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BLOOD RADIATION DOSE AFTER ^{131}I THERAPY OF THYROTOXICOSIS

CALCULATIONS WITH REFERENCE TO LEUKAEMIA

BY

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Although ^{131}I has been extensively used for the treatment of thyrotoxicosis there is occasionally some hesitation in choosing this form of treatment. Possible hazards that come to mind are the induction of neoplastic changes and genetic damage.

Carcinoma of the thyroid may be induced by exposure of the gland to ionizing radiations in infancy or childhood (Duffy and Fitzgerald, 1950; Simpson *et al.*, 1955; Clark, 1955; Fetterman, 1956; Simpson and Hempelmann, 1957; Wilson *et al.*, 1958), and neoplasms of the thyroid have been reported after the use of ^{131}I therapy for thyrotoxicosis in childhood (Sheline *et al.*, 1959). However, ^{131}I therapy should certainly not be used for the treatment of juvenile thyrotoxicosis. Thyroid carcinoma has rarely been reported to follow the use of *x*-rays for the treatment of thyrotoxicosis (Quimby and Werner, 1949; Wilson *et al.*, 1958; Goolden, 1958; Willis, 1959), and so far no cases have been attributed to ^{131}I therapy in adults.

The possibility that ^{131}I therapy may predispose to the development of leukaemia has until recently not been so fully considered. However, there is a known association between exposure to ionizing radiations and the subsequent development of leukaemia (Court Brown and Doll, 1957). Our own interest was stimulated by the occurrence of acute monocytic leukaemia in a patient treated for thyrotoxicosis with ^{131}I one and a half years previously (Blomfield *et al.*, 1959). This case is now reported in detail, and further investigations have been made in an attempt to measure the radiation dose to the blood and bone-marrow resulting from ^{131}I therapy of thyrotoxicosis and to relate this to work on the development of leukaemia after irradiation.

Case Report

A married woman aged 60 complained of nervousness, palpitations, heat intolerance, and excessive sweating during the previous three years. Her weight had decreased by 12 kg. When she first attended hospital on February 13, 1957, she was emaciated and hyperkinetic, and had bilateral exophthalmos, lid lag, and lid retraction. The thyroid was slightly enlarged and irregular. Although the skin was warm and moist, finger tremor was not present. There was a regular tachycardia of 100 a minute. No other abnormal physical signs were observed. The blood film was normal, the haemoglobin being 17.1 g./100 ml., white-cell count 4,000/c.mm. (50% neutrophils, 4% eosinophils, 38% lymphocytes, 8% monocytes). The serum cholesterol was 195 mg./100 ml. There was no radiological evidence of tracheal compression or abnormality of the chest. A radioactive iodine tracer test showed a four-hour uptake of 58% and a 48-hour uptake of 69%. The 48-hour plasma-protein-bound ^{131}I was 0.74% dose per litre.

A diagnosis of thyrotoxicosis was made, and on April 10 a therapeutic dose of 4.9 mc of ^{131}I was given to produce an estimated dose of 7,000 rads to the thyroid. Subsequent measurements showed that the uptake of the therapeutic dose was slightly higher than that of the preliminary tracer dose, so that the dose to the thyroid was about 8,200 rads.

When seen on May 16 the patient was thought to be euthyroid, but by September she had gained 10 kg., and complained of intense cold and drowsiness. She presented the typical appearance of myxoedema. Her face was swollen, the features coarse, the skin rough, and the voice deep. The pulse rate was 76 a minute with sinus rhythm. There were no enlarged lymph nodes and the liver and spleen were not palpable. A radioactive iodine tracer test showed no significant thyroidal uptake and a urinary T index of 1.1 (Fraser *et al.*, 1953). The serum cholesterol was 390 mg./100 ml. and the basal metabolic rate minus 17%. Although the patient was not anaemic, the following investigations were carried out as part of a study of the blood in patients with hypothyroidism (Tudhope and Wilson, 1960). Haemoglobin was 15.4 g./100 ml., white-cell count 7,000/c.mm. (68% neutrophils, 1% eosinophils, 23% lymphocytes, 8% monocytes), and blood film normal. The platelet count was 216,000/c.mm. Sternal bone-marrow was normal. The preparations were retained and subsequent examination confirmed the normal appearance. The total red-cell volume using ^{51}Cr (30 μc) was 1.71 litres. The red-cell utilization of iron using ^{59}Fe (1 μc) was within the normal range.

Treatment with L-thyroxine sodium 0.1 mg. daily was started on October 30, and after increasing to 0.15 mg. daily a month later, she was judged to be euthyroid by February, 1958. On April 2 the haemoglobin was 14.8 g./100 ml., and the blood film normal. On April 11 the total red-cell volume using 42 μc of ^{51}Cr was 1.86 litres. The total blood-irradiation dose contributed by the ^{51}Cr and ^{59}Fe studies was calculated as 0.24 rad. During April, 1958, she complained of a burning sensation at the tip of the tongue, for which she was advised to stop smoking. She failed to do so and successive courses of treatment with riboflavin and vitamin B_{12} failed to relieve the symptom. At this time she

also complained of frequent headaches and a nasal discharge. *X*-ray examination showed an opaque left antrum and a fluid level in the right antrum. The antra were washed out.

She was admitted to hospital on September 5, having been ill two weeks with a cough productive of purulent sputum. She had initially been treated at home for three days with tetracycline without improvement. On examination she was breathless at rest, and had a regular tachycardia of 120 a minute and a pyrexia of 101° F. (38.3° C.). There were coarse crepitations at both lung bases but no signs of heart failure and no other abnormal physical signs. A diagnosis of bronchopneumonia was made and treatment with tetracycline 0.25 g. six-hourly was continued. The haemoglobin was 18.4 g./100 ml., the white-cell count 123,000/c.mm. (4% neutrophils, 6% lymphocytes, 8% blast cells, 82% monocytes), most of the monocytes being of abnormal morphology. Bone-marrow biopsy showed the changes of acute monocytic leukaemia. Treatment with prednisolone and mercaptopurine was started, but she died 12 hours later.

At necropsy red marrow was found up to the mid-shaft of the femur and all organs were infiltrated with atypical large mononuclear cells showing variations in nuclear size and shape, hyperchromaticity, large nucleoli, and numerous mitoses. Only a remnant of thyroid tissue was present, and this was largely fibrous. The few surviving follicles were well filled with colloid and the cells showed irregularities of size and nuclear configuration suggestive of irradiation damage.

Other Cases of Leukaemia After ^{131}I Therapy of Thyrotoxicosis

Eight cases, including the present one, of leukaemia developing after treatment of thyrotoxicosis with ^{131}I have been recorded (Table I), and Pochin (1960) mentioned 10 other unpublished cases. In addition there have been reports of leukaemia after the use of ^{131}I for the treatment of thyroid carcinoma, but in these cases the doses have been very much greater (Seidlin *et al.*, 1952; Delarue *et al.*, 1953; Blom *et al.*, 1955; Seidlin *et al.*, 1956). In all the cases summarized in Table I the leukaemia was of an acute type and the interval between administration of ^{131}I and the diagnosis of leukaemia was 14 to 26 months. However, Pochin (1960) reported that the latent interval in the unpublished cases showed much wider variation.

TABLE I.—*Details of Cases of Leukaemia Reported After ^{131}I Therapy for Thyrotoxicosis*

Authors	Sex and Age	Interval between ^{131}I Therapy and Diagnosis of Leukaemia (Months)	Type of Leukaemia Reported	Dose of ^{131}I Administered (mc)	Authors Estimate of Dose to Blood	Estimate of Dose to Blood Using Fig. 3 (Rads)
Pochin *et al.* (1956)	F 41	24	Acute	7·1	10 rep	13
Abbatt *et al.* (1956)	F 67	19	Acute monocytoid myelogenous	17·0		38
Childs, D. (1956)	M 46	14	Acute myelocytic	5·3		10
Chapman (1956)*	M 63	26	Acute monocytic	6·0		12
Werner and Quimby (1957)	F 28	18	Acute myeloblastic	2·1	2–6 rads	3
Vetter and Höfer (1959)	M 50	18	Acute	7·1	6–10 rads	14
Kennedy and Fish (1959)	M 38	22	Acute granulocytic	5·5		10
Blomfield *et al.* (1959)	F 60	17	Acute monocytic	4·9		9

* Wrongly attributed to Werner.
Time intervals above are those given by Pochin (1960) after personal communication with the authors.

Previous estimates of the irradiation dose to the blood had suggested that this was below 25 rads in most patients treated with ^{131}I for thyrotoxicosis (Blomfield *et al.*, 1959). Other estimates have been slightly higher (Halnan, 1958). In view of the importance of a possible association between the dose to the blood and the development of leukaemia more accurate measurements have been performed and an attempt has been made to calculate the dose received by the bone-marrow.

Patients Studied and Method of Measuring Blood Dose

One hundred and ninety-one patients attending the Sheffield Royal Infirmary between October, 1958, and February, 1960, for ^{131}I therapy for thyrotoxicosis were investigated. They were divided into three groups. The first group consisted of patients who had previously received no treatment for thyrotoxicosis other than antithyroid drugs in some cases; the second group comprised patients who had already been treated with ^{131}I on a previous occasion and were still thyrotoxic; and the third group were patients with a recurrence of thyrotoxicosis after partial thyroidectomy.

Estimates of the blood-radiation doses arising from the therapeutic use of ^{131}I for carcinoma of the thyroid, based largely on measurements of the radioactivity circulating in the blood over a period of time, have been reported (Marinelli and Hill, 1950; Stanbury *et al.*, 1952; Seidlin *et al.*, 1952). A similar method has been adopted in the present investigation.

The blood dose has been considered in three parts: (*a*) in the first phase when the radioactivity is circulating as iodide, (*b*) in the second phase when the radioactivity in the blood is mainly protein-bound, and (*c*) from the radioactivity in the thyroid. The contributions from the circulating ^{131}I consist of both β and γ doses; that from the ^{131}I in the thyroid consists of γ-radiation only and varies considerably throughout the body. The average dose has been calculated.

Iodide Phase

In thyrotoxic patients the radioactivity circulating as iodide decreases in an approximately exponential way with a half-period of about two hours (Pochin *et al.*, 1956). The dose due to this is small compared with the total dose received during ^{131}I therapy and can be adequately calculated.

The standard β-ray dose formula is $D_\beta = 51.2\ \bar{E}_\beta \frac{Co\ T_{\frac{1}{2}}}{0.693}$ rads, where Co is the initial concentration of the radioactivity in μc/g., $T_{\frac{1}{2}}$ is the half-period in days, and $\bar{E}_\beta$ is the mean β-ray energy in MeV.

Assuming an iodide space of 30% of the body weight (Myant and Pochin, 1950) the β-ray dose to the blood is $D_\beta = 51.2\ \bar{E}_\beta \frac{0{\cdot}4}{W}(1 - H + HB)$ rads/mc of ^{131}I administered, where W is the body weight in kg, H is the haematocrit, and B is the ratio of the concentration of ^{131}I in the erythrocytes to that in the plasma.

The γ-ray dose formula is $D_\gamma = 0.024 \rho I_\gamma \bar{g} \frac{Co\ T_{\frac{1}{2}}}{0.693}$ roentgens, where ρ is the average density of the patient, I_γ is the γ-ray dose rate at a distance of 1 cm. from a point source measured in roentgens/hour/mc and $\bar{g}$ is a geometrical factor relating to the shape and size of the tissue throughout which the ^{131}I is distributed.

When relating this to the body the γ-ray dose becomes

$$D_\gamma = 0.024 \rho \cdot I_\gamma \bar{g}\ 0.12 \text{ roentgen.}$$

Values for $\bar{E}_\beta$ (0.197 MeV) and I_γ (2.25 r/hour/mc) were taken from the British Standard of Radioactive Iodine (^{131}I) (Bullard, 1952), W and H were measured for each patient, B was assumed to be 0.65 (Myant *et al.*, 1950), $\bar{g}$ was taken from tables published by Hine and Brownell (1956), and ρ was assumed to be 1.

Thyroxine Phase

After the initial clearance of ^{131}I as iodide the radioactivity circulating is mainly protein-bound. The level of radioactivity varies from patient to patient, and in any one patient varies with time. Blood samples were therefore taken from each patient at 1, 2, 5, 9, 14, and 28 days after ^{131}I therapy and the total plasma radioactivity at the time of sampling was measured. The total plasma activity in μc/g./mc of ^{131}I administered was plotted against time in days (Fig. 1). The graph was extrapolated to infinite time, assuming the same rate of fall of activity as that measured between 14 and 28 days. The activity remaining in the plasma at 28 days was generally very low. The plasma dose rate due to β-irradiation is 51.2 $\bar{E}_\beta$ C rads day, where C is the concentration of activity in the plasma in μc/g.

In Fig. 1 the area of a unit rectangle having sides corresponding to 1 μc/g. and one day is equivalent to a dose of 51.2 $\bar{E}_\beta$ rads. The β dose to the plasma is

$$51.2\ \bar{E}_\beta \frac{\text{area under curve}}{\text{area of unit rectangle}} \text{ rads/mc of } ^{131}\text{I given.}$$

Since some 80% to 90% of the plasma activity is protein-bound, the level of activity in the erythrocytes is very low and has been neglected. The dose to the blood in the thyroxine phase is thus:

Plasma dose $\times$ (1 − H) rads/mc of ^{131}I administered.

To estimate the γ dose from the circulating ^{131}I in this phase it is necessary to know the average concentration of ^{131}I throughout the body. It has been assumed that the radioactivity in the plasma has a distribution space equal to that of thyroxine, and a figure of 15% of the body weight has been used. Myant and Pochin (1950) found the thyroxine space to be 20% of the body weight using 3′:5′-labelled thyroxine; but they and Sterling *et al.* (1954) obtained values of between 10% and 15% using naturally labelled thyroxine. It is realized that, apart from thyroxine, there are other protein-bound iodinated compounds together with up to 20% non-protein-bound iodinated substances in the plasma at this stage which may not have the same value of distribution as thyroxine. However, the possible error in the total blood dose from this source should not exceed 5%. The γ-ray dose is therefore

$$D_\gamma = 0.024\ I_\gamma \bar{g} \frac{\text{area under curve}}{\text{area of unit rectangle}} \times 0.15 \text{ roentgens/mc } ^{131}\text{I}$$

administered.

Blood Dose from ^{131}I in the Thyroid

The γ dose to the body due to ^{131}I in the thyroid depends on the amount of ^{131}I taken into the gland and its effective half-life in the gland. It can be shown that the average γ dose to the body from this source is approximately 0.072 roentgen/day/mc of ^{131}I in the gland. The effective half-life of ^{131}I in the thyroid after therapy is not commonly measured, but, using the preliminary tracer test as a basis (Blomfield *et al.*, 1955), the average dose is 0.54 U_{48} roentgen/mc administered, where U_{48} is the fractional uptake of the tracer dose 48 hours after administration.

In summating the different contributions to the total blood radiation dose it has been assumed that the average dose from the β particles in rads and the average dose from the γ rays in roentgens are additive in their biological effect although there is a small difference in the absorbed energy (1 rad≡100 ergs/g., 1 roentgen≡97 ergs/g. in soft tissue).

Results of Measurement of Blood Irradiation Dose After a Single Therapeutic Administration of ^{131}I

The blood doses received after a single treatment with ^{131}I are shown in Table II. They are similar in each group, but the dose in rads/mc is slightly higher in the patients previously treated with ^{131}I than in the other two groups. The range of blood doses is shown in Fig. 2. In the majority the blood dose resulting from a single administration of ^{131}I was less than 10 rads.

The radiation dose to the blood is related to the amount of ^{131}I administered and to the proportion of ^{131}I passing from the thyroid into the circulation. In

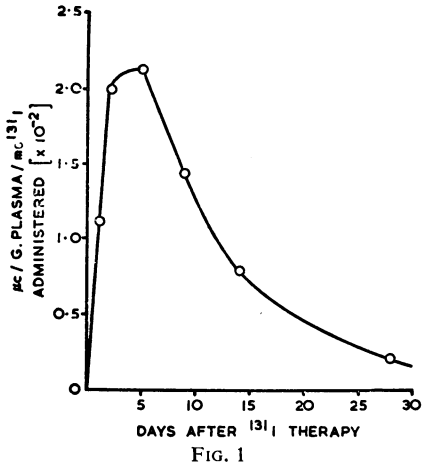

FIG. 1

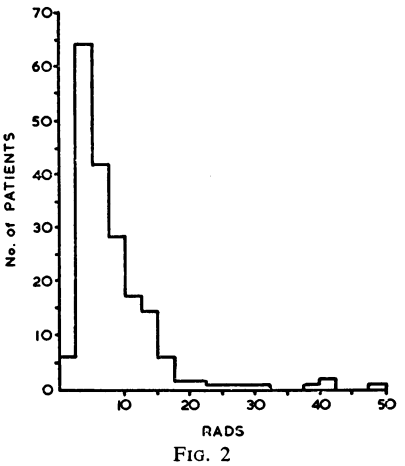

FIG. 2

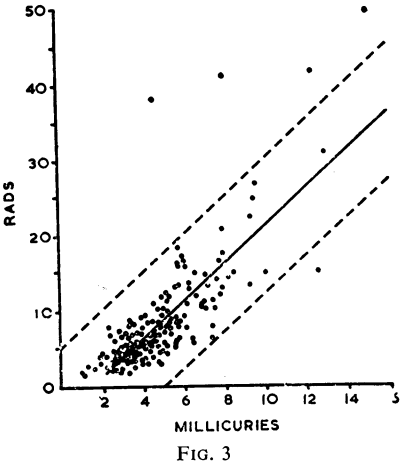

FIG. 3

FIG. 1.—Typical set of results and plasma radioactivity curve. Area under curve=69.5 cm.^{2} Area of unit rectangle=250 cm.^{2} W=47 kg. H=0.40. $\bar{g}$=111. Blood dose per mc ^{131}I administered: (*a*) iodide phase=0.089 rad, (*b*) thyroxine phase=1.915 rads, (*c*) thyroid=0.360 rad. Total=2.364 rads/mc ^{131}I. FIG. 2.—Range of blood radiation doses in 191 patients after a single administration of ^{131}I. FIG. 3.—Relationship between the blood radiation dose and the therapeutic dose of ^{131}I. 95% confidence limits are shown and for the best line y=2.46x−3.34.

TABLE II.—*Blood Radiation Doses and Therapeutic Doses of ^{131}I in 191 Patients*

Clinical Condition at Time of ^{131}I Therapy	No. of Cases	Age in Years Mean± S.E.	Therapeutic Dose (mc) Mean± S.E.	Blood Dose (Rads) Mean± S.E.	Blood Dose (Rads/mc) Mean± S.E.
Previously untreated thyrotoxicosis ..	128	53·3±0·7	5·0±0·2	8·7±0·64	1·6±0·08
Thyrotoxicosis previously treated by ^{131}I therapy ..	50	50·8±1·3	4·0±0·1	7·7±0·76	1·9±0·08
Thyrotoxicosis recurring after partial thyroidectomy ..	13	49·7±3·2	4·7±0·7	7·7±0·88	1·4±0·18
Total	191	52·4±0·6	4·7±0·2	8·4±0·51	1·7±0·06

centres where protein-bound ^{131}I is not regularly measured the number of millicuries given is the only available indication of the blood radiation dose. There is a definite correlation though the confidence limits are wide (Fig. 3). The results shown in this figure have been used to calculate the blood doses of the cases shown in Table I. The plasma radioactivity after ^{131}I therapy is not measured routinely. It is, however, closely related to the plasma radioactivity observed in the preliminary tracer test (Fig. 4). The ratio of protein-bound ^{131}I to non-protein-bound ^{131}I (the conversion ratio) 48 hours after tracer and therapy doses is similar (Fig. 5). The measurement of P.B. ^{131}I made in the preliminary tracer test can therefore be used as an indication of the P.B. ^{131}I after the therapeutic dose. If the radiation dose to the blood per mc of ^{131}I administered is plotted against the tracer P.B. ^{131}I a close correlation is obtained (Fig. 6). These results mean that a reasonably accurate prediction may be made of the blood radiation dose that any patient will receive as the result of ^{131}I therapy for thyrotoxicosis. Two-thirds of the predictions will be correct to within ±0.5 rad/mc, and the nomogram shown in Fig. 7 can be used for this purpose.

Total Blood Doses Received During ^{131}I Therapy for Thyrotoxicosis

The blood doses in 802 patients treated at this hospital between 1949 and February, 1960, have been calculated, using the nomogram (Fig. 7). The intention was to give an initial irradiation dose of 7,000 rads to the thyroid (Blomfield *et al.*, 1959). In approximately 70% of the patients only a single treatment with ^{131}I was given. In 30%, however, multiple doses were necessary, and in such cases the blood radiation doses have been summated. The doses received are shown in Fig. 8. The mean total blood dose was 16.6 rads and the highest dose was 160 rads in a patient who had received five treatments with ^{131}I.

Relationship Between the Blood Dose and the Bone-marrow Dose

The dose to the bone-marrow has usually been estimated by assuming that the radioactivity per gramme of marrow is identical with that in the blood (Seidlin *et al.*, 1952; Rall *et al.*, 1953). On two occasions we have compared the radioactivity of the blood and material aspirated from the iliac marrow cavities after therapeutic doses of ^{131}I and found close agreement. However, the marrow is interspersed with bony trabeculae between 40 and 250 μ in thickness, the cavities being from 200 to 700 μ thick (Robertson and Godwin, 1954). Because the bony trabeculae contain no ^{131}I the β-radiation dose will be smaller than that calculated for the blood, since the dimensions of the marrow sections are comparable to the range of β particles from ^{131}I (400 μ in soft tissue for β particles of average energy). Assuming that the density of the bone is 2 g./ml., and allowing for ^{131}I in adjacent marrow sections, the average dose to the marrow as a fraction of the blood dose is calculated to be as shown in Table III. The γ-ray contribution is, however, increased because of secondary electron emission from the bony trabeculae. Because the γ rays are relatively hard the increase will be less than 5% for marrow layers 500 μ wide separated by bony layers 100 μ wide. The γ dose

TABLE III

Width of Bone-marrow Layer	Marrow Dose as a Percentage of Blood Dose for Bony Trabeculae of Following Widths		
	40 μ	100 μ	250 μ
200 μ	62	53	46
500 ,,	83	73	64
700 ,,	86	77	69

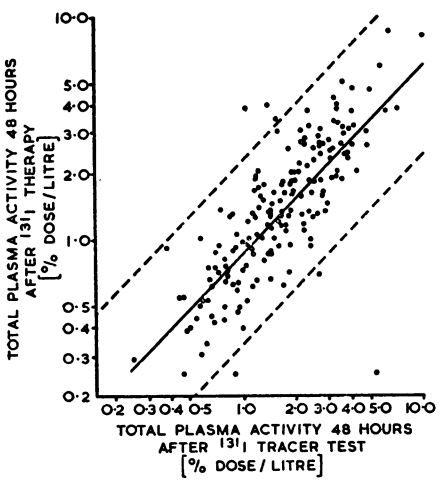

FIG. 4

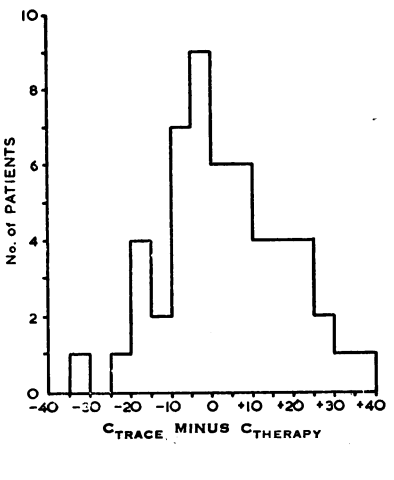

FIG. 5

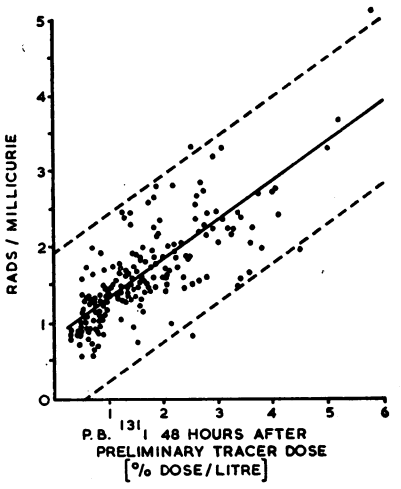

FIG. 6

FIG. 4.—Relationship between the total plasma ^{131}I after the therapeutic dose and after the preliminary tracer test. A double log scale is used and 95% confidence limits are shown. For the best line log y=0.86 log x−0.06. FIG. 5.—Difference in conversion ratio in 52 patients after the tracer test (C_{trace}) and after ^{131}I therapy ($C_{therapy}$). The mean conversion ratio after the tracer test was 85% and after therapy 81%. FIG. 6.—Relationship between the radiation dose to the blood per millicurie of ^{131}I administered and the P.B. ^{131}I 48 hours after the preliminary tracer test. 95% confidence limits are shown and y=0.54x+0.76.

is only 30% of the total dose in this site, and combining β and γ rays suggests that the total bone-marrow irradiation will be about 80% of the total blood dose.

Discussion

In the majority of patients treated with a single dose of ^{131}I for thyrotoxicosis the bone-marrow dose is less than 10 rads. In a few of the cases requiring multiple treatments the marrow dose may be much larger. It is difficult to relate these marrow radiation doses with any subsequent liability to develop leukaemia. The detailed study of irradiation and leukaemogenesis of Court Brown and Doll (1957) was based on patients treated for ankylosing spondylitis by *x*-ray therapy. The irradiation was delivered to limited sections of the body in a series of isolated doses and the spinal marrow was particularly exposed. In the treatment of thyrotoxicosis the whole body is exposed to less intense internal irradiation by β and γ rays over a period of at least a month. Clearly there may be a considerable difference in the leukaemogenic effect of the two methods of irradiation. However, in the absence of other evidence a comparison may be attempted between the irradiation doses to the marrow occurring during ^{131}I therapy of thyrotoxicosis and *x*-ray therapy of ankylosing spondylitis.

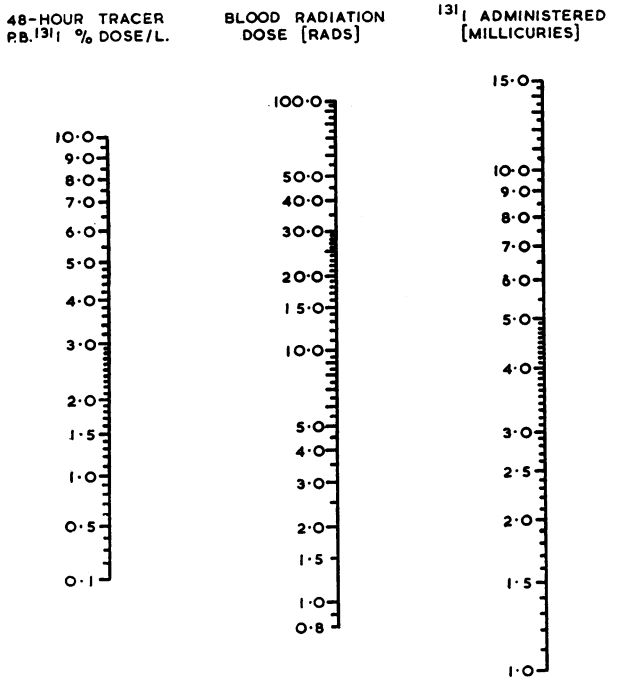

FIG. 7.—Nomogram which can be used to estimate the blood radiation dose from a knowledge of the tracer P.B. ^{131}I and the therapeutic dose of ^{131}I.

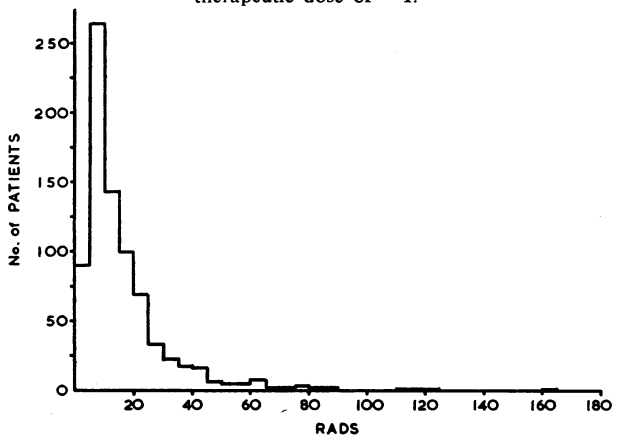

FIG. 8.—Total blood radiation doses received by 802 patients treated by ^{131}I for thyrotoxicosis since 1949.

In the patients who developed leukaemia after irradiation by *x*-rays the mean spinal-marrow dose varied from 112 to 3,535 roentgens, most of the cases receiving 1,000 to 1,500 roentgens. Court Brown and Doll estimated that a dose of 30 to 50 roentgens for radiations of the same energy as those used in the treatment of ankylosing spondylitis by *x*-rays might double the natural incidence of leukaemia. Under these conditions a factor of 0.9 rad per roentgen might be accepted and the doubling dose for the natural incidence of leukaemia might lie between 27 and 45 rads. Among the 802 patients reported in this paper, 79 (9.8%) received a mean marrow dose of this order or over, 67 of these being patients who received several doses of ^{131}I.

In view of the differences in the manner in which the bone-marrow is irradiated it may be relevant to compare the integral doses for the two types of patient. Court Brown and Doll state that there is no significant evidence of increased incidence of leukaemia at integral doses less than 7.5 Mg. roentgens. The estimate of integral doses in patients receiving ^{131}I therapy for thyrotoxicosis is not easy. The total energy absorbed can be calculated from a knowledge of the amount of ^{131}I administered and its effective half-life in the body. The average integral dose per mc of ^{131}I administered is 130 kg. rads. For a mean ^{131}I dose of 5 mc this gives 0.65 Mg. rad as the average integral dose. Only 0.3% of the treated cases received an integral dose of the order of 7.5 Mg. rads.

It will be appreciated that there are several uncertainties in the above calculations. Nevertheless they suggest that the risk of leukaemia induction after ^{131}I therapy of thyrotoxicosis is slight. This view is in keeping with the results of the epidemiological survey conducted by Pochin (1960). Among at least 60,000 patients treated by ^{131}I for thyrotoxicosis there are 18 known cases of leukaemia. This is no higher than might be expected purely by chance. Though the results of this survey and the conclusions drawn from the blood-dose measurements are thus consistent, these can only be regarded as preliminary assessments of the hazard. It is therefore important that any case of leukaemia developing after ^{131}I therapy should be reported so that the situation can be kept under close observation.

Summary

A case of acute leukaemia diagnosed 17 months after ^{131}I therapy for thyrotoxicosis is reported. In an attempt to assess the relationship between ^{131}I therapy and the subsequent development of leukaemia the radiation dose to the blood after a single therapeutic dose of ^{131}I has been measured in 191 thyrotoxic patients. The mean irradiation to the blood was 8 rads per therapeutic dose. The irradiation dose to the blood is related to the amount of ^{131}I administered and the fraction passing into the plasma as protein-bound ^{131}I. A nomogram taking into account these two factors has been constructed from the measurements made on the 191 patients, so that the irradiation dose to the blood can be estimated in other patients treated by ^{131}I for thyrotoxicosis.

The blood irradiation dose for complete treatment of the disease was estimated from the nomogram in 802 patients previously treated with ^{131}I. The mean dose was 16.6 rads, but in some patients receiving multiple treatments it was much greater, ranging up to 160 rads. The bone-marrow dose is estimated as 80% of the blood dose.

Consideration of these results suggests that the risk of leukaemogenesis is slight and does not contraindicate ^{131}I therapy of thyrotoxicosis. Nevertheless it is important to record all cases of leukaemia occurring after ^{131}I therapy so that the validity of these conclusions may be examined.

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PROGNOSIS IN BELL'S PALSY

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The rate of complete recovery in Bell's palsy is often stated to be 80–85%, without further support, even by authors whose own results by no means approach this level (Cawthorne and Haynes, 1956; Sullivan and Smith, 1959; Dalton, 1960). Patients referred to hospital must always be selected, and it seems to have been accepted that the lack of agreement between the observed recovery rates and the orthodox 80% is due to many palsies resolving so quickly that the patients are never referred to hospital or, perhaps, never even seen by a doctor. This difficulty can never be fully overcome, but if the assumption is correct the earlier the patients are seen the better the rate of recovery should be. This is obviously true with patients specifically referred because of delayed recovery, but it is of some importance to establish the prognosis in cases seen within a few days of the onset.

To be effective any treatment must prevent degeneration of the nerve, and it is probable that this could be achieved only very early in the course of the palsy. Unless the natural prognosis of patients seen at this stage is known it is not possible to assess the results. It is claimed that treatment can be effective within the first week (Korkis, 1961), but no satisfactory control series exists for patients first observed within the same period. An attempt was made to obtain a relatively unselected group of patients by an appeal to local practitioners to refer patients early, and this paper is an account of the results.

Method

For the purpose of the present investigation Bell's palsy was defined as a unilateral facial palsy of peripheral type unassociated with other evidence of nervous disease or with otitis media or other discoverable cause. Patients with herpes zoster at the time of the palsy or later were included. The time of onset was dated from when the patient first noticed weakness and not from any premonitory symptoms. A careful examination was carried out to determine whether the palsy was complete or partial, those cases with any detectable movement being classified as partial. Electromyography was not available until late in the series, and as the results are not comprehensive they are not mentioned further. The patients did not go entirely untreated, the great majority being given nicotinic acid by mouth. Galvanism was used occasionally when recovery was delayed and the patient anxious. The patients' progress was observed at intervals, and in most of them the final result was noted.

The results were assessed as complete recovery or in three grades of partial recovery, no instance of persistent complete paralysis being seen. Recovery was defined as complete restoration of voluntary movement without any evidence of faulty reinnervation or contracture. The grades of incomplete recovery were defined as follows:

1. *Incomplete Recovery with No Disability.*—These patients stated that the face was normal, but residual signs could be detected in the form of associated movements. This is a small but important group vitiating the results of studies based on a postal questionary (James and Russell, 1951).