

# The absorbed dose to bone marrow in the treatment of polycythaemia by $^{32}\text{P}$

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Human Studies Project

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## ABSTRACT

This paper reports the determination of absorbed dose to bone marrow in the treatment of polycythaemia by  $^{32}\text{P}$ , based on the measurement of activities in bone and marrow biopsies taken at various times from 1 to 27 days after injection of the radionuclide. Activities were measured in the cortex, trabeculation and marrow of biopsies taken from the iliac crest, and also in sternal marrow. The biological half-life of  $^{32}\text{P}$  in marrow from the iliac crest was found to be nine days; that derived for sternal marrow was lower, but the difference was not statistically significant; the value for trabecular bone was 27 days. The biological half life for  $^{32}\text{P}$  in the body, as measured by whole-body counting, was 39 days. Calculations of the dose-rate to trabecular marrow have been made by a method based on that of Whitwell and Spiers (1971), but modified to allow for the presence of  $^{32}\text{P}$  in the marrow as well as in trabecular bone. The dose-rates follow a single exponential decay with a half-life of 6.7 days. The integrated dose including that during the first day is 24 rad per mCi injected.

The use of radioactive phosphorus,  $^{32}\text{P}$ , as a treatment of primary polycythaemia has been widely adopted since the method was first introduced by Lawrence in 1939 (Lawrence, 1940). Methods for determining the therapeutic dose (in mCi) have varied, but in general they have been empirical and based on the observed clinical response of the red-cell volume (RCV). One method, widely used, has been to give repeated small doses until the desired reduction in RCV is achieved (Reinhard *et al.*, 1946; Lawrence, 1955); another, to give single large doses adjusted according to the patient's weight (Abbatt *et al.*, 1954; Harman, Hart and Ledlie, 1955). A further refinement was introduced by Hume, Cowell and Goldberg (1966), who observed that the fall in RCV was linearly related to the radioactivity given, irrespective of weight, over quite a wide dose range. They were able to use an experimentally-obtained regression line to predict the therapy dose required to reduce the RCV to normal in a given patient provided that his actual and (predicted) normal RCV were known. However, in about 15 per cent of the cases the expected result was not achieved.

Such methods have been evolved largely because little data exists upon which a more fundamental

approach, based on radiation dose and biological effectiveness, could be made. Osgood (1965) has compared the effectiveness of intravenous injections of  $^{32}\text{P}$  with that of total body irradiation by X rays in the treatment of chronic granulocytic and lymphocytic leukaemias. Calculations of the dose to bone marrow following intravenous administration of  $^{32}\text{P}$  have also been made by Seltzer, Kereiakes and Saenger (1964) and by Mays (1973). Low-Ber, Blais and Scofield (1952) produced a dosage scheme based on the assumption that the concentration of  $^{32}\text{P}$ , three days after injection, was up to ten times greater in those tissues most avid for phosphorus (bone, liver and spleen), but did not consider whether differences existed in the doses received by these individual tissues. In the present paper the dose to marrow in trabecular bone is determined from contributions by  $^{32}\text{P}$  in the marrow itself, in the trabecular bone and in the cortical bone surrounding the trabeculation. Some dose estimates are also made for haemopoietic tissues in other sites.

The determination of the dose-rate to bone marrow is based on the measurement of  $^{32}\text{P}$  activity in the bone and marrow of bone biopsies taken at different times after administration of the isotope, followed by dose calculation using methods developed recently (Spiers, 1969; Whitwell and Spiers, 1971; 1975). More realistic dose data are thereby obtained, and these are discussed in the light of earlier estimations.

## EXPERIMENTAL PROCEDURES

The subjects were nine patients with primary polycythaemia, clinical details of whom are given in Table I. Four had previously been treated with  $^{32}\text{P}$ ; the remainder were new, untreated patients. The object of the investigation was explained to each patient and each agreed to take part. The standard procedure adopted was as follows.

Initially red-cell and plasma volumes were measured for each patient by standard techniques,

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TABLE I  
CLINICAL DETAILS OF THE PATIENTS

Patient	●	●	●	●	●	●	●	●	●
Sex	M	M	F	M	F	M	F	M	M
Age (years)	59	55	67	68	62	48	65	76	46
Weight (kg)	78.0	81.7	69.9	61.9	69.9	64.2	62.0	49.7	77.0
Haemoglobin (gdl <sup>-1</sup> )	20.8	22.7	22.8	19.2	14.0	14.1	17.8	14.4	24.0
Red-cell count × 10 <sup>12</sup> (l <sup>-1</sup> )	7.6	7.4	7.8	8.8	4.6	6.0	5.8	7.2	6.6
Platelets count × 10 <sup>9</sup> (l <sup>-1</sup> )	750	525	258	303	415	600	228	280	180
White-cell count × 10 <sup>9</sup> (l <sup>-1</sup> )	36.2	10.8	8.9	17.7	27	11.3	6.2	7.0	16.0
Blood volume/bodyweight (ml kg <sup>-1</sup> )	111.3	106.9	83.1	107.5	76.0	84.2	81.9	119.3	71.2
Plasma volume/bodyweight (ml kg <sup>-1</sup> )	45.8	38.3	29.7	43.5	47.6	49.2	41.7	61.2	30.1
Red cell volume/bodyweight (ml kg <sup>-1</sup> )	65.5	68.6	53.4	64.0	28.5	35.0	40.2	58.1	41.0
Spleen palpable (cm below costal margin)	7	3	0	5.7	15	Tip	Tip	0	0
Activity administered (mCi)	6.0	6.0	6.0	6.0	3.9	6.1	5.2	3.9	6.1
Previous <sup>32</sup> P treatment	no	yes	no	no	no	yes	yes	yes	no
Number of times		2				1	2	5	
Activity per treatment (mCi)		?				3	3	3	
Dates		1964, 68				1970	1970, 71	1968, 69 70, 71, 72	

N.B. Blood values measured on Coulter S and Thrombo Counter.

using <sup>51</sup>Cr-labelled red cells plus <sup>125</sup>I HSA (ICSH Report, 1973). Six of the patients were then given intravenously 6 mCi <sup>32</sup>P and the remainder, for clinical reasons, given smaller quantities. Prior to the <sup>32</sup>P injection, each patient's counting-rate was measured on a whole-body radiation counter, and then measured again within half an hour of administration. Whole-body counter measurements were taken at frequent intervals up to 28 days thereafter, and blood samples were also obtained at frequent intervals throughout this period. A trephine biopsy from the anterior aspect of the left iliac crest and a marrow aspirate from the first part of the body of the sternum were taken from each patient.

*Whole-body radiation counting*

The whole-body retention of <sup>32</sup>P was estimated by measuring the Bremsstrahlung emitted from the body using a whole-body radiation counter, made up of eight unshielded NaI (TI) scintillation detectors housed in a steel cubicle, in a way which has been shown to make its response relatively independent of the distribution of activity in the body (Burkinshaw *et al.*, 1972). The Bremsstrahlung of <sup>32</sup>P gives a continuous spectrum, and the total counting-rate above 400 keV was measured, the lower limit being chosen to exclude the  $\gamma$  rays of <sup>51</sup>Cr. The counting-rate from the patient was compared with that measured on the same day from an aliquot of the injected dose placed at the centre of the array of eight detectors.

*Measurement of blood activity*

Whole-blood and plasma samples were measured in an M6 liquid geiger counter,\* which was calibrated for its response to <sup>32</sup>P in solutions of differing density. The response of the counter to <sup>51</sup>Cr and <sup>125</sup>I was shown to be insignificant. The separation of plasma from whole blood was completed within an hour of the sample being taken in order to minimize the effect of <sup>32</sup>P eluting off the red cells. The activity ( $\mu$ Ci/gm) of the blood and plasma were determined by applying density corrections to the count-rates and comparing the results with the count-rate from a <sup>32</sup>P standard. Haematocrits were also determined using the standard Wintrobe technique.

*Measurement of sternal marrow activity*

The sternal marrow aspirate consists of two components, marrow and excess blood. By comparing <sup>51</sup>Cr and <sup>125</sup>I activities in blood samples and marrow aspirate, allowance could be made for this excess blood. <sup>32</sup>P activities were again determined by counting samples in an M6 geiger counter, and <sup>51</sup>Cr and <sup>125</sup>I activities by counting in a NaI well-counter. The <sup>32</sup>P activity ( $\mu$ Ci/g) of the sternal marrow could then be obtained.

*Measurements of activities in the iliac-crest biopsy*

The specimen was received in the laboratory

\*20 Century Electronics Ltd., England.

The absorbed dose to bone marrow in the treatment of polycythaemia by  $^{32}\text{P}$ TABLE II  
 $^{32}\text{P}$  RETENTION IN TERMS OF BIOLOGICAL HALF-LIFE

Patient	Whole body Days	Whole blood		Plasma	
		Fast component Days	Slow component Days	Fast component Days	Slow component Days
[REDACTED]	41.3	1.4	18.2	—	—
	36.3	1.2	17.8	0.3	16.8
	34.8	2.4	24.8	—	—
	44.0	2.2	24.6	1.5	20.9
	37.0	0.6	14.3	—	—
	41.4	1.15	21.8	0.4	16.0
	33.3	—	—	—	—
	38.3	1.9	25.1	1.0	17.7
	46.8	2.8	33.3	0.6	28.5
	Mean	39.2	1.7	22.5	0.8
s.d.	4.5	0.7	5.9	0.5	5.1

TABLE III  
NORMALIZED  $^{32}\text{P}$  ACTIVITIES IN THE STERNAL AND ILIAC CREST BIOPSIES

Patient	Iliac crest biopsy				Sternal marrow aspirate	
	Time after injection (days)	Trabeculation $\mu\text{Ci g}^{-1}$	Cortex $\mu\text{Ci g}^{-1}$	Marrow $\mu\text{Ci g}^{-1}$	Time after injection (days)	$\mu\text{Ci g}^{-1}$
[REDACTED]	7	0.825	0.137	0.152	—	—
[REDACTED]	2	0.368 0.389	0.205	0.329	—	—
[REDACTED]	—	—	—	—	2	0.287
[REDACTED]	7	0.289 0.194	0.186	0.344 0.203	2	0.283
[REDACTED]	1	0.390	0.429	0.555	7	0.339
[REDACTED]	1	0.316 0.465	0.359	0.455 0.341	7	0.355
[REDACTED]	15	0.415 0.209	0.129	0.122 0.170	13	0.176
[REDACTED]	10	0.194 0.296	0.304	0.144 0.087	10	0.048
[REDACTED]	27	0.235 0.163	0.045	0.066 0.051	27	0.028

shortly after removal. The surface fluids and extraneous tissues were gently removed from the biopsy specimen with filter papers and the specimen (approximately 1.5 cm long and 0.5 cm diameter) cut into trabecular portions and a cortical slab. Each trabecular portion was then placed in a wire mesh cage suspended in a conical flask and the marrow cavity tissues flushed out with an air-pressurized water-spray and collected in the flask. The washings

were evaporated to 2 ml., dissolved in 10M nitric acid and measured in an M6 counter. The trabecular portions and untreated cortical slab were separately dissolved in nitric acid and similarly measured. Activities in  $\mu\text{Ci/g}$  were calculated for trabecular bone, cortical slab and marrow.

## RESULTS

The results of the procedures described in the

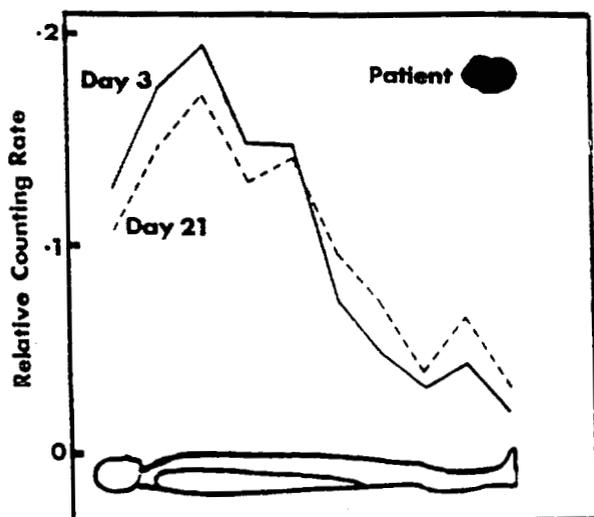


FIG. 1.  
Variation of counting-rate along the body at Day 3 and Day 21 for patient

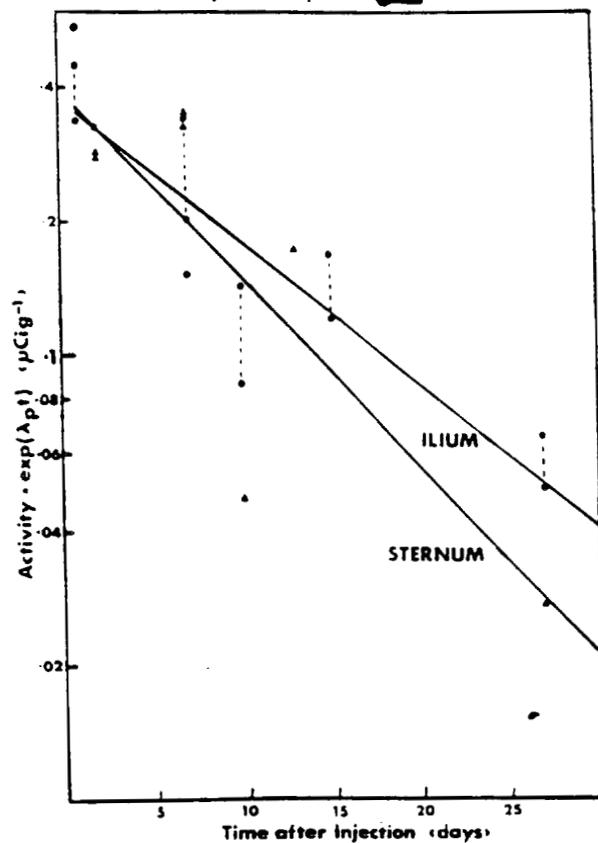


FIG. 2.  
Activities in aspirated sternal marrow ( $\lambda_B = 0.0976 \pm 0.0311$  (s.e.)  $d^{-1}$ ) and in marrow removed from iliac crest biopsy ( $\lambda_B = 0.0720 \pm 0.0114$  (s.e.)  $d^{-1}$ ), all activities adjusted to time  $t=0$ . The broken lines link points determined for the same patient (the trabecular portion having been divided into two parts).

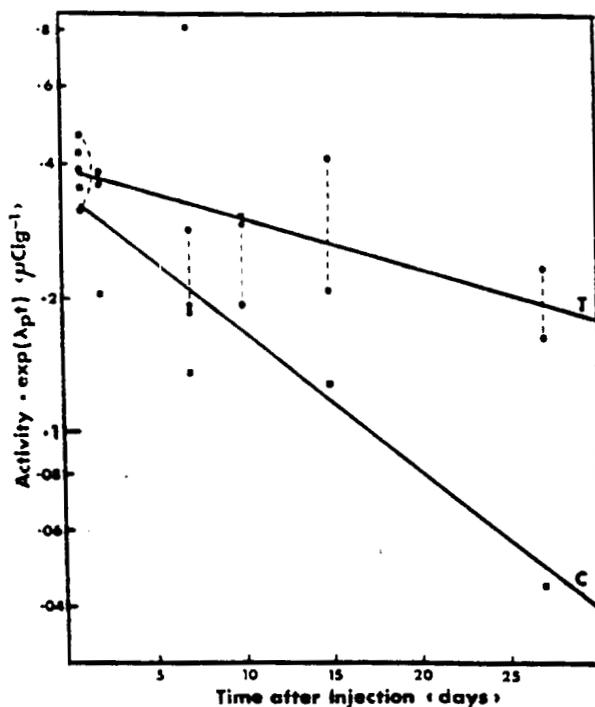


FIG. 3.  
Activities in trabecular bone, T, ( $\lambda_B = 0.0260 \pm 0.0119$  (s.e.)  $d^{-1}$ ) and cortical slab, C, from iliac crest biopsy; all activities adjusted to time  $t=0$ . Again the broken lines link points determined for the same patient.

previous sections are summarized in Tables II and III and in Figs. 1-3. In order to compare the activities in different patients it was necessary to adopt some method of normalization. In the first place all  $^{32}P$  activities were adjusted to 6 mCi administered activity. The patients differed, however, in weight, stature and in other ways, as shown in Table I. Bearing in mind the findings of Hume *et al.* (1966) that weight alone was an unsatisfactory basis on which to adjust the administered activity, it was decided to normalize the results to a fixed total plasma volume, taken as 2.94 l—the average value for patients seen in the Leeds Clinic. The question of "normalization" will be discussed further at the end of this paper, but it was considered reasonable to normalize by plasma volume because our results are then expressed as those for the same initial activity per litre of plasma—*i.e.* for tissues initially offered the same radionuclide concentration.

*Retention of  $^{32}P$  in blood, plasma and whole body*

The retention curves of activity in the whole blood and plasma were analysed to determine the biological half-lives. In each case a two-component

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exponential function was assumed and the exponents estimated by a statistically weighted ( $1/\text{activity}^2$ ) least squares method. The results, which show fast (~one day) and slow components, are given in Table II. Patient  $\bullet$  did not have serial blood samples taken, and the plasma-activity retention curves were not estimated for patients  $\bullet$  and  $\bullet$  because the plasma was not separated sufficiently quickly from some of the blood specimens.

On the other hand, the retention curves for the whole-body activity measurements were found to follow single exponential functions from day one onwards; the whole-body half-lives are also given in Table II.

*Retention as a function of anatomical position*

In addition to the whole-body counting measurements the gross distribution of  $^{32}\text{P}$  was also measured in three of the patients, using collimated  $\gamma$ -ray detectors placed beneath the supine patients. Figure 1 shows how the counting-rate varied along the body of one of the patients at three and 21 days after injection. The other two patients gave similar patterns. The distributions changed gradually with time and in each case the counting-rates over the extremities fell more slowly than those over the trunk. In fact, the relative counting-rate over the extremities, after allowing for physical decay, increased with time, indicating  $^{32}\text{P}$  accretion in these parts. Redistribution of  $^{32}\text{P}$  continued during the measurements, but since most of the activity was in the trunk, the whole-body effective half-life remained close to that measured over the trunk.

*Activities in the sternum and iliac crest biopsies*

The activities in marrow from the sternum and iliac crest are shown in Table III and Fig. 2, where it can be seen that the results for each site can be treated as a single group. Single exponential functions have therefore been fitted to each set of values (by least squares on the logarithms of the values). The two values of the biological half-life thus obtained, ~9 days for iliac marrow and ~7 days for sternal marrow, however, do not differ significantly ( $P > 0.9$ ).

The activities measured in the trabecular bone and the cortical slab from the iliac crest are shown in Fig. 3. (The cortical slab consists mainly of cortical bone, with some adhering soft tissue and trabecular bone edges.) Best-fit curves are also shown in Fig. 3 for the trabecular and cortical slab activities.

marrow from radionuclides incorporated in bone (Whitwell and Spiers, 1971; 1975) can be applied in a modified form to the present cases, where radionuclide activity is also found in the bone marrow. The calculations were designed to determine the average dose-rate to the red marrow at the time of the bone biopsy and hence to study the variation of dose-rate with time after injection. This inevitably involves certain assumptions: first that the activities per gram measured from the iliac specimens of marrow, trabecular bone and the cortical slab are representative of the activities in other corresponding parts of the skeleton; and second that the patients behave as a homogeneous group in respect of uptake, location and retention of the radionuclide. The measured activities were multiplied by average skeletal dose factors, derived from the data of Whitwell and Spiers, to give average red-marrow dose-rates on the biopsy day.

*Dose from activity in trabecular bone, cortical bone and marrow*

In calculating the dose to bone marrow, the dose factors given by Whitwell and Spiers cannot be applied directly because they relate only to deposition of the radionuclide in the trabeculae. No method has so far been given for the situation in which two inter-penetrating non-equilibrium depositions (in the trabeculae and in the marrow) co-exist. The principle by which the combined dose-rate from both trabecular and marrow activities can be calculated is shown in Fig. 4. If the trabecular activity is greater than the marrow activity, as in

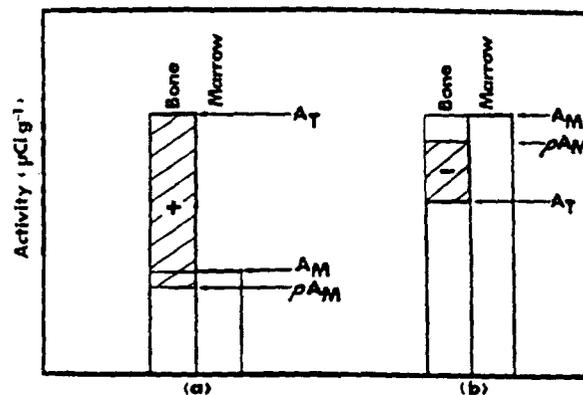


FIG. 4.

Diagram illustrating principle of calculating the combined dose-rate to marrow from activity  $A_T$  in the trabecular bone and  $A_M$  in the marrow.

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Fig. 4a, we could first calculate the dose rate from an "infinite" medium having a notional activity,  $A_M$ , equal to that of the marrow, and then add on the dose-rate from the excess activity,  $A_T - A_M$ , in the trabeculae, where  $A_T$  is the trabecular activity. This procedure is not quite exact, however, because the mass stopping power in bone is less than in marrow and, consequently, a smaller activity,  $\rho A_M$ , in bone will give the same dose to a small mass of tissue within bone as will activity  $A_M$  in a uniform soft-tissue medium. The excess bone activity should therefore be adjusted to  $A_T - \rho A_M$ , where  $\rho$  is the ratio of the particle mass stopping powers, bone/marrow. The value of  $\rho$  varies slowly with  $\beta$ -particle energy, and has been calculated to be 0.90 for  $^{32}\text{P}$  from the data of Berger and Seltzer (1966), assuming that the mass stopping power of marrow is the same as that of muscle.

The first part of the combined dose-rate is calculated from the usual formula:

$$D_1 = 51 \cdot 2 \bar{E}_\beta A_M \text{ rad/day} \quad (1)$$

where the activity is in  $\mu\text{Ci/g}$  and  $\bar{E}_\beta$  is in MeV ( $\bar{E}_\beta = 0.695$  for  $^{32}\text{P}$ ). The second part of the combined dose-rate is given by:

$$D_2 = \bar{G} D_0 (A_T - \rho A_M) \text{ rad/day} \quad (2)$$

where  $\bar{G}$  is the average dose factor for skeletal red marrow in trabecular bone ( $= 0.276$  for  $^{32}\text{P}$ ) and  $D_0$  is the dose-rate to a small tissue inclusion from  $1 \mu\text{Ci/g}$  of  $^{32}\text{P}$  in surrounding bone having dimensions greater than the  $\beta$ -particle range ( $= 39.5$  rads/day), taken from the data of Whitwell and Spiers (1975).

The dose-rate  $D_{MT}$  from the combined activities in both marrow and trabeculae is then:

$$D_{MT} = D_1 + D_2 \quad (3)$$

If the activity in the marrow is greater than that in the trabeculae, a similar procedure is followed, which is illustrated in Fig. 4b, but the value of  $D_2$  is negative. It must be emphasized that  $D_1$  and  $D_2$  are notional dose-rates used to calculate the combined dose rate  $D_{MT}$ , and do not represent the actual contributions to the dose-rate from the marrow and trabecular activities. These can be deduced, however, once  $D_{MT}$  is known.

The contribution from the trabecular activity is:

$$D_T = \bar{G} D_0 A_T = 10.9 A_T \text{ rad/day} \quad (4)$$

and hence that from the marrow activity is:

$$D_M = D_{MT} - D_T = (51 \cdot 2 \bar{E}_\beta - \rho \bar{G} D_0) A_M = 24.5 A_M \text{ rad/day} \quad (5)$$

A small contribution to the dose to marrow in trabecular bone is made by the  $^{32}\text{P}$  in the cortex. The average value for the cortical dose factor for the skeleton as a whole is 0.052 for  $^{32}\text{P}$  (Whitwell, 1973) and hence the contribution  $D_C$  from the cortex can be given as:

$$D_C = 0.052 D_0 A_C = 2.05 A_C \text{ rad/day} \quad (6)$$

Where necessary a factor (0.96) has been introduced to allow for lack of particle equilibrium in those bones from which a small fraction of the particle energy escapes (Spiers, 1966; Whitwell, 1973).

*Calculated dose-rates from 1 to 27 days post injection*

Dose-rates have been calculated at the time of the bone biopsy for each patient, using equations (4), (5) and (6), and the measured activities  $A_T$ ,  $A_M$  and  $A_C$ . The total dose-rates to bone marrow,  $D_T + D_M + D_C$ , are shown in Fig. 5, two points being shown (linked by broken lines) for the five cases when two measurements of  $A_T$  and  $A_M$  were

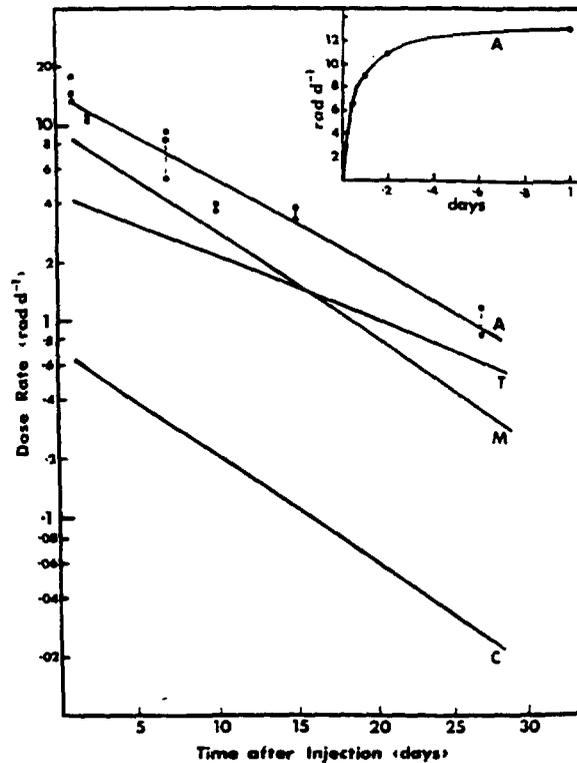


FIG. 5. Curve A: Best fit single exponential to the total dose rates to skeletal bone marrow ( $D_T + D_M + D_C$ ). (Curves T, M and C) Best fit curves for the dose-rate contributions from trabecular bone, marrow and cortex respectively. Insert: Approximate total dose rates calculated for first day.



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be made using equation (1) and assuming the measured value for  $A_M$  at that time. The effective half-life would be approximately that for trabecular marrow, and the total dose from Day 1 would be about 112 rads, including a small cortical contribution. The total dose would then be about 125 rad or about 20 rad per mCi injected. Similar considerations suggest that the dose to extra-medullary haemopoietic tissues, as in liver and spleen, would not be higher than the estimated value of 20 rad per mCi injected for marrow in bone shafts.

Finally, it can be seen from Table II that the whole-body biological half-life has a mean value of 39.2 days with a standard deviation of 4.5 days. It is suggested that if the whole-body half-life as determined by whole-body radiation counting lies in the range  $39 \pm 9$  days, the dose to trabecular marrow should be approximately that found in these investigations—24 rad per mCi  $^{32}\text{P}$  injected. Because the whole-body counting-rates were found to be accurately represented by a single exponential function, the half-life can be readily determined by a few clinically convenient measurements.

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## Book review

*Textbook of Anatomy and Physiology in Radiologic Technology*. By Charles A. Jacobi, 2nd edn, pp. xvii+437, 1975 (C. V. Mosby, distributed by Henry Kimpton Publishers), £7.00.

This book is written for radiographers and aims to relate anatomy and physiology to their routine work.

There are some excellent tables throughout the book, and the sections on pathology, injuries and technique will

be of interest to the student. Unfortunately, many radiographs and skeletal photographs used as illustrations are poorly reproduced, and there is a noticeable lack of clear diagrams.

There are other anatomy and physiology texts which are more suitable at a similar price.

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