Medical Radiations and Leukaemia: a Retrospective Survey*

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Ionizing radiation is the only extraneous factor known to be capable of causing leukaemia in man. This has been shown beyond doubt by the American studies on leukaemia incidence following the atomic bombing of Hiroshima and Nagasaki (Wald, 1958 ; Heyssel *et al.*, 1960 ; Brill *et al.*, 1962) and by the British investigation of patients who had developed leukaemia after radiation therapy for ankylosing spondylitis (Abbatt and Lea, 1956 ; Court Brown and Doll, 1957). But although it is certain that radiations can cause leukaemia, very little is known about the actual part which they may play in producing the disease in the population at large. They clearly cannot account for the steady rise in leukaemia mortality that has been noted throughout the world in the past decades (Witts, 1957 ; Burnet, 1958 ; Martin, 1958 ; Stewart *et al.*, 1958), but it appears distinctly possible that a proportion of the sporadically occurring leukaemia cases may have resulted from exposure to radiation. The present report, preliminary results of which have been published (Gunz, 1961a, 1961b), gives details of a survey of the histories of patients with leukaemia. Its main objective was to compare the patients' experiences of ionizing radiation with those of a series of matched controls, and to assess the degree to which radiation exposure could have been responsible for the causation of the disease.

Materials and Methods

The material consisted of 590 unselected cases of leukaemia comprising 87.3% of all leukaemias known to have occurred in New Zealand between 1 March 1958 and 31 December 1961 ; there were also 122 cases of myelomatosis and 712 controls. A further 86 (12.3%) cases were known to have occurred in the same period but could not be included because information on them was incomplete. The age, sex, and type distributions of the 590 fully documented cases are shown in Table I ; those of the other 86 were identical.

As soon as possible after diagnosis patients or their closest relatives were interviewed by a medical practitioner with the aid of a uniform questionary. This included questions concerning a history of past radiation, and also the patients' medical, occupational, and family histories, the purpose being to establish the incidence of other factors of possible aetiological significance, besides radiations. Control patients were chosen from the local hospital population and matched for age and sex. They were otherwise unselected, except for exclusion of any known to be suffering from blood diseases. Each pair of leukaemia (or myelomatosis) and control patients was interviewed by the same practitioner. All reports were centrally coded and analysed.

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TABLE I.—*Age Distribution of Leukaemia Population*

Age	Leukaemia				Myeloma
	Acute	Chronic Granulocytic	Chronic Lymphocytic	Total	
<1	8	—	—	8	—
1	11	—	—	11	—
2	11	—	—	11	—
3	10	—	—	10	—
4	12	—	—	12	—
5	7	—	—	7	—
6	7	—	—	7	—
7	9	2	—	11	—
8	9	—	—	9	—
9	2	—	—	2	—
10	5	1	—	6	—
11	1	—	—	1	—
12	4	—	—	4	—
13	1	—	—	1	—
14–15	3	—	—	3	—
16–20	18	2	—	20	—
21–25	9	3	—	12	—
26–30	12	2	1	15	—
31–35	10	3	—	13	—
36–40	9	3	—	12	3
41–45	17	5	4	26	1
46–50	15	8	6	29	7
51–55	11	4	4	19	10
56–60	18	5	12	35	16
61–65	25	7	13	45	23
66–70	32	10	32	74	24
71–75	35	9	27	71	10
76–80	26	10	32	68	14
81–85	12	3	21	36	12
86–90	4	1	5	10	2
91–95	2	—	—	2	—
Total ..	355	78	157	590	122
Sex ratio (M : F)	1·13	1·30	2·02	1·33	0·94

Radiation Data

The initial radiation histories were compiled from the recollection of either the patients or their relatives or both. Efforts were made to confirm from hospital records all histories so obtained. This proved possible in all but a very few instances where the administration of radiotherapy was reported. It was much more difficult with radiodiagnosis. Because of this uncertainty we decided to discard all diagnostic histories except those for the 10 years preceding the onset of the leukaemia or, in the case of controls, that of the illness for which they were admitted. For similar reasons dental *x*-ray examinations were also excluded. No exposures were counted if they had been made for the diagnosis of symptoms possibly due to the leukaemia or the disease for which the control patient had been admitted. Verification of diagnostic radiations was possible in many cases in which repeated exposures were claimed to have been made. No means existed, however, of verifying negative histories, and it is therefore likely that the figures are incomplete. On the other hand, there are probably some false-positive histories ; this became clear when we failed to confirm a number of exposures which were claimed to have been given.

Calculation of Radiation Dosage

For therapeutic irradiation, dates, numbers of treatments given, field positions and sizes, and radiation factors were supplied by the radiologists concerned. Calculations of both the integral dose and that to the bone-marrow were made as previously described (Gunz, 1961b). No attempt was made to assume marrow-cavity dimensions and to apply roentgen to rad conversions so that doses might be stated in terms of absorbed dose.

For *diagnostic* irradiation an initial rough estimate was made of the probable skin doses received, on the basis of average figures supplied by the Dominion *x*-ray and Radium Laboratory for the various radiology departments concerned. For the years beginning with 1955, the dose estimates used corresponded closely to those given by Webster and Merrill (1957), but for earlier years were some three times greater.

Bone-marrow doses were calculated for all patients assessed as having skin doses totalling 10 r or more in 10 years, the method of calculation being the same as that for therapeutic exposures. Where complete radiation data were lacking, the marrow doses were based on good current practice. The adopted marrow doses were of the order of those published in the UNSCEAR (1962) Report, and by Epp *et al.* (1961) and J. Buhl (personal communication).

An alternative method of calculating doses received in diagnostic exposures was also used. This consisted in the introduction of rankings for the various examinations, the subsequent weighting of the examinations on the basis of these rankings, and the determination of the total of all weighted examinations for each group of patients. The rankings were as follows:

Barium enema	20	Abdomen, plain	4
Barium swallow	15	I.V. pyelography	4
Barium meal	15	Chest, mass min.	2
Cholecystogram	12	Head, neck, skull	1
Pelvis, lumbar spine	11	Chest, radiograph only	1
Dorsal spine	7	Arm, hand, leg, and foot	negligible
Chest, incl. fluoros.	6		

They were derived as in the example given in the footnote.[1]

Results

Therapeutic Irradiation

Among the patients there were 355 with acute, 78 with chronic granulocytic, and 157 with chronic lymphocytic leukaemia, as well as 122 with myelomatosis and 712 controls. No attempt was made to subdivide acute leukaemia according to cellular type.

Treatment by means of *x* rays or radio-isotopes had been given in the past to 47 patients subsequently found to have leukaemia, to 7 with myelomatosis, and 38 controls (Table II). Twenty-two of the isotope cases had been treated with radium, four with ^{131}I (for the sake of convenience three patients who had had only tracer—that is, diagnostic—doses of ^{131}I are included), two with ^{32}P, and one with ^{106}Ru. Integral and/or bone-marrow doses were calculated for all patients, except the following five: one woman with chronic lymphocytic leukaemia who had received 15.9 mc of ^{131}I for thyrotoxicosis four years before its onset; one man with chronic granulocytic leukaemia following on polycythaemia vera for which he had had large quantities of ^{32}P over many years; and three control patients who had been given tracer doses of ^{131}I, respectively two months, four years, and more than ten years before the onset of their disease. The integral and marrow doses of the remaining 87 patients are summarized in Table III.

TABLE II.—*Distribution of Radiotherapy*

Therapy	Number of Patients				
	A.	C.G.	C.L.	M.	C.
X-ray alone	18	7	7	6	25
X-ray and isotope	1	—	5	1	—
Isotope alone	6	2	1	—	13
Total	25	9	13	7	38
% of all patients in group	7	11·5	8·3	5·7	5·3

A = Acute leukaemia. C.G. = Chronic granulocytic leukaemia. C.L. = Chronic lymphocytic leukaemia. M = Myelomatosis. C = Control.

TABLE III.—*Doses from Therapeutic Irradiation*

	Number of Patients				
	A.	C.G.	C.L.	M.	C.
Integral doses (mega-g r)					
Less than 0·1	10	4	6	6	18
0·1–1	2	—	3	—	2
1·1–1·5	—	1	—	—	3
1·6–10	7	2	2	1	6
11+	4	1	1	—	1
Marrow doses (r):					
Less than 10	11	4	7	6	24
10–100	6	2	2	—	9
100+	8	2	3	1	2
Total	25	8	12	7	35

Table III shows that 26 of the leukaemia patients and 23 of the control patients had received radiotherapy at integral doses of less than 1.5 mega-g r, while 22 leukaemia and 24 control patients had had marrow doses below 10 r. These low-dose treatments were given for the following reasons (total 52):

Skin lesions, non-malignant	16	Gynaecological conditions	3
Skin lesions, malignant	26	Cancer of lip	2
Sepsis	2	Polyp of larynx	1
Bursitis	1	Unknown	1

In contrast with this group, Table III shows that 17 leukaemia patients but only 7 controls had received integral doses over 1.5 mega-g r, while 23 leukaemias but only 11 control patients had had marrow doses above 10 r. The excess becomes much more striking when those patients are excluded who had had therapy more than 15 years before the onset of their disease (Table IV). Twenty leukaemia patients but only four controls had had therapeutic doses of more than 1.5 mega-g r (integral) or 10 r (marrow) within the preceding 15 years. Significance tests on this group gave the following results[2]:

TABLE IV.—*Time Intervals: Cases Receiving Therapeutic Marrow Doses of 10 r or Over*

Time interval (years) Radiation to onset	Marrow dose (r)	No. of Patients				
		A.	C.G.	C.L.	M.	C.
0–15	10–100	3	2	2	–	3
	100+	8	2	3	1	1
>15	10–100	3	–	–	–	6
	100+	–	–	–	–	1
Total		14	4	5	1	11

Group	χ^2	χ^2 Corrected for Continuity	P	Fisher's Exact Probability
A v. controls	11·00	9·24	<0·01	0·0016
CG v. controls	14·62	10·42	<0·01	0·0045
CL v. controls	8·63	6·26	<0·02	0·0122

Other intergroup differences were not significant.

[1] Example of calculation of ranking for barium meal:
(*a*) *Radiography:* Average views taken (from UNSCEAR, 1958, Report), 1 AP, 2 PA, 1 LAT. Average number of films (from Adrian Report, 1960), 5.4. Skin dose (from Webster and Merrill, 1957), 4.9 r. Mean marrow dose (from UNSCEAR (1958) Report), 0.5 r. Ratio marrow/skin dose, 0.102.
(*b*) *Fluoroscopy:* Average time (from Adrian Report, 1960), 2.8 minutes. Average skin dose (multiplying 2.8 by skin-dose rate of 5 r/min. for N.Z. conditions), 14 r. Calculated marrow dose (applying marrow/skin-dose ratio of 0.102 as for radiography), 1.43 r. Marrow dose corrected for smaller field size than for radiography (by using a factor of 0.25), 0.36 r.
(*c*) *Total marrow dose:* 0.5 + 0.36 = 0.86 r. This was approximately 15 times the marrow dose for simple radiography of the chest; hence weighting factor 15 for barium meal.

[2] We gratefully acknowledge the help given on statistical problems by Miss M. T. K. Chung, M.Sc., Applied Mathematics Laboratory, D.S.I.R., Wellington.

Table V gives details of irradiation in the " high-dose " group. Among the acute cases, the lowest bone-marrow dose of 10 r was given to a boy of 2 for the treatment of a large keloid scar. We believe this dose to be equivalent to one of at least 50 r given to an adult. In the same group the case of polycythaemia vera is of doubtful significance, since acute leukaemia

TABLE V.—*Cases Receiving Therapeutic Marrow Doses Exceeding 10 r Within 15 Years: Reasons for Irradiation, Weighted Marrow Doses, and Site of Irradiation*

Acute:
Carcinoma of breast: 200, 290, 1,000 r; chest (3 cases). Arthritis of spine (spondylitis, osteoarthritis): 110, 280, 480 r; spine (3 cases).
Induction of menopause: 65, 65, 190 r; pelvis (3 cases).
Polycythaemia vera; 184 r, also ^{32}P; chest, legs (1 case).
Irradiation of keloid: 10 r; shoulder, etc. (1 child aged 2).
Chronic Granulocytic Leukaemia:
Carcinoma of breast: 143 r; chest (1 case).
Arthritis of spine: 55, 385 r; spine (2 cases).
Induction of menopause: 57 r; pelvis (1 case).
Chronic Lymphocytic Leukaemia:
Multiple skin cancers: 10, 16·6, 200 r; face, head (3 cases).
Carcinoma of cervix: 113, 300–400 r; pelvis (2 cases).
Myelomatosis:
Pain back of neck: 140 r; neck and chest (1 case).
Controls:
Arthritis of lumbar spine: 65 r; lumbar spine (1 case).
Arthritis of cervical spine: 55 r; cervical spine (1 case).
Dermatitis: 40 r; face, neck, arm, wrists (1 case).
Carcinoma of cervix: 194 r; pelvis (1 case).

may be a " natural " sequel of this disease in the absence of radiotherapy. More doubtful still are the five cases in the chronic lymphocytic group. In all of these radiation was given because of single or recurrent malignancies. Since there is a strong association between chronic lymphocytic leukaemia and second malignancies in the same patient (Gunz, 1961a), and since no less than 17.2% of the chronic lymphocytic patients in the present series showed this association, the leukaemia in the treated patients may possibly have arisen because of a genetic predisposition rather than as a result of radiotherapy. For this reason the further analysis excludes the chronic lymphocytic group.

As it has been shown (Court Brown and Doll, 1957; Heyssel *et al.*, 1960; Brill *et al.*, 1962) that both acute and chronic granulocytic leukaemia can be caused by radiation, whereas there is no similar evidence in the case of myelomatosis, we shall compare the combined acute and chronic granulocytic groups with the combined myelomatosis and control groups. In the latter there were 834 cases, 5 with histories of bone-marrow doses of 10 r or more received during the preceding 15 years. The incidence was thus 0.6%, whereas among the former groups it was 15/433 or 3.8%, the excess being significant ($\chi^2=15.06$, corrected $\chi^2=13.27$, $P<0.001$, exact probability 0.0002). Since the expected incidence among the control and chronic granulocytic groups was 2.6 cases (0.6×433), it may be concluded that 15–2.6, or 12.4, cases were possibly induced by therapeutic radiation (11.4 if the case of polycythaemia vera is excluded). This is 2.86% of all acute and chronic granulocytic leukaemias.

Diagnostic Radiation

During the 10 years preceding the onset of the disease 49% of patients with acute leukaemia, 72.9% of those with chronic granulocytic leukaemia, 62.3% with chronic lymphocytic leukaemia, 55.8% with myelomatosis, and 61.2% of controls had had diagnostic radiation. The approximate skin doses are shown in Table VI, and the marrow doses for the 116 patients with skin doses in excess of 10 r are given in Table VII. This

TABLE VI.—*Diagnostic Radiation: Skin Doses*

Dose (r)	No. and Percentage of Patients Receiving Stated Dose				
	A.	C.G.	C.L.	M.	C.
0	181 (51·0%)	21 (27·0%)	59 (37·6%)	54 (44·3%)	286 (40·3%)
1– 5	132 (37·2%)	38 (48·6%)	71 (45·2%)	44 (36·1%)	312 (43·8%)
6– 9	20 (5·6%)	6 (7·7%)	13 (8·3%)	16 (13·1%)	55 (7·7%)
10–19	18 (5·1%)	9 (11·5%)	11 (7·0%)	5 (4·1%)	50 (7·0%)
20+	4 (1·1%)	4 (5·2%)	3 (1·9%)	3 (2·5%)	9 (1·3%)

shows that the percentage of " high-dose " cases in the chronic granulocytic group was double that in the controls ($\chi^2=5.96$, corrected $\chi^2=4.991$, $P<0.05$, exact probability 0.0178). Also, the average dose in chronic granulocytic leukaemia was higher than that in the other groups. There were no other significant intergroup differences. If a single case (No. 1,121) was omitted

TABLE VII.—*Diagnostic Radiation: Bone-marrow Doses of 116 Patients With High Skin Doses*

Dose (r)	No. of Patients Receiving Dose				
	A.	C.G.	C.L.	M.	C.
<1 ..	5	3	4	1	14
1–1·9	12	5	6	6	27
2–2·9	2	3	4	–	11
3–3·9	–	–	–	1	6
4–7 ..	3	2	–	–	1
Total ..	22 (6·2%)	13 (16·7%)	14 (8·9%)	8 (6·6%)	59 (8·3%)
Average dose (r)	1·55	2·04	1·29	1·31	1·43

from the chronic granulocytic group, the average dose in it became 1.57 r, or nearly the same as in the other groups. Case 1,121 scored the highest total marrow dose in the series (7.5 r), but there was considerable doubt about the details of exposures.

Because of the uncertainties involved in calculating doses based on patients' statements which could often not be checked, an alternative estimate of probable bone-marrow doses was obtained by means of the " weighting " method. The total number of each type of examination was determined in each group of patients and multiplied by the weighting factor (see above). The weighted totals were added and compared with each other. These figures, in arbitrary units, are shown in Table VIII.

TABLE VIII.—*Weighted Total of Diagnostic Examinations Received by All Patients*

Nature of Examination	Weighted No. of Examinations in Group				
	A.	C.G.	C.L.	M.	C.
Chest, convent. (incl. fluoros.)	209	94	110	106	760
Chest, M.M. ..	202	38	60	102	342
Abdomen, plain ..	40	28	32	24	172
Gall-bladder ..	216	168	132	168	456
I.V. pyelogram ..	40	12	36	24	80
Barium meal	570	210	255	195	840
Barium swallow ..	45	—	15	15	75
Barium enema ..	100	60	140	160	580
Spine (T or L) ..	333	81	108	126	522
Pelvis, etc.	176	110	110	44	550
Total, trunk	1,931	801	998	964	4,377
Average per patient	5·45	10·06	6·35	7·89	6·15
Legs, arms	—	—	—	—	—
Skull, neck	34	9	13	9	51

Table VIII shows that in all groups the average doses contributed by examinations of the limbs, head, and neck were unimportant compared with those received during examinations of the trunk. For this reason only the latter figures were used for analysis. It could again be seen that the average radiation for the patients with chronic granulocytic leukaemia was much higher, at 10.06, than that for the other groups (5.45–7.89). However, there were again very pronounced disparities between the doses received by individual patients. When the two top-scoring patients (Cases 835 and 1,121) were omitted from the chronic granulocytic group, the total score for this group became reduced from 801 to 485 and the average per patient to 6.28; in the myelomatosis group omission of Case 1,175 reduced the average to 7.2. Given the uneven age distribution in the various groups (see below), the means in Table VIII could not thus be said to be dissimilar, and it appeared that any excess of diagnostic radiation exposure calculated for some groups of patients resulted from an unusually heavy irradiation of a few individuals rather than from a raised exposure of the group as a whole.

Intrauterine Irradiation

Information on diagnostic radiation given to the mother during the pregnancy which led to the birth of the affected child was available for 102 leukaemic children under 15 but for only 89 controls (Table IX). No foetal doses could be calculated in any of these cases.

TABLE IX.—*Intrauterine Irradiation*

Radiation Site	No. of Mothers Given Radiation	
	Leukaemia Cases	Controls
Abdomen	14 (13·7%)	11 (12·3%)
Chest	8	8
Other	2	2
None	78	68
Total	102	89

Discussion

Material

The 590 cases of leukaemia constituted 87.3% of all new cases occurring in New Zealand during a period of 46 months. The other 86 cases known to have occurred were excluded solely because their data were incomplete. The age, sex, and type distributions of both groups were identical, so that our sample can be regarded as representative of the total leukaemia population in the country.

The matched controls were chosen from the local hospital population and interviewed by the same practitioners as the leukaemia patients in order to minimize observer bias. The choice of hospital rather than healthy controls was dictated by their availability. As previously described (Gunz, 1961a, 1961b), in order to test for the presence of systematic bias due to this choice, the controls were compared with a smaller non-hospital and a second hospital group, and no significant difference was found in the radiation exposure of all three groups. It therefore seemed unlikely that serious systematic bias was introduced by the choice of hospital controls, but it is realized that some bias is probably unavoidable, whatever the method by which controls are selected in this type of investigation.

The rate of exposure to radiotherapy in our patients—an average of 6.5%, or 5.3% to 11.5% in the various groups—was high compared with that in other published series (2.8%, Stewart *et al.*, 1962 ; 2.5%–8%, Lilienfeld, 1959). Because most of the patients' statements could be objectively confirmed, we believe that our figures give a valid measure of exposure to radiotherapy ; however, they almost certainly underestimate that to diagnostic radiation, because here the recall of patients was much more uncertain. Even so, the findings appear reasonable when compared with those of others. Thus we found a history of diagnostic radiation, within 10 years of the onset of the disease, in 49%–72.9% of our groups, as against 48%–54% in the series of Stewart *et al.* (1962) and only 20% in Faber's (1958) earlier material. As a further check on completeness of reporting, a calculation of the total number of exposures was made by multiplying the known examinations with the average number of exposures per examination as given in the Adrian Report (1960). The sum of 5,216 so obtained corresponded to 0.37 annual exposure per individual ; this may be compared with an annual rate of 0.46 obtained in an earlier New Zealand survey (UNSCEAR, 1958), which included some examinations deliberately excluded by us ; and with the British rate of 0.26 annual exposure per individual which we calculated from the figures quoted in the Adrian Report (1960). We conclude that the degree of exposure to diagnostic radiation, as reported to us, though certainly inaccurate, was of a reasonable order of magnitude compared with the probable true one prevailing in New Zealand.

Interpretation of the Findings

We found a significant excess of *therapeutic irradiation* in the histories of leukaemia patients. This was restricted to patients who had received relatively large doses (integral doses above 1.5 mega-g r or bone-marrow doses above 10 r), lower doses being equally common in patients and controls. The excess became clearer when individuals irradiated more than 15 years prior to the onset of the disease were excluded. Since it has been shown (Cobb *et al.*, 1959) that the effect of radiation is probably unimportant at more remote periods, such a procedure seemed justified. The excess of high-dose radiotherapy was found in patients with acute as well as the two chronic forms of leukaemia ; it amounted to a little less than 3% of all patients with acute and chronic granulocytic leukaemia, and since the doses received were of the same order as those thought to have led to the onset of these forms of leukaemia in other circumstances (such as in Hiroshima and during the treatment of spondylitics), it seems reasonable to attribute an aetiological influence to the radiation in these patients. In the patients with chronic lymphocytic leukaemia, however, who had had high-dose radiotherapy there was a complicating relationship between chronic lymphocytic leukaemia and the cancers for which the irradiation had been applied, and it is therefore impossible to assert that the latter was causally related to the onset of the leukaemia. Other evidence (Court Brown and Doll, 1957 ; Brill *et al.*, 1962) also suggests that in chronic lymphocytic leukaemia radiation may be of relatively little importance compared with its role in acute and chronic granulocytic leukaemia.

Exposure to *diagnostic radiation* was low in the great majority of patients. Most received skin doses in the very low range (Table VI), and fewer than 10% had skin doses which, according to our rough estimates, exceeded 10 r. The marrow doses all lay below 10 r (Table VII). However, there were more patients with relatively high exposures in the acute and chronic granulocytic than in the control groups, and the chronic granulocytic group also showed a higher average score when weighted mean doses were used for the calculations (Table VIII). Because the various groups were not comparable in the age distribution of their members (Table I), the acute group having especially an excess of children and the chronic lymphocytic group an excess of old people, the patients in each group were matched with their own controls ; it was then seen that the excess of high-dose patients in the acute group was confined to adults ; in the other groups the separation of controls left the previous findings unaltered. In both adult acute and chronic granulocytic leukaemia the removal of one or two high-scoring patients caused a reduction of the average radiation experience to a level comparable with that in the other groups. The pronounced skewing of the dose distribution in our acute and chronic granulocytic leukaemia patients makes it appear tempting to conclude that, if diagnostic radiation was concerned in the aetiology of any cases of leukaemia, it was so only in those who received the highest marrow doses ; the figures suggest a maximum of 1% of all acute and chronic granulocytic leukaemias as being possibly so determined.

We are not aware of any published work on bone-marrow doses produced by diagnostic radiation in leukaemia patients. Neumann (1962) found no excess of leukaemia over the expected incidence in a large group of patients with chronic tuberculosis who had had frequent diagnostic procedures, including fluoroscopy, over many years ; however, he gave no dose measurements, nor did Birch and Baker (1960), who came to similar negative conclusions in children under the care of a cardiac clinic and with histories of repeated fluoroscopic examinations. The lack of dose estimations also makes it difficult to evaluate the recent finding by Stewart *et al.* (1962) of an 8% excess of diagnostic irradiation of the trunk in acute and chronic granulocytic leukaemia. (It should be noted that in our comparable groups there was an excess of the high-dose examinations of the spine and gastro-intestinal tract, but a marked

deficit in chest exposures, compared with the controls, especially in adults with acute leukaemia.)

The question of the possible leukaemogenic action of diagnostic *x* rays must be examined in the context of what is known about dose levels in accepted cases of "radiation leukaemia." It is emphasized that in all those cases in which leukaemia most clearly followed irradiation the doses received were large or very large (Court Brown and Doll, 1957 ; Cronkite *et al.*, 1960 ; Brill *et al.*, 1962) and were applied either to the whole or to very substantial parts of the body. Only relatively few such "radiation leukaemias" have been reported: as late as 1960 their total, including the Japanese cases, was only 226 (Cronkite *et al.*, 1960). An important problem concerns the relationship between the size of the dose and the risk of leukaemogenesis, a linear (Lewis, 1957), quadratic (Burch, 1960), and quantal (Mewissen, 1959) relationship having been variously postulated and criticized (Brues, 1958 ; Lamerton, 1958). Because of the paucity of accepted cases and the lack of satisfactory dose measurements in some of them, the shape of the dose-response curve remains uncertain: there are indications that it may be linear at radiation levels exceeding 50–100 rads (Cronkite *et al.*, 1960 ; Upton, 1961 ; Brill *et al.*, 1962), but no satisfactory data exist below this range, and, in particular, it is unknown whether there is a threshold below which radiations do not cause leukaemia. Next to nothing is known about the effect, in the human, of partial (especially small-field) body irradiation.

The "high therapeutic" doses in our patients lay within the range accepted as potentially leukaemogenic. However, none of those derived from diagnostic exposures approached this range. If diagnostic radiation was responsible for the disease in any patient, this would therefore indicate that the potentially leukaemogenic range must be extended downwards. It is, of course, likely that the size of the radiation dose is not by itself decisive: such features as the timing and repetition of the examinations (Mole, 1958), their site, their interaction with the pathological processes for whose diagnosis they were made, and others yet unknown, may all be of significance in determining whether leukaemia will follow irradiation.

In the special case of intrauterine diagnostic irradiation, Stewart *et al.* (1958) showed that 13.7% of leukaemic children but only 7.2% of controls had been exposed and concluded that such irradiation may have been of significance in the aetiology of some cases of childhood leukaemia. MacMahon (1962) confirmed Stewart's finding of a significantly increased number of foetal irradiations in leukaemic children. Here the dose-response curve is even less certain than in other forms of medical irradiation: although, from an average diagnostic examination, the foetus may receive only a total body dose of 1–1.5 rad, it has been shown (Gunz *et al.*, 1958) that in certain circumstances the dose received can be very much higher. The total number of children in our survey was too small to make it possible to say whether the slight excess of irradiation among leukaemia patients (13.7% against 12.3% in controls) was significant. If the figures quoted by MacMahon (1962) are generally applicable, it can be calculated that a 25-year study would be necessary before a statistically significant excess of irradiation in the mothers of leukaemic children could be shown in the small New Zealand population.

Summary

Histories of exposure to medical radiations were obtained from 590 patients with leukaemia, 122 with myelomatosis, and 712 controls.

Integral and bone-marrow doses were calculated for radiotherapy, and marrow doses for diagnostic exposures.

Patients with acute and chronic granulocytic leukaemia showed greater exposure to radiotherapy than controls, the excess amounting to nearly 3% of all cases.

Bone-marrow doses due to diagnostic exposures were much lower than those due to radiotherapy. Some patients had much heavier diagnostic doses than the great majority of the others. If diagnostic radiation was concerned in the aetiology of any cases, it seemed unlikely that their number could exceed 1% of acute and chronic granulocytic leukaemias.

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