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Epidemiological Studies of Radiation Leukaemogenesis in Man, with Particular Reference to the Possible Nature of the Dose-Response Relationship

By Dr. W. M. Court Brown[1]

There is now no doubt that man is susceptible to the induction of leukaemia following exposure to nuclear and allied radiations. In a world in which the level of background radiation is known to have been increased (and to be increasing) by man's own scientific ingenuity, the extent to which exposure to man-made radiation is hazardous is a matter for serious consideration. Public concern about radiation hazards has found expression in reports on this subject by the British Medical Research Council (1), the U.S. National Academy of Sciences (2), and the World Health Organization (3). More recently the United States Congressional Hearing has further underlined the extent of our ignorance (4).

This symposium is devoted to the study of the possible hazards of low levels of radiation dose, particularly from atmospheric pollution by radioactive material. Everyone is aware of the crux of the problem as far as leukaemogenesis is concerned; it is whether any dose of radiation above that of natural background radiation, no matter how small, will confer on the individual concerned an increased probability of developing of leukaemia. All conversant with this problem are also aware that no data exist, drawn from a study of men or animals exposed to really low levels of radiation, which throw direct light on this problem. We are forced, therefore, to examine the existing data to see what reasonable inferences may be made in regard to the possible nature of the relationship between radiation dose and the incidence of leukaemia.

Since 1952, the year in which data were first published on the incidence of leukaemia in the survivor populations of Hiroshima and Nagasaki (5),

[1] The author is indebted to Dr. *Richard Doll* for his help in the composition of this paper.

several reports have appeared relating to surveys of the leukaemia incidence in irradiated human beings. These include more recent accounts of the Japanese cases (6–9), reports on the leukaemia incidence in patients treated with X-rays for ankylosing spondylitis (10–13), and data on the long-term leukaemogenic effects of the irradiation of young children for suspected thymic enlargement (14, 15). These three lines of investigation are based essentially on prospective studies of irradiated groups of people. In contrast, there are two major retrospective studies which are based on investigation of the histories of patients presenting with leukaemia, with particular regard to the extent of their previous X-ray exposure for either diagnostic or therapeutic purposes and for unassociated clinical conditions. These are the studies of *Faber* on cases of leukaemia notified to the Danish Cancer Registry (16, 17), and those of *Stewart* and her colleagues on cases of childhood leukaemia (18). Finally, there are the several reports drawing attention to the numbers of deaths from leukaemia among American radiologists (19–24). Taken individually all these various investigations can be criticized, on the grounds that either the control material is inadequate, or the estimates of dose inaccurate, or of the difficulties entailed in undertaking accurate searches of hospital records, or on epidermiological grounds for the manner in which the data have been used. Taken as a whole, however, these studies provide convincing evidence of man's susceptibility to radiation leukaemogenesis.

The first studies to provide evidence of a direct relationship between the radiation dose and the incidence of leukaemia were those on the Japanese survivor populations. The data presented in table 1 are based on information provided by the Atomic Bomb Casualty Commission to the British Medical Research Council in 1955. From these data it was possible, using the published Japanese national mortality rates, to calculate the expected numbers of deaths at the various distances from the hypocentre and to compare these expected deaths with those observed (25). The great increase in the incidence of the disease is well shown, and the fact that this is related to the distance of individual survivors from the hypocentre, at the time of the explosion, clearly indicates the presence of a dose-response relationship. The question of the amount of radiation received by these survivors is, however, a controversial one, particularly because of the difficulties involved in estimating the components of dose due to fast neutrons and from local fallout. The most recent authoritative figure, given by *Hempelmann* in 1957 (26), is that the mean dose for the zone 1,500 to 1,999 m from the hypocentre was about 50 rem.

In this zone by the end of 1954, 6 certain cases of leukaemia and 1 sus-

Table 1

The Incidence of Leukaemia among Survivors of the Hiroshima Atomic Bomb Explosion

Distance from hypocentre at time of explosion	No. of survivors on 1/10/50*	No. of cases of leukaemia				Incidence per 10,000 persons (Total cases)	No. of expected deaths, among survivors in an 8-year period 1947–54 ***	Ratio of cases observed (1947–54) to expected
		Confirmed		Suspected				
		All years	1947–54	All years	1947–54			
Less than 1,000	1,250	16	15	0	0	128.0	0.15	100.0:1
1,000–1,499	10,350	28	28	1	1	28.0	1.32	22.0:1
1,500–1,999	18,450	6	6	1	1	3.8	2.33	2.6:1
2,000–2,999	30,350	7	6	0	0	2.3	3.96	1.5:1
3,000 or more	37,700	4	4	2	2	1.6	4.83	1.2:1
All distances	98,100	61	59**	4	4	6.6	12.59	4.7:1

* Rounded off to the nearest 50.

** Two cases are omitted in comparison with the "All years" group. The onset of symptoms in one was in 1955, and in another, dying in 1955, the date of onset is unknown.

*** Calculated from Japanese mortality data for 1952 (24). The figures must be regarded as approximate estimates.

pected case had occurred whereas 2.3 cases were expected. The difference is on the border-line of significance ($P = 0.03$); it is not possible to be sure that the cases were radiation-induced, but the data are certainly suggestive. It may be noted that three factors could be held to cast doubt on the direct applicability of the Japanese data to European and American populations. The first factor is the latent period. Table 2 shows the incidence of leukaemia per 10,000 persons among the Japanese survivors for each year from 1946 to 1954 inclusively. Bearing in mind that in these people the A.B.C.C. recorded the latent period as the time lapse between exposure in August 1945 and the onset of symptoms, it is evident that up to the end of 1954, there was no striking fall in the annual incidence when the years 1948 to 1954 are compared. It is reasonable to suppose that a few cases of leukaemia were alive in 1954 who had developed symptoms but who would not be recognized until the subsequent year.*

This finding contrasts sharply with the latent periods among the male spondylitics who developed leukaemia after a single course of X-ray treatment, which are shown in table 3.

No case has yet been found in which the latent period, in this instance measured from exposure to the clinical recognition of the leukaemic

* Attention is drawn to data published by *Wald* (29) in1958 of the total cases which had occurred in Hiroshima by the end of 1957. These data now suggest that a peak incidence occurred during the sixth, seventh and and eighth post-exposure years.

Table 2

The Incidence of Leukaemia in Different Years among Survivors of the Hiroshima and Nagasaki Atomic Bomb Explosions

			Incidence per 10,000 persons		
Years of onset	Hiroshima*	Nagasaki*	Hiroshima	Nagasaki	Hiroshima and Nagasaki
1946	0	1	0.0	0.1	0.05
1947	3	2	0.3	0.2	0.3
1948	10	3	1.0	0.3	0.7
1949	5	3	0.5	0.3	0.4
1950	7	6	0.7	0.6	0.7
1951	11	10	1.1	1.0	1.1
1952	11	8	1.1	0.8	1.0
1953	10	3	1.0	0.3	0.7
1954	6	7	0.6	0.7	0.7
All years	63	43	6.6	4.5	5.6

* Both confirmed and suspected cases.

Table 3

The Relative Frequency of Different Latent Periods in Leukaemia Following One Course of Treatment

(*Court-Brown* and *Doll* 1957)

Latent period (months)	Morbidity rate* per 10,000 man-years
0–	0
24–	4.0
36–	10.3
48–	13.4
60+	0

* Based on 10 cases of leukaemia.

The Distribution of Latent Periods – Including More Recent Cases of Leukaemia

Latent period (months)	Number of cases of leukaemia
0–	0
24–	2
36–	5
48–	6
60+	0

state, has exceeded 5 years. In addition in 3 further cases that have occurred since 1955 following a single course of treatment, the latent periods have been less than 5 years in length. Only one case has been

Table 4

Age-Specific Death Rates for Leukaemia: England and Wales and Japan (1952 – Both Sexes)

Age groups (years)	Deaths per million living persons	
	England and Wales	Japan
0–4	51.1	26.8
5–9	32.4	14.7
10–14	22.6	15.6
15–24	19.8	13.5
25–34	17.2	12.8
35–44	26.5	17.3
45–54	40.9	18.3
55–64	81.0	18.3
65–74	128.0	15.1
75+	149.6	9.3
All ages	46.3	16.6

found, which is not a survey case, in which the latent period exceeded 5 years. In this case, the only female so far observed to have developed leukaemia after a single treatment course, the latent period was 8 years. Although the cases are few in number there is every indication that the maximum probability of the clinical development of the disease is in the fourth and fifth year subsequent to exposure. This is further borne out by the work of *Faber* who found that the incidence of a history of therapeutic or diagnostic X-ray exposure for an unrelated condition in cases of acute leukaemia was significantly raised, in comparison with that in cases of chronic lymphatic leukaemia and with non-leukaemia control cases. Furthermore, he found that this evidence only related to exposure within 5 years of the diagnosis of acute leukaemia. The incidence of exposure in such cases more than 5 years before the diagnosis did not differ significantly from the controls. For chronic myeloid leukaemia, however, *Faber* found evidence that the latent period could exceed 5 years. The second factor of difference is that in contrast to the data for Western European nations and the United States, the age specific death rates for leukaemia in Japan do not increase appreciably with advancing age (27) (table 4). This difference is only partly due to the absence of chronic lymphatic leukaemia in Japan. Experience among European populations shows that this rise in the incidence of chronic lymphatic leukaemia with age, is not the only explanation of the rising age-specific death rates, as other types of leukaemia also increase. The third factor refers again to a comparison of the Japanese survivors and

Table 5

Age (years)	Standardized incidence rates, per 1,000 patients (both sexes)	The average amount of radiation given to men of different ages (mean spinal marrow dose)
14–	1.1	858 r
25–	2.6	894 r
35–	2.4	840 r
45–	5.2	776 r
55+	5.6	576 r

the cases of spondylitis. Amongst the former the incidence of leukaemia also did not appear to increase with age whereas in the spondylitics such a tendency was undoubtedly present in spite of the fact that the average dose to the older patients was appreciably less than that to the younger ones (table 5). While other explanations may be forthcoming to account for these differences, it could well be that they reflect differences in racial and environmental factors. It seems, therefore, opportune to sound a note of caution against the too free application of the Japanese data to the problem of the leukaemogenic hazard amongst populations predominantly of European origin.

Turning to the other surveys which have been done on the incidence of leukaemia in irradiated groups, all of which have been European or American, it seems that, with one exception there is little information on the relevant radiation dose. In addition two of the studies are related to the developing child. If the work of *Stewart* and her collaborators on the effect of exposure of the child *in utero* is substantiated, then it appears that doses of the order of 5 r or less may well be leukaemogenic to the foetus. Only a preliminary report, however, has been made of this work, and it is yet to be determined whether there is any particular phase of foetal development which is specifically sensitive to the induction of leukaemia. *Simpson* and her colleagues have studied the development of leukaemia in children irradiated in infancy for suspected thymic enlargement; the details of dosage are incomplete but it appears that in these children a dose of 200 r, restricted to the thorax, may be leukaemogenic. The studies of *Faber*, already alluded to, give a strong hint that doses of X-rays as low as those currently employed in medical diagnosis may be leukaemogenic.

The study carried out by *Court-Brown* and *Doll* on the incidence of leukaemia in cases of ankylosing spondylitis treated with X-rays, was designed to investigate the nature of the dose-response relationship. It was realized from its outset that the investigation could not possibly provide

data on the effects of low levels of dose; it was hoped, however, that sufficiently reliable data would be obtained of the effects of comparatively high levels of dose to permit of some confident extrapolation to the effects of low doses. Ankylosing spondylitis is a disease primarily affecting the joints of the spinal column, although, in approximately a third of the cases the larger peripheral joints are also involved. Because the spinal column is the most common site to be irradiated, measurements were made of the distribution of the radiation dose within the spinal marrow. These were done in a full-scale phantom in which was incorporated the trunk skeletal structure and artificial lungs with scattering properties comparable to those of normal lung tissue. These measurements included not only the dose contributions to the spinal marrow from X-ray fields directly over the spine, but also from fields directed to such extra-spinal sites as the hip joints, the shoulder joints, and the ischial tuberosities. They did not, however, make allowance for the radiation dose to marrow without the spinal column, which was irradiated during the treatment of the extra-spinal areas. The examination of the dose-response relationship was confined to the 11,287 male cases studied, out of a total number of 13,352 patients, 37 cases of leukaemia were found to have occurred amongst these men, of which 18 had occurred in men subjected only to irradiation of the spinal column: of these latter 8 followed a single course of X-ray treatment.

Considerable thought was given as to what was the most suitable parameter of dose to measure in the spinal marrow, and ultimately to relate to the incidence of leukaemia. In fact three different modes of expression of dose were studied; the total body energy absorption or the integral dose, the maximum dose received at a point in the spinal marrow, and the mean dose throughout the spinal marrow. Under the conditions in which these patients were irradiated there is no reason to believe that the total body integral dose bears any particularly close relationship to the marrow integral dose, and no further consideration will be given to this parameter. The choice, however, between the maximum dose at a point in the spinal marrow and the mean spinal marrow dose immediately raises the basic problem of the presence or absence of a threshold dose below which no increased risk of leukaemogenesis is incurred. If the first parameter is chosen, in effect this choice postulates the possibility of a threshold and sets out to prove or disprove its existence; the choice of the mean spinal dose, on the other hand, carries with it the implication that no threshold exists. Both hypotheses were entertained, and the appropriate dose-response relationships were evaluated. It was thought, however, that the use of the maximum spinal

dose probably introduced a systematic bias into the results, as its examination in relationship to the incidence of leukaemia should only be made in a group of individuals in whom a constant volume of marrow has been irradiated. Too few cases of leukaemia were available, so irradiated, to allow of this being done. It is worth noting, however, that the analysis, for what it is worth, using this parameter of dose failed to support the postulate that a threshold dose might exist, as the estimates of incidence appeared to be proportional to the dose.

If it is postulated that no threshold dose exists then one would expect the incidence of leukaemia to be proportional to the relevant mean marrow dose, i.e. the mean spinal marrow dose. It becomes justifiable, also, to include in the analysis those cases in whom only a part of the spinal column was irradiated, and, if the resulting relationship supports the hypothesis, it is justifiable to convert the mean spinal marrow dose into a mean dose to the total body red marrow, if the appropriate conversion factor is known.

The results of relating the incidence of leukaemia to the mean spinal marrow dose in the whole group of patients, that is including those given extra-spinal irradiation, is shown in fig. 1. Both in this and the next figure the incidence of leukaemia for zero therapeutic irradiation has been calculated from national mortality statistics and adjusted to allow, as far as possible, for errors in death certification and for living cases of leukaemia. Although the relationship is curvilinear, there appears no evidence of a threshold. The inclusion, however, of cases with extra-spinal irradiation is unsatisfactory, and fig. 2 shows the relationship for cases receiving only spinal irradiation. As there are only 18 cases of leukaemia, instead of 37, there is a greater degree of uncertainty about the points and it can be seen that in the higher ranges of dose the position of these varies considerably depending on which groupings of dose are chosen. Nevertheless, it was felt that the most satisfactory relationship was a linear one, and in calculating the equation to the line the point for zero dose was included, and the estimate adjusted to permit the regression line to pass through this point. This has been criticized, but it was done because it was felt that the estimated incidence for zero therapeutic dose was no less reliable than the observed incidences for the various levels of dose. From the equation to the line it was calculated that the dose which doubled the incidence of leukaemia, i.e. increased it by 0.49 cases per 10,000 men per year, was a mean spinal marrow dose of 94 r. Assuming that between one-third and one-half of the total red marrow lay in the spinal column, it was deduced that a

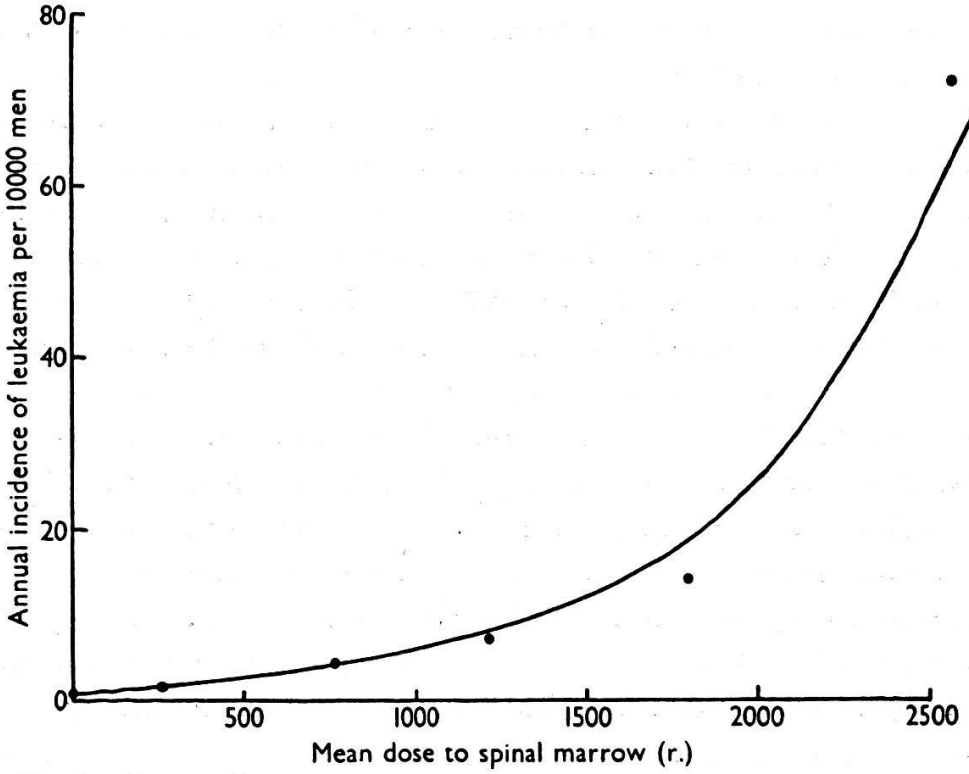

Fig. 1[1]. The incidence of leukaemia, standardized for age, in relation to the mean dose of radiation to the spinal marrow: all male patients in the study series.

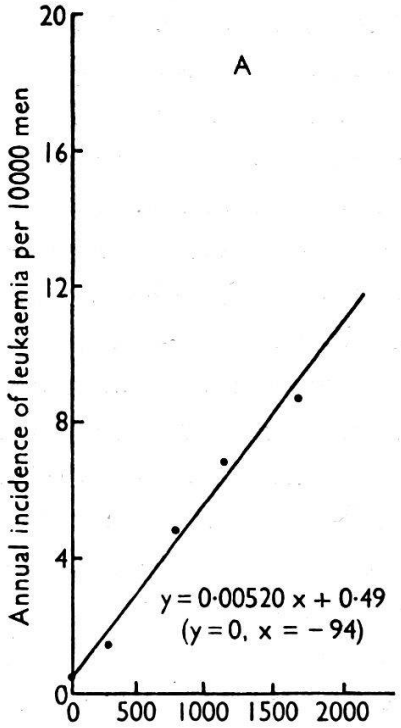

Fig. 2[1]. The incidence of leukaemia, standardized for age, in relation to the mean dose of radiation to the spinal marrow: patients given extra-spinal irradiation have been excluded. (Some variations occur in the position of the points depending on the chosen groupings of dose: for details see *Court Brown* and *Doll* [1957].)

[1] Reproduced from Medical Research Council Special Report No. 295 «Leukaemia and Aplastic Anaemia in Patients Irradiated for Ankylosing Spondylitis» with the permission of the Controller of Her Britannic Majesty's Stationery Office, London W-C. 2.

mean dose to the whole red marrow of between 35 and 50 r would double the incidence of leukaemia.

Recently at the suggestion of *Pochin* (28), the equation to the line has been re-calculated omitting the point for zero-therapeutic dose (13). As a result of also calculating the probable limits of the regression line, and assuming that all the observed cases of leukaemia were radiation-induced, it has been concluded that a threshold will have either zero-value or a value anywhere between zero and 400 r of mean spinal dose. The situation now becomes complex, for if a positive threshold dose exists it cannot be expressed in terms of a mean marrow dose. Rather it would be necessary to express it in terms of the maximum dose at a point in the spinal marrow which just fell short of increasing an individual's probability of developing leukaemia. In short, if the examination of a group of individuals using the mean marrow dose as the parameter of dose reveals evidence of a dose threshold, then, to define this threshold, it will be necessary to re-examine the group using the maximum dose at a point in the marrow as the appropriate parameter.

Two further interrelated problems remain to be considered in relation to the examination of dose-response relationships. These are the influence of the latent period, and the weighting to be given to repeated radiation exposures in regard to their possible leukaemogenic effect. It has already been stressed that, in contrast to the Japanese data, current information from European sources indicates that following a single exposure, or a single course of treatment, assumed for present purposes equivalent to a single exposure, the maximum probability of developing leukaemia occurs during the fourth and fifth post-exposure years. There is little evidence to suggest that subsequent to the fifth year the risk is to any extent enhanced. When the spondylitic survey was carried out it was felt at that time that greater weight should be given to the Japanese experience, and as there was no evidence of a fall in incidence amongst the Japanese by the end of 1954, it was decided that each irradiated spondylitic would be considered at risk to the same degree in each year after a treatment course, except for the first year. No case was found in which a clinical diagnosis of leukaemia was made within 1 year of the first course of treatment, and consequently the first year was given zero weighting and each subsequent year equal weighting. An attempt was made to re-calculate the results weighting the doses in regard to the differing probabilities of leukaemia developing in each year subsequent to exposure. While the resulting curve was less regular than the others it also failed to reveal any evidence to support the existence of a threshold. A further development of this problem is that of

how to deal with the individual who has had more than one exposure or course of treatment. Again in introducing weighting factors under these circumstances one is faced with having to decide whether the initial effect, which leads to the development of leukaemia, is a threshold one or not. If there is a threshold then by implication some degree of repair of the initial effect is possible and additional weighting requires to be made to allow for this. In our present state of limited knowledge there is no information which would permit the extent of this recovery with time to be evaluated. If the effect is a non-threshold one, then, by implication, no recovery occurs and no additional weighting needs to be made. Under these latter circumstances, appropriate weighting for the probability of developing leukaemia may be introduced provided sufficient knowledge is available on the frequency distribution of the length of the latent period following a single exposure.

There is one final problem to discuss, and one which it is essential not to overlook when extrapolations are made from the types of relationships discussed above to the possible effects of radiation from natural background sources and fallout. In all the surveys that have been quoted, the individuals irradiated have been exposed at comparatively high dose rates, say in excess of 20 r per minute. These rates contrast sharply with the low-dose rates from natural background radiation and presumably from radioactive fallout. If the dose-response relationship reveals no evidence of a threshold then it is not unreasonable to postulate that the initial effect which leads to the ultimate clinical state of leukaemia is a somatic mutation. In theory, therefore, any dose of radiation will confer an increased probability of developing the disease if in fact it was certain that the initial effect was a point mutation, as the incidence of such mutations has been shown to be, for a given total dose, independant of fractionation and intensity. In other words, with a point mutation, a man who receives from diagnostic radiology in 1 year an average marrow dose of 0.1 r at 100 r/min., will be likely to incur the same risk of leukaemogenesis as he would from natural background radiation absorbed over the same period.

On the other hand, it is conceivable that some mutations result from small structural changes in chromosomes, themselves the product of a chromosome break, and in some instances of more than one chromosome break, and conceivably the occasional mutation may occur from more gross forms of chromosome damage. When more than one break is involved the number of mutations produced is likely to be in some degree dependant on the intensity of irradiation, and the lower the intensity the less likely is the observed effect to occur. If these latter types of

structural change are more likely to result in leukaemogenesis than point mutations, then, it would appear unwise to extrapolate, as *Lewis* has done (28), from the type of evidence already discussed to the possible effects of very low level background activity.

In conclusion, it appears reasonable to postulate, as a working hypothesis, that the induction of leukaemia by irradiation is a non-threshold effect. Fewer uncertainties are involved than in the postulation of a threshold effect, and by doing so there is the advantage, from the point of view of those involved in radiological protection, that the worst possible series of circumstances are visualized. As a working hypothesis, however, it is only put forward as a guide to the planning of future studies, undertaken to prove or disprove its validity. There is little doubt that much more progress could be made towards the settlement of the vexed question of a threshold dose by the more rigorous and wider application of epidemiological techniques to the study of populations of men and women irradiated in the course of medical practice, and at lower dose levels than have hithertofore been examined.

Summary

The sources of information on radiation leukaemogenesis in man are reviewed, particular attention being paid to the information available on the nature of the possible relationship between the radiation dose and the incidence of leukaemia. The extent to which data derived from studies of the Japanese cases of leukaemia and those caused by exposure for medical purposes can be applied to the consideration of the possible effects of very low doses of radiation are discussed.

Zusammenfassung

Es wird ein Überblick über die Berichte über strahlenbedingte Leukaemogenesis beim Menschen gegeben und den Arbeiten über die Beziehungen der Strahlendosis zum Auftreten von Leukämie besondere Aufmerksamkeit geschenkt. Die Ergebnisse der Untersuchungen über die japanischen Leukämiefälle und die Fälle, welche infolge von Bestrahlung zu medizinischen Zwecken verursacht wurden, werden für die Beurteilung der möglichen Wirkungen schwacher Strahlendosen herangezogen.

Résumé

Revue des travaux relatifs à la leucémogénèse chez l'homme par les radiations ioniques, en faisant particulièrement le rapport possible entre la dose d'irradiations et le nombre de leucémies éventuelles sub-

séquentes. En se basant sur les faits observés chez les Japonais et les leucémies consécutives à des irradiations pour des indications médicales, l'auteur discute les effets de très faibles doses d'irradiations.

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Discussion:

A. Zuppinger, Bern:

Herr *Court Brown* hat mit seinen Mitarbeitern bei einer ersten Publikation von 4, in einer zweiten von 3 Leukämiefällen berichtet, die im ersten Jahr nach Beginn der

Röntgenstrahlung zur Beobachtung kamen und die nicht als Behandlungsfolge aufgefaßt werden können. Er hat selbst den Gedanken ausgesprochen, daß unter Umständen eine Beziehung zwischen Spondylitis ankylopoetica und Leukämie bestehen könnte. Wenn auch an einer Beziehung zwischen Bestrahlung und Leukämie nicht gezweifelt werden kann, so erhebt sich doch die Frage, ob die Verhältnisse, wie sie bei der Bestrahlung dieser Krankheit vorliegen, verallgemeinert werden können, besonders im Hinblick auf sehr viele und langjährige Beobachtungen bei Mamma- und Uteruskarzinomen, bei denen eine erhöhte Zahl von Leukämien doch hätte auffallen müssen.

W. M. Court Brown, Edinburgh:

Prof. *Zuppinger* has asked two questions. Firstly he raises the question of whether there exists a specific association between leukaemia and ankylosing spondylitis, and secondly he wonders why leukaemia has not been more often seen as a sequel to the radiotherapy of malignant tumours.

The answer to the first question is that a slight association between the two diseases cannot be excluded. A study, however, of a group of unirradiated cases of ankylosing spondylitis seems to exclude any significant degree of association (for details see *Court-Brown, W. M.*, and *Doll, R.*: Special Report Series Medical Research Council, No. 295, Her Majesty's Stationery Office, London 1957).

To the second question I would answer that a more vigorous research will disclose the cases of leukaemia. I have personal experience of quite a number of such cases. Such a search will involve an accurate determination of the cause of death in every case, dying after radiotherapy.