow injection which has the property of almost immediately stimulating haematopoiesis in the bone marrow undamaged by irradiation. This is borne out by the observation of Kurnick *et al.* (1958), who demonstrated by means of serial marrow punctures that haematopoietic foci only became evident two weeks after the infusion of marrow.

It is well seen in Table II that there is considerable evidence of marrow regeneration 13 days after the marrow infusion.

Progress.—The patient, on completion of treatment on October 7, soon began to feel much better, so much so that by October 22 she insisted on returning to her home in Ireland and was not seen at the Westminster Hospital until November 19, when she complained of a severe dry cough. By December 10 this cough began to be accompanied by dyspnoea, which became progressive and necessitated her readmission on December 15. The respiratory distress became more severe with persistent cyanosis. The patient became progressively weaker and died on December 23. Radiographs of the chest had shown no regression of the metastatic malignant disease nor indeed any progression. Permission for a post-mortem examination was not obtained.

TABLE II.—*Bone-marrow Differentials in Case* 1

	Before Irradiation	14 Days after Completing Irradiation	8 Weeks after Completing Irradiation
Date	16/9/58	21/10/58	5/12/58
Total nucleated count	50,000 c.mm.	22,000 c.mm.	41,000/c.mm.
Myeloblasts	1·6%	0·0%	0·6%
Promyelocytes	1·6%	0·2%	2·4%
Myelocytes, neutrophil	9·4%	2·4%	13·2%
Metamyelocytes, ,,	7·8%	1·6%	8·4%
Polymorphs, ,,	34·2%	52·4%	47·6%
Myelocytes, eosinophil	0·6%	0·0%	0·2%
Polymorphs, ,,	2·4%	0·4%	0·8%
Myelocytes, basophil	0·0%	0·0%	0·0%
Polymorphs, ,,	0·0%	0·2%	0·2%
Proerythroblasts	0·2%	0·4%	0·4%
Normoblasts, early	9·6%	11·0%	7·8%
,, intermediate	6·2%	7·2%	5·2%
,, late	0·0%	0·0%	0·0%
Lymphocytes	16·6%	8·8%	5·0%
Monocytes	8·2%	11·4%	7·4%
Plasma cells	0·4%	1·0%	0·4%
Reticulum cells	0·8%	1·4%	0·0%
Macrophages	0·4%	1·6%	0·2%
Megakaryocytes	0·0%	0·0%	0·2%
Myeloid/erythroblast ratio	3·6: 1	3·07: 1	5·65: 1

Case 2

A young woman aged 21 was referred to Sir Stanford Cade on October 20, 1956, and treated by 2 MeV *x* rays to 5,500 r for a Ewing's tumour of the left ischium. Following this treatment she remained well until July 2, 1958, when a routine radiograph of the chest revealed multiple small bilateral pulmonary metastases. In spite of the administration of chlorambucil ("leukeran"), 7 mg.

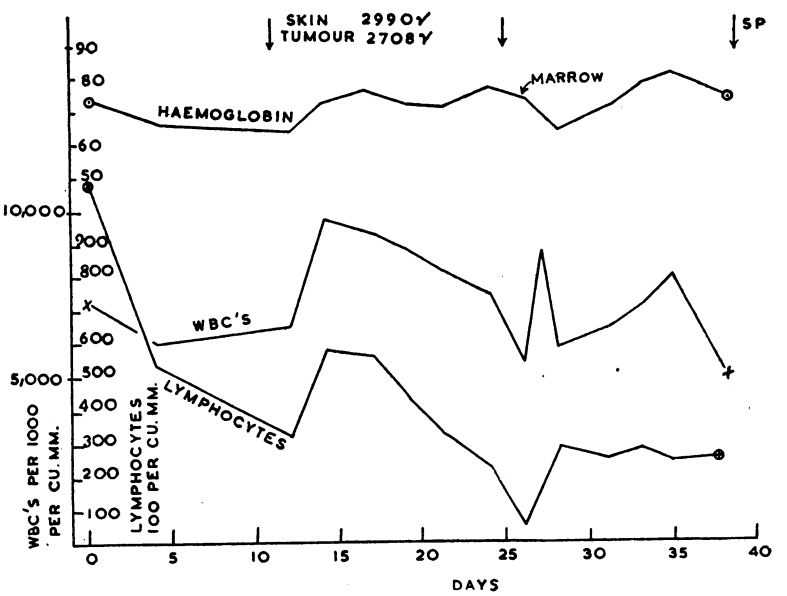

FIG. 1.—Case 1. Haematological findings.

daily, these metastases steadily increased in size. It was therefore decided to treat the entire thorax contents as in the previous patient.

On October 23 marrow was aspirated under general anaesthesia from the right iliac crest spines of the lumbar vertebrae and sternum, a total of approximately 0.75×10^9 cells being obtained. The marrow was then frozen and stored.

On October 24 treatment to the entire thorax was started.

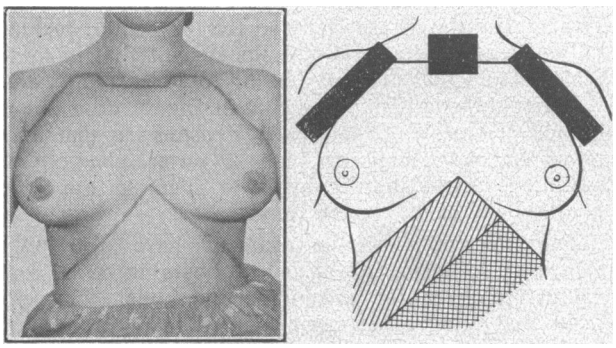

FIG. 2.—Method of delineating the field.

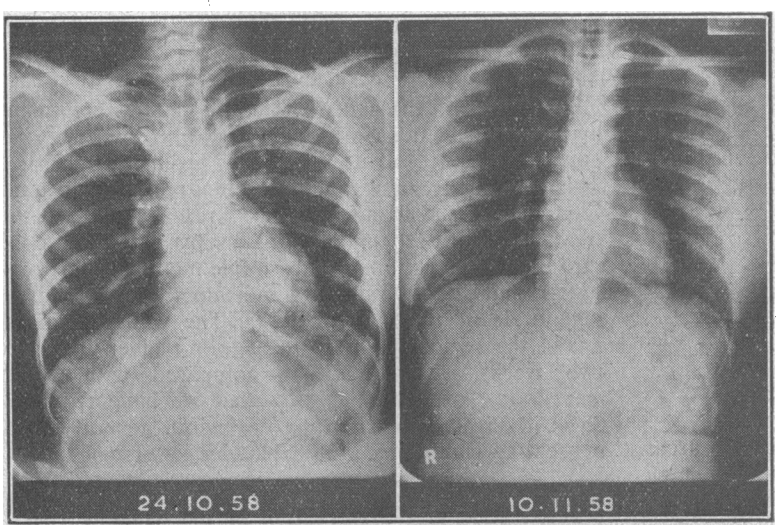

FIG. 3.—Case 2. Showing rapid effect on pulmonary metastases.

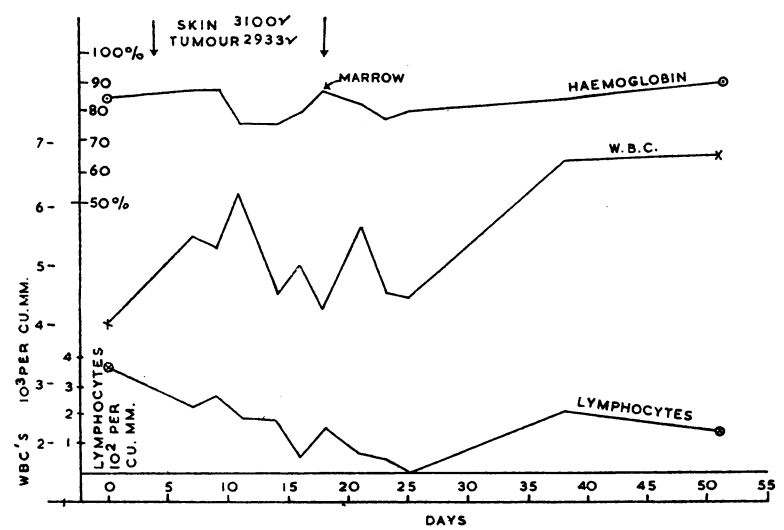

FIG. 4.—Case 2. Haematological findings.

Details of Radiotherapy

October 24 to November 7, 1958. Period of treatment, 2 weeks. All with 2 MeV *x* rays. F.S.D. 122 cm. Two opposing fields, each 26×31 cm. approx.

Total skin dose	=	3,100 r
Total maximum tumour dose	=	2,933 r
Total minimum tumour dose	=	2,518 r

These are equivalent to absorbed doses:

Total skin dose ..	=	3,023 rads
Maximum total soft tissue dose ..	=	2,860 rads; maximum total "average bone dose"=2,552 rads
Minimum total soft tissue dose ..	=	2,455 rads; minimum total "average bone dose"=2,191 rads
Estimated integral dose	=	45.3 megagram-röntgens.

As in the previous patient, prednisone 20 mg., vitamin K 100 mg. daily, and perphenazine 4 mg. t.d.s. were prescribed as before, during and after treatment.

The method of delineating the field by means of lead blocks is shown in Fig. 2.

Throughout the two-weeks course of treatment this patient insisted that she felt well in every way and ate with good appetite. On November 7 the marrow was thawed and reinjected intravenously as described below, the whole procedure taking one and a half hours and being quite free of untoward effects.

The effect on the pulmonary metastases was rapid (Fig. 3).

Haematological Findings.—Fig. 4 shows a rapid rise in the total white-cell count following the injection of marrow.

The sequence of events is represented diagrammatically in Fig. 5.

Table III demonstrates one month after the marrow infusion that regeneration is taking place.

At the time of writing this patient was well; her only complaint was a dry cough, but the chest radiographs remained entirely clear of any suspicion of recurrent malignant disease.

Physical Aspects of the Radiotherapy

Two-million-volt *x* rays (H.V.L. 7.4 mm. Pb) from a Van de Graaff electrostatic generator (Wilson and Perry, 1952) were chosen for treating these patients for a number of reasons. The apparatus provides large fields of penetrating radiation such that by means of an opposing field-treatment technique it is possible to obtain fairly good dosage homogeneity throughout thick masses of tissue. It also provides dose rates great enough to enable treatments to occupy a reasonable time even at quite large F.S.D.s. The differential *x*-ray absorption in bone and soft tissue is relatively small, so that differences between the energy absorbed in bone and soft tissue are minimal.

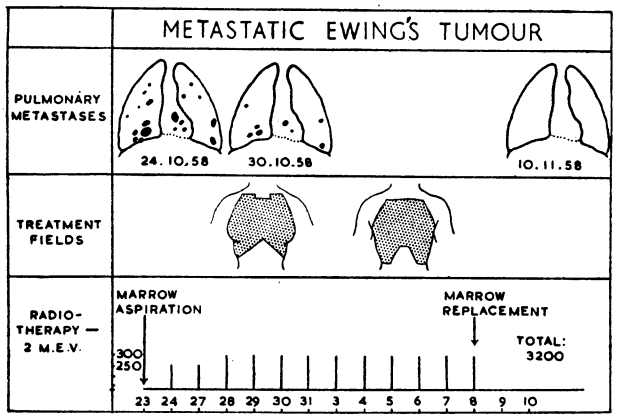

FIG. 5.—Case 2. Sequence of events.

TABLE III.—*Bone-marrow Differentials in Case 2*

	Prior to Irradiation	1 Month after Marrow Infusion
Date	21/10/58	10/12.58
Total nucleated count	130,000/c.mm.	31,000/c.mm.
Myeloblasts	2·2%	0·2%
Promyelocytes	6·4%	1·2%
Myelocytes, neutrophil	22·8%	23·0%
Metamyelocytes, ,,	8·4%	7·8%
Polymorphs, ,,	20·6%	31·2%
Myelocytes, eosinophil	2·8%	0·4%
Polymorphs, ,,	3·8%	0·2%
Myelocytes, basophil	0·0%	0·2%
Polymorphs, ,,	0·2%	0·6%
Proerythroblasts	0·4%	1·4%
Normoblasts, early	10·6%	8·2%
,, intermediate	8·0%	10·4%
,, late	0·0%	0·0%
Lymphocytes	8·0%	5·8%
Monocytes	4·0%	7·0%
Plasma cells	0·6%	1·2%
Reticulum cells	0·2%	1·2%
Macrophages	0·4%	0·0%
Megakaryocytes	0·6%	0·0%
Myeloid/erythroblast ratio	2·1: 1	3·57: 1

The treatments necessitated irradiation of large areas, and in order to do this with the least ambiguity a single field to cover the whole area is normally preferred. Therefore, in order to obtain a sufficiently large field area, it was usually necessary to treat at an F.S.D. of more than 100 cm. Our standard depth-dose data for this radiation (Wilson and Perry, 1952) were measured for 100 cm. F.S.D., so that it was necessary to extrapolate these in order to assess the depth doses for the conditions used. In practice the fields used were not regular geometrical shapes. They were shaped so as to delineate the boundaries of the lung fields and afford protection so far as was possible to adjacent structures by means of lead bricks 1½ in. (3.8 cm.) thick (permitting only about 3% transmission), which were simply and easily mounted on a platform attached to the machine and situated between the patient and the adjustable diaphragm. To facilitate this the patients were treated lying down with the beam directed vertically downwards. The treatment comprised anterior and posterior fields, both being applied at each treatment session.

The dose values quoted previously for individual patients are all based on water phantom measurements. The skin dose is the dose 4 mm. beneath the skin surface where electronic equilibrium is established. The maximum tumour dose is the greatest dose estimated to have been received by the tumour-bearing area, and the minimum tumour dose is the smallest dose estimated to have been received by the same area. In deriving the latter the fall in dose towards the edge of a beam has been taken into account. The three dose values taken together indicate the degree of dose homogeneity that was obtained throughout the treated volume. In fact, of course, because chiefly lung tissue is irradiated, the true dose values may be somewhat different from those calculated in this way. The work of Burlin (1957) with cobalt-60 gamma rays shows that the true values will be greater, and this is especially so for the central regions of the treated tissue. His results suggest that in these regions the actual dose may be up to 20% greater, and this should be borne in mind considering the dose values quoted previously. The greater transmission that lung tissue has as compared with a water phantom is advantageous in that it helps to increase the dose homogeneity in the treated tissue.

The incident doses in röntgens have also been expressed in terms of absorbed doses in rads, and values are given for soft tissue and bone. For soft tissue one röntgen has been equated to 0.975 rad for 2 MeV *x* rays and 0.968 rad for 250 kV *x* rays. For bone it is more difficult to be definite, so that values have been assumed which correspond to average for bone as interpreted by Spiers (1951). These are 0.870 rad per röntgen for 2 MeV *x* rays and 1.22 rads per röntgen for 250 kV *x* rays.

In relation to the general toleration of the treatment by the patient it seemed of interest to evaluate the approximate integral dose that was given in each case. This was done by evaluating the approximate total volume of tissue irradiated (field area × thickness of treated tissue) and multiplying this by the mean dose throughout the volume. This simple method is not very precise but should suffice to indicate the approximate magnitude of the integral dose. The values obtained are in the region of 40–50 megagram-r given in about two weeks. This may be compared with 20–30 megagram-r of 2 MeV *x* rays that we have regularly given in 35–50 days without any obvious general effects in treating carcinoma of the bladder.

Preparation and Preservation of the Marrow Cell Suspension

Marrow is obtained by aspiration from multiple punctures of the anterior and posterior iliac crests, lumbar vertebral spines, and sternum (Humble and Newton, 1958) under a general anaesthetic. Normally 30–60 ml. of marrow is aspirated in this manner, yielding a total of $0.5–1.5 \times 10^9$ nucleated cells.

The aspirated marrow is delivered under strictly aseptic conditions into McCartney bottles containing 10 ml. of a cell suspension medium composed of Hanks's balanced salt solution (Hanks and Wallace, 1949) with 10% inactivated human AB serum, 0.1% Bacto yeast extract (" difco "), 0.25% glucose, penicillin (100 u./ml.), streptomycin (0.1 mg./ml.), and heparin (2.5 mg./ml.). The suspension is then sieved by a modification of Thomas's (1955) method. In our technique the suspension is passed 20 times through a coarse stainless-steel mesh (40 strands per inch) followed by 10 passages through a finer mesh (200 strands per inch). A micro-filter syringe supplied by R. B. Turner and Co. is used for this purpose, steel mesh supplied by Messrs. Johnson Matthey being inserted between the rubber washer and the perforated screen at the end of the

syringe. The marrow suspension is now centrifuged at 200 *g* for 20 minutes. The fat and supernatant fluid are aspirated using a 17-gauge blunt needle attached to a filter pump, as it is possible by this method to remove the entire disk of fat in one piece.

The sedimented cells are resuspended in 10 ml. of the cell-suspension medium and transferred through the fine stainless-steel mesh into an equal volume of cell-suspension medium containing 30% "analar" glycerol, a small portion being retained for a nucleated cell count. Thus the final glycerol concentration is 15% v/v. After equilibration for 10 minutes the suspension is sealed in 7-ml. aliquots in glass ampoules, and cooled at 1° C. per minute to −15° C. and thereafter at a rate not exceeding 10° C. per minute to −79° C. as described by Barnes and Loutit (1955). Originally we attempted to use the apparatus of Polge and Lovelock (1952), but, like Barnes and Loutit (1955), we found that our model failed to produce the desired characteristics, and we have now developed a simple apparatus capable of producing automatically a wide range of two-stage cooling curves. Details of this apparatus will be published elsewhere. The frozen marrow is stored in Dewar flasks containing methylated spirit and solid carbon dioxide, the flasks themselves being kept in an insulated cabinet packed with solid carbon dioxide (Polge and Lovelock, 1952).

When required, the marrow cells are reconstituted by the method of Sloviter (1956) as modified by Ferrebee *et al.* (1957). In this procedure, which is designed to reduce the osmotic trauma to the cells, the ampoules are rapidly thawed in a water-bath at 38° C. and immediately added to 3.5 ml. of Hanks's balanced salt solution (Hanks and Wallace, 1949) to which has been added 35 g. of glucose per 100 ml. After two minutes 7 ml. of the basic cell suspension without heparin is added, and mixed well. This is repeated after a further two minutes. We have found the marrow reconstituted in this manner to be rather unstable, and we therefore administer it within five minutes of the final dilution.

Discussion

Large-volume high dosage radiotherapy is justified in the treatment of cancer should it be thought possible to eradicate even though temporarily disseminated disease. That it is possible to destroy permanently metastatic disease in a radiosensitive tumour at a dose level in the order of 3,000 r is clearly shown by Prossor (1959), who gives a 10-year survival figure of 15% in those patients who presented with glandular metastases from testicular tumours.

It would seem at first sight that the use of stored autogenous marrow is contraindicated should a diagnostic marrow puncture reveal the presence of malignant cells. This may certainly be true, but it is worth pointing out that the marrow is reinfused intravenously, and it is accepted that the percentage of circulating malignant cells in the blood which actually form metastases is extremely small (Roberts *et al.*, 1958).

The whole premise for the use of stored autogenous marrow is the known damage which results following the application of radiation to large areas of marrow-containing spaces. The ability of the body to accept autologous grafts is well known, and there is good evidence that this applies to bone marrow itself (Kurnick *et al.*, 1958).

It is desirable that irradiation to large volumes should be accomplished with minimal upset to the patient. That this is possible is shown by our second patient, who experienced no immediate untoward side-effects whatsoever directly attributable to the irradiation.

The severe dyspnoea and respiratory symptoms which followed the radiotherapy to the first patient may possibly have been due to progress of the metastatic disease and/or diffuse parenchymatous pulmonary fibrosis. It was not possible to obtain permission for a post-mortem examination.

Possible Future Applications

(1) The immediate prospect is an extension of the treatment volumes. There would seem to be no good reason why considerably larger volumes should not be treated. It is recognized that individual organs—for example, the kidney (Paterson, 1952)—are unable to withstand homogeneous irradiation in excess of 2,000 r in five weeks or less. Nevertheless it is possible to shield such organs and lessen the given irradiation dose.

(2) It is now clear that the entire thorax can be irradiated to 3,000 r in two weeks with no constitutional disturbance.

(3) The more widespread the metastatic disease the greater would be the indication for chemotherapy. In the later stages of the radio-sensitive tumours it is not uncommon for the patient to develop widespread cutaneous and other metastases. Technically it is difficult to give total body irradiation, and in these cases a reasonable alternative would be the use of massive chemotherapy provided that stored autogenous marrow is used to restore the cellularity of the bone marrow itself. This massive quick chemotherapy has already been done with marrow replacement, and will be the subject of a separate report.

Summary

Total thoracic supervoltage radiation to 3,000 r tissue dose in two weeks has been given to two patients with metastatic pulmonary disease. An attempt has been made to combat the haematological depression by the used of stored autogenous marrow.

We gratefully acknowledge the constant encouragement and interest shown by Sir Stanford Cade in this work and his ready permission to use his cases. We also acknowledge our indebtedness to Dr. Sidney Farber, of the Children's Hospital, Boston, U.S.A., for the method of charting Case 2. We thank Miss P. Wheatley and Miss B. Hedley-Prole for their help in the preparation of the manuscript, and Dr. Peter Hansell for the photographic illustrations.

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