by comparing the children's names with the list of names of all the children who had died of leukaemia in Britain between 1945 and 1958.

Altogether information was obtained about 39,166 liveborn children whose mothers were known to have been subjected to abdominal or pelvic irradiation during their pregnancy. Among their children, nine were discovered to have died of leukaemia before the end of 1958. The expected number was estimated to be 10.5. There was no evidence of any disproportionate occurrence of leukaemia among the children who had been most heavily irradiated nor among the children who had been irradiated early in intrauterine life.

Published data on the leukaemogenic effect of irradiation *in utero* are conflicting. It is concluded that an increase of leukaemia among children due to radiographic examination of their mother's abdomen during the relevant pregnancy is not established.

We are most grateful to the Registrars-General for England and Wales and for Scotland and to the individual registrars and local authorities who assisted us in obtaining information from the birth and death registers; to the consultant staff of the Eastern General Hospital, Elsie Inglis Memorial Hospital, Royal Infirmary and Western General Hospital, Edinburgh, and of the Central Middlesex Hospital, Hammersmith Hospital, Paddington General Hospital, and Queen Charlotte's Maternity Hospital, London, who allowed us to examine the records of their patients; to the members of the radiological and records departments of the hospitals who assisted in the extraction of the hospital data; and to Mrs. R. Ash, Miss F. Callaby, Mrs. A. Frackiewicz, Mrs. E. A. O. Gray, Miss K. Jones, Mrs. M. Kidd, and Mrs. V. Peaty, who extracted the basic data and assisted in the analysis of the results.

REFERENCES

- Court Brown, W. M., Doll, R., and Hill, A. B. (1960). To be published.
 — Spiers, F. W., Duffy, B. J., and McHugh, M. J. (1960). *Brit. med. J.*, **1**, 1753.
 Ford, D. D., Paterson, J. C. S., and Treuting, W. L. (1959). *J. nat. Cancer Inst.*, **22**, 1093.
 Hewitt, D. (1955). *Brit. J. prev. soc. Med.*, **9**, 81.
 Kaplan, H. S. (1958). *Amer. J. Roentgenol.*, **80**, 696.
 Kjeldsberg, H. (1957). *T. norske Lægeforen.*, **77**, 1052.
 MacMahon, B. (1958). Paper read to the American Public Health Association, December, 1958.
 Murray, R., Heckel, P., and Hempelmann, L. H. (1959). *New Engl. J. Med.*, **261**, 585.
 Polhemus, D. W., and Koch, R. (1959). *Pediatrics*, **23**, 453.
 Stewart, A., Webb, J., Giles, D., and Hewitt, D. (1956). *Lancet*, **2**, 447.
 — and Hewitt, D. (1958). *Brit. med. J.*, **1**, 1495.

During the year under review the total sum committed to research by the Mental Health Research Fund was £31,477. By March 31 this year the Fund had awarded grants to research workers of £99,844 from money contributed directly to it, besides serving as an agency for funds amounting to £33,500: a total expenditure of £133,344. One of the largest grants (£3,320) was made for a study of family patterns of psychological illness as seen in general practice and the possible treatment of such illness by a combination of social worker and general practitioner; £2,100 went to the biochemistry department of Oxford University for fundamental research into the chemical structure of certain constituents of the urine in normals and schizophrenics, and another £2,510 was given for the study of chemical changes occurring in association with mood swings in manic-depressive patients. A grant of £3,000 was made towards elucidating the response of the endocrine system to stress, and £1,632 towards clarifying the nature of the intellectual changes occurring in senile dementia. (*Annual Report, 1959-60*, Mental Health Research Fund.)

LEUKAEMIA FOLLOWING RADIOIODINE TREATMENT OF THYROTOXICOSIS

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At least 60,000 patients have been treated for thyrotoxicosis with radioiodine during the last 20 years, and it is to be expected that leukaemia will have developed fortuitously in some of these patients, particularly since this treatment is most commonly given at ages at which the natural leukaemia incidence is high.

Reports have already been published of eight cases of leukaemia in patients previously treated with radioiodine for thyrotoxicosis (Pochin *et al.*, 1956; Abbatt *et al.*, 1956; Childs, 1956; Chapman, 1956; Werner *et al.*, 1957; Blomfield *et al.*, 1959; Vetter and Höfer, 1959; Kennedy and Fish, 1959), and 10 further unpublished cases are known to have occurred. It is obviously most important (1) to assess the number of cases that would be expected to have occurred purely on a chance basis, whether radioiodine treatment had been given or not; and (2) to establish the total number of cases that have in fact occurred.

In the present report an attempt is made to deal with the first of these problems as regards the United Kingdom, by determining the numbers of thyrotoxic patients that have been treated with radioiodine in this country, with estimates of their sex and age distribution and so of the leukaemia incidence to be expected since treatment on a purely chance basis. Preliminary estimates are given for certain other countries also.

The second problem is the more difficult, since the "follow-up" of these patients after treatment is unlikely to be complete and since a previous thyrotoxicosis, successfully treated with radioiodine, may presumably not always be recorded on the death certificate of a patient dying of leukaemia. It is hoped, however, that the evaluation and discussion of the first problem may in itself help to elicit information about further cases of leukaemia which may have occurred; and a study of the characteristics of such cases might give some evidence whether all could have arisen by chance or whether some may have been induced by the radioiodine treatment.

Survey in the United Kingdom

Letters were written to all physicians or hospitals in the United Kingdom that were believed to be using radioiodine in the treatment of thyrotoxicosis, a list having been prepared of all those authorized by the Medical Research Council (1948) to receive radioiodine for this purpose. This list was checked against one including all addresses to which any consignment of radioiodine greater than 10 mc. had been issued by the Radiochemical Centre, Amersham, during the previous year. The letters asked for information of any case of leukaemia known to have occurred since such treatment, the total numbers of patients treated, the numbers treated in each particular year, and the sex and age distribution of patients at the time of treatment.

*Work undertaken on behalf of the Medical Research Council.

Replies were received to all of the letters, and gave the following information:

(a) No cases of leukaemia were reported other than those already published (Pochin *et al.*, 1956; Abbatt *et al.*, 1956; and Blomfield *et al.*, 1959).†

(b) The total numbers of patients treated were estimated in all cases. A total of 10,542 patients had been treated at the 47 centres by mid-1959 (Fig. 1), mainly in clinics dealing with substantial numbers of cases (Table I).

TABLE I

No. of patients treated	1-24	25-49	50-99	100-199	200-399	400-799	800-1,599
No. of centres	8	6	6	8	12	5	2

(c) Information about the numbers treated in each year was given in respect of 85% of all patients (Table II). The remaining eight centres gave total numbers and the year in which the treatment was introduced, or gave numbers individually for recent years only. In these instances,

FIG. 1.—Values for the United Kingdom of total patients treated with radioiodine for thyrotoxicosis (upper curve); and numbers of new patients treated per year (lower block diagram).

FIG. 2.—Graph illustrating the present rate of increase in the United Kingdom of the total experience of patient-years since radioiodine treatment for thyrotoxicosis.

numbers were assigned to years according to proportions observed in the main sample. The patient-years since treatment were estimated by assuming that dates of treatment were uniformly distributed throughout the year of treatment; so that, for example, patients treated in 1950 were taken as having a mean period of nine years from treatment until mid-1959 (Fig. 2).

(d) The age and sex of patients were given by 10-year intervals for each sex for 1,901 patients (12 centres), and by 20-year intervals for each sex for a further 4,638 patients (24 centres), 11 centres giving no analysis, or combining the male and female distributions.

Table III indicates the distribution observed in these groups. An estimate of the sex and age distribution in decades of all cases treated was obtained by assigning

†One further case has since been reported in which lymphatic leukaemia was diagnosed four months after radioiodine treatment. In this patient, however, it was subsequently found that a blood count done one month before the dose already showed presumptive evidence of leukaemia with a white-cell count of 27,300 per c.mm., of which 90% were lymphocytes.

the numbers of patients in the 20-year classes of the larger sample into decades, according to the proportions observed in the smaller sample for which such data were available.

In the absence of information on the leukaemia rate in patients after treatment for thyrotoxicosis, rates for the populations of England and Wales were used, being derived from the deaths from "leukaemia and aleukaemia" (Registrar-General, 1958) as related to the numbers of persons living of the sex and ages concerned. It was found that for a population of people of the age and sex of the patients at the time of treatment with

TABLE III

Age:	-29	30-9	40-9	50-9	60-9	70-9	80-	Total	Mean Age
Females ..	11	80	374	526	444	144	9	1,588	56.2
Males ..	3	9	75	129	86	11	0	313	55.2
(12 centres)								1,901	
Females ..		397		3,337		1,674	21	5,429	
Males ..		79		710		314	7	1,110	
(36 centres)								6,539	

Percentages assumed:

Females ..	0.7	5.3	21.1	29.8	19.3	6.3	0.3	82.8	54.9
Males ..	0.3	0.9	4.0	6.9	4.4	0.6	0.1	17.2	54.5

Leukaemia rates (cases per million per year):

Females ..	15.5	21.4	37.2	53.8	97.5	136.8	148.0		
Males ..	22.0	26.4	40.5	66.5	148.5	262.6	349.0		

Product: fraction in each sex and age group multiplied by leukaemia rate

Females ..	0.11	1.13	7.85	16.00	18.80	8.48	0.44	52.81	
Males ..	0.07	0.24	1.62	4.59	6.53	1.58	0.35	14.98	

Age-and-sex-weighted leukaemia rate (cases per million patient-years)

67.79

FIG. 3.—United Kingdom data on distribution of patients by sex and age groups at the time of radioiodine treatment (lower block diagrams, for female and male patients); natural leukaemia rate by age and sex (upper continuous curves, cases per million per year).

TABLE II

	1949	1950	1951	1952	1953	1954	1955	1956	1957	1958	Half 1959	Total
Stated Nos. of new patients treated in year (39 centres)	12	110	202	268	497	753	1,043	1,441	1,698	1,986	1,101	9,111
Estimate for whole series	12	112	206	280	532	817	1,134	1,665	1,978	2,438	1,368	10,542
Contribution to follow-up (patient-years by mid-1959)	120	1,008	1,648	1,960	3,192	4,085	4,536	4,995	3,956	2,438	342	28,280

radioiodine (Fig. 3), the incidence of leukaemia would be 67.8 cases per million per year (Table III).

With the progress of follow-up, this population will increase in mean age, and the leukaemia rate appropriate to mid-1959 is estimated as 77.8 cases per million per year, this figure being based on a population older than at the time of treatment by 2.7 years, the mean period of follow-up. With sufficient accuracy, the mean natural incidence during the period of follow-up can therefore be taken as 73 cases per million per year.

The estimate of patient-years at risk will be unduly high, since it is uncorrected for patients dying since treatment. In the absence of accurate information from complete follow-up of any groups of these patients, an approximate correction has been derived by applying the normal death rate for England and Wales to a population of the age and sex of patients at the time of treatment. On this basis, and with the observed mean follow-up of 2.7 years from treatment until mid-1959, the loss would amount to 4.5% of the estimated patient-years.†

The number of patient-years at risk for the fortuitous occurrence of leukaemia has therefore been taken as 4.5% lower than that given in Table II, and is thus estimated as 27,000 patient-years.

When this figure is combined with an age-and-sex-weighted leukaemia incidence of 73 cases per million patient-years, it appears that 2.0 cases of leukaemia should have arisen by chance in treated patients in the United Kingdom by mid-1959.

By mid-1960 the total of 28,280 patient-years will have been increased owing to the addition of one year for each patient treated before mid-1959 (adding 10,542 patient-years) and owing to new patients treated during the year (taken as 2,800) with a mean period of half a year for each, giving an estimated total of about 40,220 patient years. This total corresponds to 13,342 patients, giving a mean follow-up of 3.0 years. On the basis already considered, the loss by natural deaths would be 5.0% and the average leukaemia rate would be 73.4 cases per million patient-years: so that a total of 2.8 cases of leukaemia would have been expected by chance by mid-1960 (Table IV).

TABLE IV

Date	Patient-Years	Average Leukaemia Rate (Cases per Million Patient-Years)	Estimated Cases
Mid-1959 ..	27,000	72.8	2.0
Mid-1960 ..	38,200	73.4	2.8

With the limited numbers involved in this country, the comparison between three cases observed and the number expected gives a very insensitive test of whether leukaemia is being induced by this treatment or whether all cases may be arising fortuitously. The expected figure of 2.8 will have a standard error of 1.7, and so would be readily consistent with any observed number from 0 to 6 and certainly with the known incidence of three cases in this country so far. These values are, of course, all dependent on the assumption that the

†The corresponding figure actually observed in groups of patients treated in the United States with radioiodine for thyrotoxicosis, and in which a follow-up better than 90% was maintained, has been 2.1% as based on a total sample of 1,849 patients during a mean follow-up period of 4.8 years. In a larger sample in which the dates of death were not recorded, a 3.7% death-rate occurred among treated patients in a mean follow-up period of 4.8 years as judged from a sample of 7,286 patients.

incidence of leukaemia in treated thyrotoxicosis is the same as in the rest of the population. The present known occurrence of leukaemia after radioiodine treatment in the United Kingdom thus does not significantly exceed the number to have been expected by chance alone. But it is clearly desirable that an estimate should be made of the number of cases that would be expected over the wider area corresponding to the 18 published and unpublished cases of leukaemia which have been reported from the United States, Canada, Austria, and the United Kingdom.

Minimum Estimate

It is comparatively easy to obtain a minimum estimate for this figure, using totals of cases known to have been treated in these countries alone, even though these totals are not comprehensive, and ignoring cases treated in all other countries. A true estimate is more difficult to derive, since full returns are not yet available even from the countries from which cases of leukaemia have been reported, and since it is clearly necessary to estimate the numbers of treatments in all countries using radioiodine therapeutically and not selectively in those in which a case of leukaemia has been observed. A minimum figure will be considered first.

With the help of Dr. H. Vetter, replies have been obtained from the three clinics dealing with the great majority of all patients treated with radioiodine in Austria. By mid-1959 461 patients had been treated, with a total of 1,303 patient-years since treatment. Table V gives the estimated total of patient-years by

TABLE V.—Estimates as for Mid-1960

Country	Replies from Main Clinics	Patients Treated	Patient-Years	Leukaemia Rate (d./m./yr.)	Cases Expected by Chance
U.K. ..	All (47)	13,300	38,200	73	2.8
U.S.A. ..	Most (67)	31,400	142,000	106	15.1
Canada ..	All (34)	13,900	40,000	80	3.2
Austria ..	.. (3)	600	1,700	(73)	0.1
		59,200	221,900		21.2 (S.D. 4.6)

mid-1960, assuming a 5% correction for deaths since treatment. (An age-and-sex-specific leukaemia incidence has been calculated on the basis of U.K. rates.)

With the help of Dr. Sidney Werner, figures have also been sought from 80 major clinics using radioiodine therapeutically in the United States. Replies were received from 67 of these, giving totals of 29,706 patients and 142,622 patient-years by the end of 1959, the mean period of follow-up being 4.8 years. The total estimated for mid-1960, using a 10% correction for deaths during the 5.0-year mean period of follow-up, is 142,000. The age and sex distribution of patients at the time of treatment was given for 6,923 patients from 19 clinics, and the normal U.S. leukaemia rate for 1957 for such a population is equivalent to 91.2 cases per million patient-years. This value would rise to 122 cases per million patient-years at the end of a period of follow-up until mid-1960, and a mean incidence of 106 has been taken for these patients.

With the help of Dr. W. J. D. Cooke, replies have been obtained from all of the 34 clinics listed as using radioiodine therapeutically in Canada, and indicate a total of 10,298 patients and 30,892 patient-years by mid-1959. An estimate is thus obtained of 40,000 patient-years of follow-up by mid-1960 using a 5% correction for natural deaths during the 3.0-year mean

period of follow-up. The sex and age distribution of Canadian cases at the time of treatment was obtained from a sample of 2,335 patients from 16 clinics and, when combined with the natural Canadian leukaemia rate for 1958, indicated an age and sex specific rate of 72.3 at the time of treatment, corresponding to an average rate of 80 during the follow-up period.

It will be seen from Table V that, on the assumptions that have been made, a total of at least 21 cases of leukaemia would have been expected to have arisen by chance by mid-1960 in those countries alone from which cases have been reported after radioiodine treatment of thyrotoxicosis. This figure, although a minimum estimate, exceeds the cases known at present to have occurred, and would be readily consistent with any actual number of cases from 14 to 28.

Certain inaccuracies in this comparison arise because the frequency with which leukaemia has been diagnosed subsequent to radioiodine treatment has been compared with an expected frequency of *deaths* from leukaemia. In a correct comparison of deaths from this cause with expected deaths, (1) the total of diagnosed patients should be decreased by the number who had not died by the date of review (one, with three unknown, at mid-1960); but (2) it should be increased by the number of patients in whom a diagnosis had been made before treatment but who had died before the date of review. Of the three patients referred to in the footnote§ (p. 1549), one had died and two were surviving at mid-1960.

It should be emphasized also that the total of diagnosed patients is that known to me at mid-1960, but replies to letters requesting information on unpublished cases were being received mainly in the last quarter of 1959 and the first quarter of 1960. It is likely that subsequent diagnoses would have been notified by the authors of these letters (or during a discussion of these figures at the International Goitre Conference in July, 1960), and subsequent notifications were received in the first quarter of 1960, but the totals cannot, in any case, be regarded as comprehensive or as complete to the date of review.

True Estimate

The laborious task of estimating the total of all patients treated with radioiodine, and the total number of cases of leukaemia to be expected fortuitously, becomes less urgent when it is found that the present known cases are at least not in excess of the chance expectation. If it was found that more cases had occurred than are at present known, it might clearly be important to know the true figure, although the application of a normal leukaemia rate to treated thyrotoxic

TABLE VI

Country	Population (Millions)	Cases per Year per Million	Patient-Years per Million	Mean Follow-up (Years)
United Kingdom	52	53	730	2.8
U.S.A.	177	39	800	5.0*
Canada	17.5	170	2,300	3.0
Austria	7.0	14	240	2.9
Australia	10.0	51	720	2.5
France	45	67	1,100	3.3†
Italy	50	22	100	2.3*
Republic of Ireland	2.9	20	120	2.0

* Data incomplete. † Approximate figures.

patients would remain quite unjustified. In different countries there is substantial variation both in the utilization of this form of treatment (Table VI) and in the age distribution and mean period of follow-up of patients treated (Table VII). It is impossible, therefore, to estimate the total number of cases of leukaemia on any basis of patient-years per million of population, although it is clear that this total will substantially exceed the minimum estimate, since many countries of large total population are known to be using radioiodine extensively.

The questions already discussed have dealt only with the numbers of cases observed, and two further points require consideration: the intervals between radioiodine treatment and the onset of leukaemia; and the types of leukaemia occurring.

Intervals Between Treatment and Diagnosis of Leukaemia

With the first few cases of leukaemia that occurred after treatment, it seemed that an interval of about 18 months between treatment and symptoms or diagnosis of the leukaemia was occurring with undue frequency if the development of leukaemia was fortuitous, and it seemed likely on these grounds alone that such cases might be being induced by radioiodine. With the rather fuller present experience of larger numbers of cases it becomes clear (Table VIII) that the intervals between radioiodine treatment (or first treatment with radioiodine) and the diagnosis of leukaemia are much more widely scattered, and it seems unlikely that the distribution of these time intervals alone gives any clear suggestion that cases are being induced by radioiodine. The distribution of time intervals is shown in Fig. 4.

An attempt has been made to compare this distribution with that to be expected if the onset of leukaemia were fortuitous and occurred at time-intervals after the radioiodine which corresponded only to the numbers of patients who had been under observation for the various intervals after the dose. The relative numbers of

TABLE VII.—Age Distribution of Patients at Time of Treatment with Radioiodine

Country	Percentage								Approx. Mean Age
	Females				Males				
	-39	40-59	60-79	80-	-39	40-59	60-79	80-	
U.K. (36)	6.1	51.0	25.6	0.3	1.2	10.9	4.8	0.1	55
U.S.A. (19)	17.2	38.8	20.7	0.4	3.5	13.0	6.2	0.2	51
Canada (17)	22.8	38.2	14.3	0.3	6.4	12.6	5.3	0.0	48
Australia*	22.6	44.6	14.8	0.0	2.8	11.8	3.2	0.0	49
Austria (1)	11.7	53.1	18.6	0.0	3.0	9.8	3.8	0.0	52
Eire (1)	6.2	53.5	28.9	0.0	0.7	7.5	3.4	0.0	55
France (3)	16.2	54.7	13.4	0.1	2.6	11.0	1.9	0.0	49
Italy (6)	24.0	42.6	8.1	0.1	5.3	18.2	1.7	0.0	46
Japan (1)	48.5	26.4	3.1	0.0	11.1	10.3	0.4	0.0	39

Figures in parentheses after the names of countries indicate the number of clinics providing data on which the age distributions are based.

* Based on a total of 653 patients "from various clinics."

patients who have passed through each of the years since treatment have been calculated from data from the U.K., U.S.A., and Canada, according to the proportion of patients treated in each year since this therapy was introduced. Fig. 4 gives a comparison between the distribution of time intervals observed between treatment and diagnosis for the 18 cases and that to be expected by chance according to the proportion of

FIG. 4.—Intervals in years between radioiodine treatment and the diagnosis of leukaemia in 18 patients (block diagram) compared with incidence expected fortuitously on the basis of numbers of patients at risk during successive years after treatment (expected frequencies indicated by symbols, as calculated according to U.K., Canadian, and U.S. figures for intervals since treatment).

patients "at risk" during each of these intervals. This analysis is considerably affected by the limits chosen for the class intervals and by the small numbers of patients involved, but at least the method adopted does not appear to indicate any significant departure from a random distribution.

It may be expected, moreover, that a number of factors will introduce bias into the intervals recorded. Cases are less likely to be observed as having developed leukaemia if this occurs later than one or two years after treatment, when the patient may be lost to the thyroid clinic, since the thyrotoxicosis is likely then to be adequately controlled by the radioiodine dose. Moreover, some clinics may publish those cases developing leukaemia at time intervals after radioiodine which appear compatible with a possible induction, but may not regard it as equally necessary to publish a record of those cases developing the disease so soon after the

radioiodine that it would be unlikely to have been induced by it owing to the shortness of this "latency"; and two such cases are known not to have been published for this reason. Moreover, routine blood examination before a therapeutic radioiodine dose may detect symptomless leukaemia, and cause a deficiency in cases diagnosed within the year or more after treatment. Three cases of leukaemia are known to have been detected in this way,[§] and would otherwise have appeared as cases developing soon after treatment.

Types of Leukaemia

On examining the types of leukaemia that have been diagnosed after radioiodine treatment, it appears that acute forms occur in a somewhat higher proportion than would be expected in a population of the ages concerned. The types of leukaemia diagnosed are shown in Table VIII. Excluding one unascertained type, they comprise 13 acute and 4 chronic or subchronic forms, a proportion of 76% therefore having been diagnosed as acute. It is difficult to obtain a representative figure for the frequency with which leukaemia presents in an acute form at various ages for populations throughout North America and Western Europe, and the figures for England and Wales are uncertain, since the form of registration of deaths from leukaemia does not allow this proportion to be defined. On the basis of a survey (Court Brown and Doll, 1959; data for the years 1955-7), however, the proportion to be expected in England and Wales in a population of the age and sex of cases at the time of treatment would be 57% with an expectation of 9.7 acute cases amongst the 17 as compared with 13 observed. The difference between the expected and observed values is such as would be equalled or exceeded fortuitously in about 5% of trials. This point is thus suggestive and merits further examination, but is obviously not conclusive of leukaemia induction. Moreover, since the classification of leukaemia as "acute" is not based on objective criteria, and since diagnoses have been quoted without review of sections or time course, too much reliance cannot be placed on these frequencies.

[§]For information on these patients I am indebted to Professor Rosenheim, Dr. Sheline, and, for the case referred to in the earlier footnote,† to Dr. K. E. Hainan.

TABLE VIII

Case	Sex	Age at Time of (1st) Dose	Dose(s) (mc. ¹³¹ I)	Interval (Months) from (1st) Dose to			Diagnosed Type of Leukaemia	Place of Origin
				Onset of Symptoms	Diagnosis	Death		
1	F	41	7.1	19	24	29	Acute	U.K. (London)
2	F	67	17.0	18½	19	19½	" myeloid	
3	M	46	5.3	?	14	24	"	U.S.A. (Rochester, Minn.)
4	M	65	4	?	26	28	Chronic monocytic	U.S.A. (Boston)
5	F	28	2.1	17	18	22	Acute ? granulocytic	U.S.A. (New York)
6	F	50	4.9	17	17	17	" monocytic	U.K. (Sheffield)
7	M	50	7.1	18	18	18	" stem cell	Austria (Vienna)
8	M	38	5.5	22	22½	24½	" granulocytic	U.S.A. (North Carolina)
9	M	60	14.3	?	86	90	Chronic monocytic	U.S.A. (Cleveland)
10	M	65	3.9	> 38	43	50	Acute	U.S.A. (New York)
11	M	73	8.9	35	36	37		U.S.A. (Iowa)
12	M	60	28	Probably 0	3	15	Subchronic lymphatic	Canada (Toronto)
13	M	64	8.5	?	60	62	Acute	U.S.A. (Rochester, Minn.)
14	M	?	4	?	(4 yr.)	?	Acute blast cell	Canada (Vancouver)
15	M	54	3.5	52	54	?	" myeloblastic	U.S.A. (New York)
16	F	64	8	?	(1 yr.)	?	Chronic monocytic	U.S.A. (Columbia)
17	?	?	?	?	(4 yr.)	?		Canada (Montreal)
18	M	58	46	32	33	42	Acute monocytic	Canada (Toronto)

Note.—In the following case, a diagnosis of lymphosarcoma appeared more probable than that of leukaemia.

	F	69	12.5	?	51	?	Lymphosarcoma or aleukaemic lymphatic leukaemia	Canada (Winnipeg)
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Conclusions

The present evidence, while giving no support to the idea that leukaemia is induced by the radioiodine treatment of thyrotoxicosis, neither excludes such induction nor sets any upper limit to its possible frequency. No estimates have been obtained, either of the frequency with which leukaemia has in fact occurred or of the number of cases to be expected from all countries using radioiodine therapeutically, nor has evidence been produced that the natural leukaemia rate is appropriate to patients with treated thyrotoxicosis. The only value of this report is in showing that the information at present available appears to give no indication of the induction of leukaemia.

It seems important that the quantitative aspect of this question shall be studied more widely and kept under review, not only to detect, or estimate the frequency of, any leukaemia induction that might occur, but also because the total of patient-years experienced since treatment is increasing rapidly in all countries concerned, and many more cases of leukaemia will occur fortuitously among these patients during the next few years. Unless the likely scale of this increase is appreciated, there is some risk that the mere multiplication of case reports will seem to afford evidence that leukaemia is being induced by the treatment.

If all the 18 known cases of leukaemia, but no others, had been induced by radioiodine among the 60,000 patients treated in the four countries primarily considered, and perhaps 100,000 in all countries, the risk of this complication within an average time of about four years from treatment would be in the region of 0.02 to 0.03%. Even if there should prove to be an induced incidence equalling the natural rate, the level of risk (at 21.2 per 60,000 patients, or 0.035%, in four years) would still be small relative to the known risks of surgery or the prolonged use of antithyroid drugs.

If it were assumed that this treatment involves an average irradiation of blood-forming organs of 10 to 15 rads, and that one case of leukaemia was induced per year per million exposed per rad, an induction rate of 10 to 15 per million per year might be expected initially, which is equivalent to about 10 to 20% of the natural leukaemia rate at the age of treatment. Such an excess would not be detectable numerically on a total present natural expectation of, say, 40 (± 6.3 , S.D.) cases, although it is possible that a study of "latencies" or types of leukaemia might reveal it.

A total leukaemia risk of 20 cases per million exposed per rad during remaining life would imply, on the same basis, a risk of 0.02% from leukaemia attaching to this form of treatment. It will be appreciated, however, that no prediction of this sort can be based with any confidence on the results of other forms of radiation exposure, particularly as higher radiation doses are received during the course of this treatment locally in the liver, and, of course, in the thyroid gland itself, in which in some cases of thyrotoxicosis active lymphoid follicles with true germinal centres may be observed. It is suggested, therefore, that the numbers of cases of leukaemia following radioiodine treatment of this condition should be kept under review, however slight the risk of leukaemia induction appears likely to be.

¶ It is easy to show that, if equal numbers of new patients are treated each year, the total of patient-years will increase with the square of the time since the introduction of the treatment. If numbers treated each year are increasing linearly, the total of patient-years, and so the expected cases of fortuitous leukaemia, will increase with the cube of this time.

Summary

Leukaemia is known to have developed in 18 patients who had previously been treated with radioiodine for thyrotoxicosis, three cases having occurred in the United Kingdom, ten in the United States, four in Canada, and one in Austria.

About 60,000 thyrotoxic patients have been treated with radioiodine in these four countries alone, with an estimated total of over 220,000 patient-years since treatment until mid-1960.

Application of natural leukaemia rates appropriate to the sex, age, and nation of these patients suggests that approximately 21 (or from 14 to 28) cases of leukaemia would be expected to have occurred fortuitously among them whether radioiodine had been given or not. The numbers of patients treated in those countries in which cases of leukaemia have not been observed would raise this total considerably.

The intervals between radioiodine treatment and diagnosis of leukaemia are consistent with a chance distribution.

Of the 17 cases in which the type of leukaemia is known, 13 were diagnosed as acute, a proportion somewhat, but not strikingly, higher than that to be expected on the basis of data for England and Wales on the frequency of acute leukaemia in a normal population of corresponding age and sex.

These estimates are held to indicate that the present known records of cases in which leukaemia has followed radioiodine treatment of thyrotoxicosis gives no indication that this treatment is inducing leukaemia. At the same time they clearly do not exclude this possibility, since the total number of cases of leukaemia might greatly exceed the number at present known to have occurred.

I wish to acknowledge with appreciation the help of Dr. W. J. D. Cooke, Dr. Murray Cunningham, Dr. D. K. O'Donovan, Dr. M. Negri, Dr. D. J. Stevens, Professor M. Tubiana, Dr. H. Vetter, and Dr. Sidney Werner in the collection of information; the advice of Dr. R. Doll on presentation of the data; and the forbearance and helpfulness of many busy clinicians in a number of countries in dealing with questionnaires.

REFERENCES

- Abbott, J. D., Farran, Helen E. A., and Greene, R. (1956). *Lancet*, **1**, 782.
Blomfield, G. W., Eckert, H., Fisher, Monica, Miller, H., Munro, D. S., and Wilson, G. M. (1959). *Brit. med. J.*, **1**, 63.
Chapman, E. M. (1956). Proceedings of Conference on Radioiodine, Argonne Cancer Research Hospital, p. 33 (line 9, in the statement erroneously attributed to Dr. Werner).
Childs, D. (1956). *Ibid.*, p. 33.
Court Brown, W. M., and Doll, R. (1959). *Brit. med. J.*, **1**, 1063.
Kennedy, W. M., and Fish, R. G. (1959). *New Engl. J. Med.*, **260**, 76.
Medical Research Council (1948). *Brit. med. J.*, **2**, 569.
Pochin, E. E., Myant, N. B., and Corbett, B. D. (1956). *Brit. J. Radiol.*, **29**, 31.
Registrar-General (1958). *Statistical Review of England and Wales for 1957. Tables, Medical*. Table 17/204, p. 142; and Table 1, Total Population, p. 2.
Vetter, H., and Höfer, R. (1959). *Brit. J. Radiol.*, **32**, 263.
Werner, S. C., and Quimby, Edith H. (1957). *J. Amer. med. Ass.*, **165**, 1558.

The Royal Society of Health has approved an application from the Malta Government that an Overseas Examination Board of the Society should be established in the island. The Malta Government's existing examination for health inspectors, qualifying for appointments in Malta, will become an examination of the new Board. Dr. J. GALEA, Chief Government Medical Officer of Malta, has been appointed chairman of the new Board.