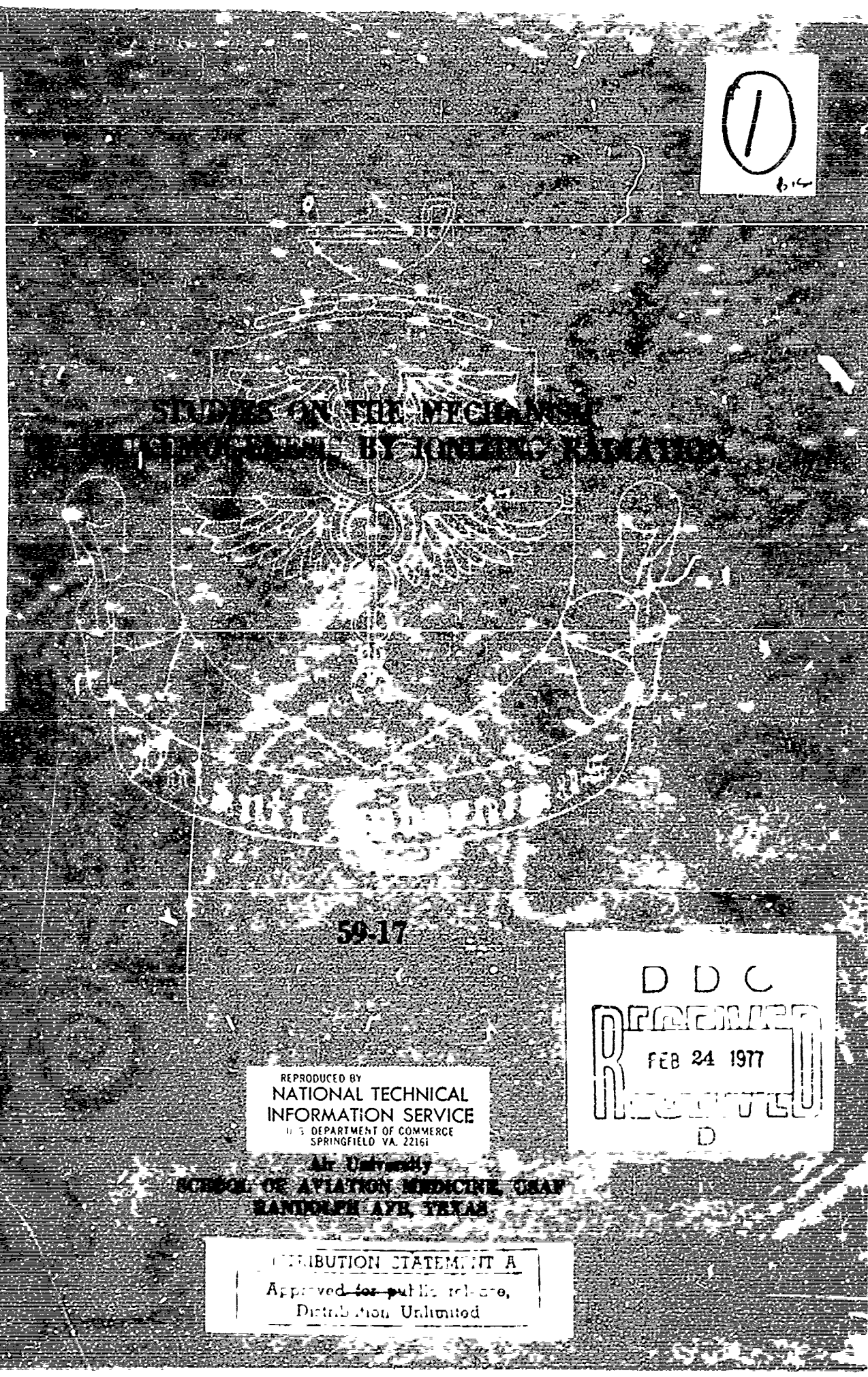
AD-A036 039

STUDIES ON THE MECHANISM OF LEUKEMOGENESIS BY IONIZING RADIATION

SCHOOL OF AVIATION MEDICINE
RANDOLPH AIR FORCE BASE, TEXAS

JANUARY 1959



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STUDIES ON THE MECHANISM OF LEUKEMOGENESIS BY IONIZING RADIATION

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January 1959

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STUDIES ON THE MECHANISM OF LEUKEMOGENESIS BY IONIZING RADIATION

The induction of leukemia by ionizing radiation is influenced by many variables, including radiation intensity, radiation dose, fraction of the body irradiated, genetic differences in susceptibility, age at irradiation, sex, and other physiologic factors. The influence of these variables on the induction of leukemia varies with the hematologic type of leukemia induced. Irradiation increases the susceptibility of adult mice to filterable leukemogenic agents that, administered after irradiation, enhance the development of leukemia.

The high carcinogenic potency of ionizing radiation is well known (14, 15, 18). Among the many types of neoplasms induced by radiation, leukemia is prominent in human beings (56) and in mice (14). Although mice are, in general, susceptible to leukemia induction, their responsiveness to a given amount of radiation varies, according to the influence of genetic, physiologic, and radiologic factors. The effects of these variables have been investigated in a series of experiments summarized in this report.

RADIOLOGIC FACTORS

Relation between leukemia incidence and radiation dose

Apart from the influence of physiologic factors, the dose, dose rate, and hematologic type of leukemia in question affect the incidence of induced leukemia.

In mice of most strains, lymphomas are readily induced by whole-body irradiation. These neoplasms develop predominantly in the thymus as lymphosarcomas and frequently become generalized, with involvement of the peripheral blood. The relation between the incidence of these neoplasms and the radiation dose is nonlinear, a break in the dose-response curve occurring between 100 and 400 r, depending on the strain of mice in question (fig. 1).

Received for publication on 5 August 1958.

Granulocytic leukemia is less often encountered in mice, those of the RF strain being a notable exception. A dose of only 150 r greatly increases the incidence of granulocytic leukemia in these animals (fig. 2). Paradoxically, as sublethal radiation dose levels are approached, the induction of granulocytic leukemia declines. This is attributed to mortality of potentially leukemic mice early in life from radiation-induced diseases other than leukemia since, when the incidence is adjusted to correct for intercurrent mortality, there is no decline in the induction rate (fig. 3). The shape of the dose-response curve for the dose range below 150 r is not definitely known. Although available data suggest that it is not linear (fig. 4), this, of course, does not necessarily imply the existence of a threshold.

The incidence of other types of leukemia and of lymphomas arising outside the thymus is not significantly increased by radiation.

Influence of radiation intensity

As first shown by Kaplan and Brown (29), the induction of thymic lymphomas may be greater for a given dose of x-rays when the radiation is administered in appropriately timed fractions than when it is administered in a single, brief exposure (63). A similarly complex time-intensity relation is suggested by the work of Mole (54). From these studies, there seems to be an optimal dose rate for lymphoma induction, below which the effectiveness of the radiation is diminished. At greatly

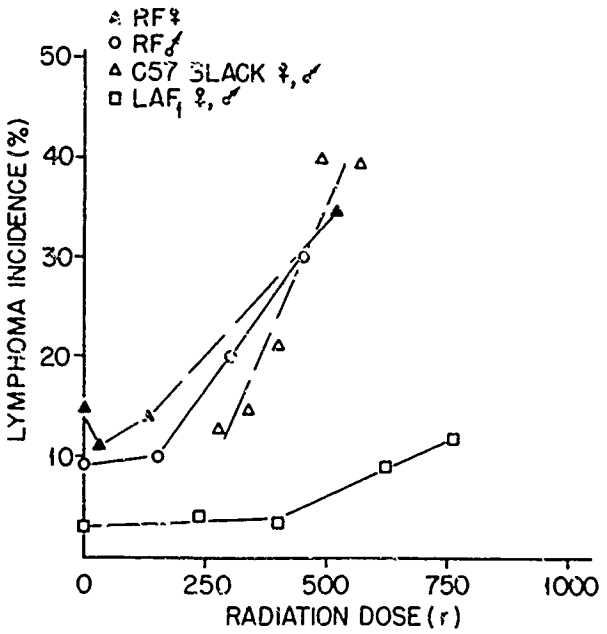

FIGURE 1

Incidence of lymphomas induced in mice by a single exposure to ionizing radiation.
Δ RF females (62).
O RF males (63).
Δ C57BL (29).
□ LAF1 (17).

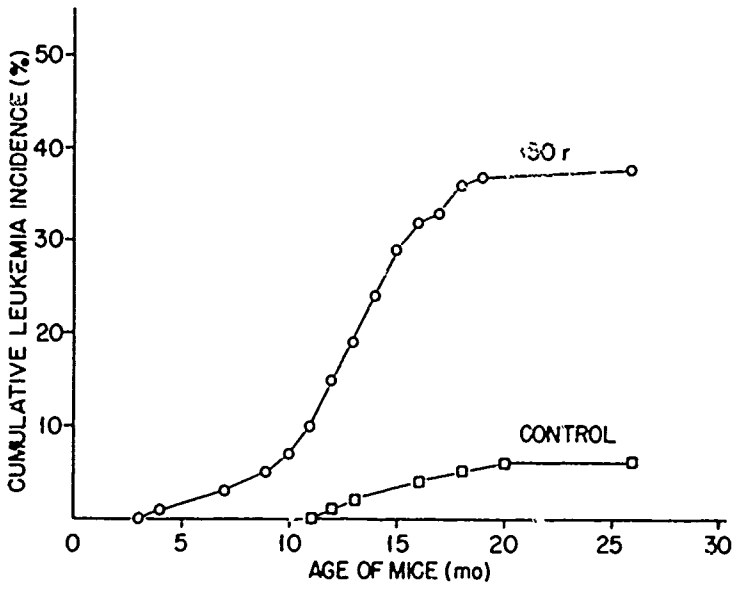

FIGURE 2

Cumulative incidence of granulocytic leukemia induced in RF male mice by a single exposure to x-rays at 10 weeks of age. Each treatment group contained 65 to 70 mice (A. C. Upton and F. F. Wolff, unpublished data).

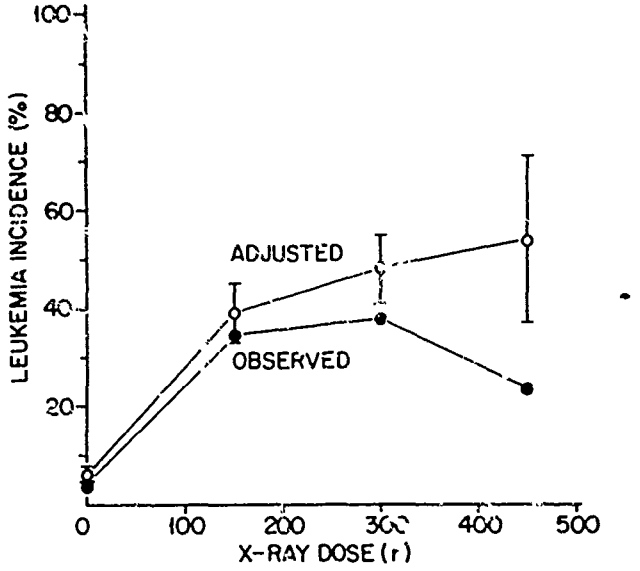

FIGURE 3

Incidence of granulocytic leukemia induced in RF male mice by a single exposure to x-rays at 5 to 6 weeks of age (63). The adjusted incidence is the observed incidence corrected for intercurrent mortality not attributable to leukemia (35).

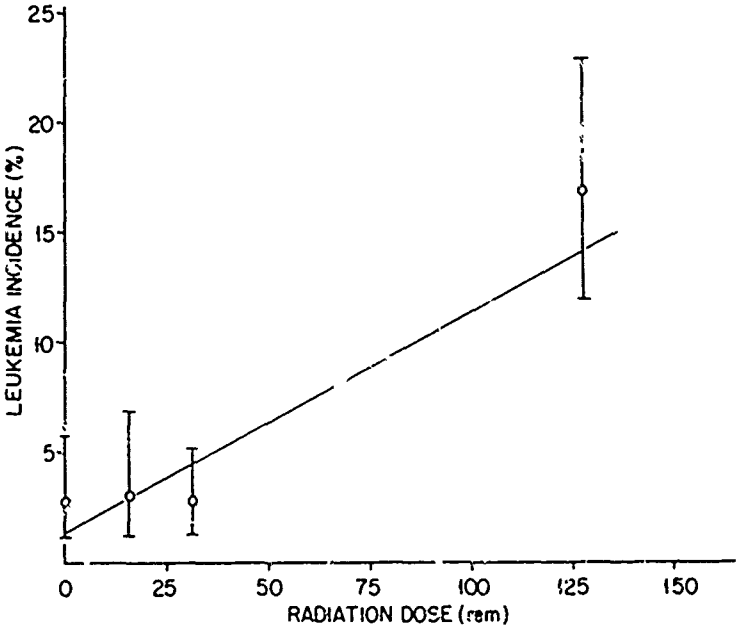

FIGURE 4

Incidence of granulocytic leukemia induced in Rf male mice by a single exposure to radiation at 6 to 8 weeks of age (62). The combined data for x-rays and thermal neutrons are plotted against the dose of radiation expressed in rem on the basis of 30-day lethality. The observed points depart significantly from the fitted straight line, i.e., $\chi^2 = 5.857$; $P < 0.01$; however, because this significance test and the 95 percent confidence intervals shown neglect the possibility of extrabinomial variation, both must be interpreted with reservation (A. W. Kimball, personal communication).

reduced dose rates, however, the incidence of leukemia exceeds the control levels (fig. 5), as noted even in mice exposed throughout life to only 0.11 r per day (47). This is consistent with the elevated incidence of leukemia in radiologists (50).

Partial-body versus whole-body irradiation

Induction of either granulocytic leukemia or lymphoma is greatly inhibited when a small fraction of the body is shielded from radiation (table I). It is noteworthy that, although such shielding essentially abolishes induction of lymphomas, it does not completely prevent induction of granulocytic leukemias. The effects of partial irradiation of different regions of the body and the possible importance of the small fraction of the radiation dose penetrating tissue beneath the shield are being investigated.

Inhibition of lymphoma formation by shielding the thigh (30) or spleen (46) or by in-

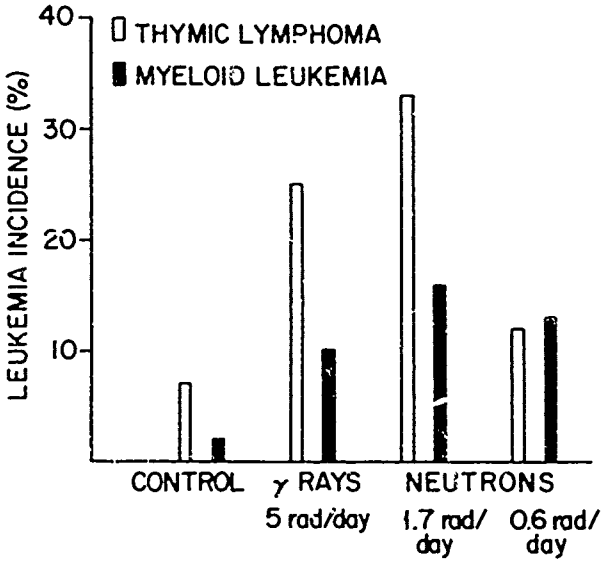

FIGURE 5

Incidence of leukemia in RF female mice exposed 23 hours daily throughout life to Co^{60} gamma rays or Po-Be neutrons. Each treatment group contained 100 to 200 animals (A. C. Upton, J. A. Sproul, Jr., and M. L. Randolph, unpublished data).

TABLE I

Effects of partial-body shielding on leukemia induction by x-rays (63)

X-ray dose*		Number of mice‡	Tissue exposed	Mean age at death (mo.)	Leukemia incidence ‖ (%)	
(r)	(gm.-r)†				Myeloid	Thymic lymphoma
0	0	314	None	19.1	6 (±2)	9 (±3)
150	3,000	104	Whole body	15.6	39 (±6)	10 (±3)
300	6,000	104	Whole body	12.5	48 (±7)	20 (±5)
450	9,000	105	Whole body	10.3	54 (±17)	29 (±6)
450	6,000	85	Upper 2/3 body§	16.0	15 (±5)	6 (±3)

* 250 kvp, 80-100 r per minute, hvl 0.44 mm. of Cu.

† Gram-roentgens.

‡ RF males, 5-6 weeks old at irradiation.

§ Pelvis and lower extremities shielded with lead.

‖ Incidence adjusted (cf. 35) to correct for intercurrent mortality from causes other than leukemia.

jection of nonirradiated, viable, isologous bone marrow (32) or spleen (7) cells after irradiation has also been noted. On the basis of existing evidence, it seems that these procedures have in common the effect of providing normal hemopoietic cells that rapidly colonize and repopulate the irradiated marrow and lymphoid tissue of the recipient (8). Hence, it is logical that they promote recovery of the weight of the irradiated thymus (4). The mechanism whereby partial shielding or injection of marrow inhibits leukemogenesis is unknown, but since lymphomas are induced in nonirradiated thymic tissue when it is implanted into irradiated recipients (31, 34, 43, 44), it is evident that systemic, radiation-induced disturbances can themselves cause neoplastic change in the thymus. Kaplan (28) has therefore postulated that the leukemogenic influence is an exaggerated stimulation of growth elicited by repair mechanisms and that only in the presence of nonirradiated marrow cells can thymic regeneration take place promptly enough to prevent this excessive stimulation. In view of the possible importance of viral agents in leukemogenesis (12), however, it is conceivable that the anti-oncogenic action of intact marrow or spleen cells results from recovery-promoting effects on the irradiated immune system of the host (9, 48, 49).

PHYSIOLOGIC FACTORS

Strain differences

Susceptibility to the spontaneous development and induction of leukemia varies greatly from one strain to another. Within the same strain, susceptibility to the leukemogenic action of any one inducing agent is not necessarily correlated with susceptibility to others (38). Although strain differences have heretofore been ascribed to genetic variables, it has also been suggested that the high incidence of lymphoma in certain strains may be caused by leukemogenic viruses that are transmitted from one generation to another in the germ cells (21). Even susceptibility to the leukemogenic action of such filterable agents, however, varies from one strain of mice to another (13, 22, 64), presumably because of genetic differences.

The spontaneous incidence of myeloid leukemia is so low in most strains of mice and other laboratory animals that only sporadic cases have been reported in the literature (10). Granulocytic leukemias have been induced in mice, however, by administration of indol (6, 11), benzol (45), and ionizing radiation (16). The unusually high susceptibility of RF mice to induction of granulocytic leukemia by radiation is transmitted in part to F_1 hybrid progeny in the one strain combination (BALB/c female x RF male) tested so far (table II). Whether this transmission of susceptibility occurs through a genetic mechanism or by some other means remains to be elucidated.

Influence of age

Although in man acute leukemia is relatively common in childhood, leukemia is rare in immature animals of other species. In mice it is a disease of adult life, increasing in frequency with age (5). Age also affects susceptibility to induction of leukemia by x-rays, its influence varying with the hematologic type of leukemia in question (table III). The decrease in susceptibility to lymphoma induction with age, observed previously with x-rays (25), chemical agents (55), and ACTH (58), occurs more rapidly than might be expected on the basis of thymic involution alone (27). This suggests the influence of other age changes, such as endocrine alterations.

The resistance of newborn mice to induction of myeloid leukemia by irradiation, despite maximal susceptibility to lymphoma induction, is unexplained. Preliminary experiments suggest that this resistance persists during the first several weeks of life, decreasing only gradually as sexual maturity is approached (A. C. Upton and F. F. Wolff, unpublished data).

In man, as in the mouse, acute lymphatic leukemia is probably induced more commonly in irradiated children than in irradiated adults (56).

TABLE II

*Relative susceptibility of parental and F_1 hybrid strain mice to induction of granulocytic leukemia by x-rays**

Strain	Sex	Number of mice	X-ray dose (r)	Leukemia incidence (%)	
				Myeloid	Thymic lymphoma
RF	M	101	0	3	5
RF	F	97	0	3	5
BALB/c	M	74	0	0	0
BALB/c	F	70	0	1	0
BALB/c x RF	M	94	0	1	2
BALB/c x RF	F	101	0	3	5
RF	M	104	300†	38	16
RF	F	101	300†	12	43
BALB/c	M	82	300‡	9	1
BALB/c	F	79	300‡	4	1
BALB/c x RF	M	99	300§	25	7
BALB/c x RF	F	91	300§	16	11

* G. E. Cosgrove, F. F. Wolff, and A. C. Upton (unpublished data).

† Whole-body exposed to 250-kvp x-radiation at 5-6 weeks of age.

‡ Whole-body exposed to 250-kvp x-radiation at 13-17 weeks of age.

§ Whole-body exposed to 250-kvp x-radiation at 12-24 weeks of age.

TABLE III

Influence of age at irradiation on susceptibility to induction of leukemia (63)

Age at irradiation* (days)	Number of mice†	Mean survival (mo.)	Leukemia incidence‡ (%)	
			Myeloid	Thymic lymphoma
1	69	12.4	6 (±3)	23 (±6)
35-42	104	12.5	48 (±7)	20 (±5)
65-75	65	14.7	59 (±9)	8 (±3)
175-185	107	15.8	51 (±9)	11 (±3)
Control	69	19.6	5 (±3)	8 (±4)

* 300 r of whole-body, 250-kvp x-radiation, 80-100 r per minute

† Male mice of the RF strain.

‡ Incidence adjusted (cf. 35) to correct for mortality not attributable to leukemia

Gonadal factors

Although in many, but not all, strains of mice estrogens enhance and androgens inhibit lymphoid tumor formation, the basis for these effects is yet unknown (36). Kaplan et al. (33) pointed out the close correspondence between the action of various hormones on thymus weight and their influence on lymphoma formation. Agents that promote thymic growth tend to augment leukemogenesis, and vice versa, with the exception of estrogen. The effect of ovariectomy on lymphoma induction in irradiated RF mice (table IV) suggests that estrogen exerts a coleukemogenic action on the thymus in this strain.

Castration does not abolish the relatively high susceptibility to granulocytic leukemia in males, and ovariectomy, although raising susceptibility in females, does not increase it to the male level. A sex difference in the incidence of the disease therefore persists even after gonadectomy (table IV). This difference is being explored further in males and females gonadectomized at birth and in castrates treated with androgens and with estrogens. Likewise, the influence of the estrus cycle on granulocyte formation (2) is being correlated with susceptibility to myeloid leukemogenesis.

Effects of thymectomy

Removal of the thymus prevents not only the spontaneous development of mediastinal lymphomas (41, 52) but also the induction of such neoplasms by chemicals (42) and radiation (26) (table V). In the absence of the thymus, other lymphoid tissues undergo neoplasia in response to irradiation (table V), an effect comparable to that noted by Kirsch-

TABLE IV

Effects of gonadectomy on leukemia induction by x-rays in RF mice (63)

X-ray dose (r)	Sex	Number of mice	Mean age at death (mo.)	Leukemia incidence* (%)	
				Mycloid	Thymic lymphoma
0	M	314	19.1	6 (±2)	9 (±3)
0	M†	103	18.5	6 (± 3)	16 (±3)
300	M	104	12.5	48 (±7)	20 (±5)
300	M†	117	13.5	43 (±7)	24 (±6)
0	F	97	20.0	4 (±2)	6 (±2)
0	F†	118	18.5	3 (±2)	9 (±3)
300	F	101	12.0	14 (±4)	53 (±9)
300	F†	102	12.7	27 (±7)	34 (±7)

* Incidence adjusted (cf. 35) to correct for mortality not attributable to leukemia.

† Gonadectomized 1 week before irradiation; i.e., at 4-5 weeks of age.

TABLE V

Effects of thymectomy on leukemia induction by x-rays in RF mice (63)

X-ray dose (r)	Number of mice*	Mice dying with leukemia						Mean age at death from all causes (mo.)
		Myeloid		Lymphoid				
				Thymic		Nonthymic		
		Percent	Mean age at death (mo.)	Percent	Mean age at death (mo.)	Percent	Mean age at death (mo.)	
0	314	3	16.3	5	15.5	29	20.6	19.1
150	105	23	10.8	21	8.5	9	15.8	10.3
450	120†	29	10.0	1	6.0	30	13.1	11.0

* Males, irradiated at 5-6 weeks of age.

† Thymectomized 1 week before irradiation.

baum and Liebelt (37) in thymectomized mice treated with methylcholanthrene. Hence, although in intact mice the thymus is apparently the lymphoid tissue of maximal sensitivity, neoplasia may be induced in other lymphoid organs by appropriate stimulation, depending on strain variations in susceptibility (63). The reactivity of the thymus may be related to its high lymphopoietic activity (1). This in turn may result from growth stimulation by local humoral factors such as the lymphocytosis principle (53), which is produced by the thymus and elevated in animals with lymphoid leukemia. Hence not only may cells of the thymus become neoplastic themselves, but the thymus may exert a leukemogenic action on lymphoid cells formed in other organs (cf. 61). The thymus apparently does not, however, affect the development of granulocytic leukemia (table V).

Influence of splenectomy

Because the spleen is invariably enlarged and infiltrated with leukemic cells in granulocytic leukemia of the RF mouse (3), as in myelogenous leukemia of man, the effects of splenectomy on the induction of this disease were investigated. Removal of the spleen either one week before or as late as one month after irradiation markedly inhibits the development of granulocytic leukemia without affecting the induction of lymphomas (table VI). The mechanism of these effects remains to be determined. It is conceivable, however, that the spleen, by virtue of its myelopoietic activity in the mouse, may constitute a major source of leukemic cells in this species On the other hand, the possibility that the spleen may elaborate a diffusible leukemogenic substance

TABLE VI

Influence of splenectomy on susceptibility of RF male mice to leukemia induction by x-rays

X-ray dose (r)	Operation*	Number of mice	Leukemia incidence (%)		
			Myeloid	Thymic lymphoma	Other
0	None	381	4	3	30
300†	None	104	38	16	15
300†	Splenectomy before	92	13	15	15
300‡	None	65	54	8	20
300‡	Splenectomy before	65	22	5	27
300‡	Splenectomy after	66	29	8	18
300‡	Sham before	58	33	17	22
300‡	Sham after	53	54	8	17

* Splenectomy or sham-splenectomy (laparotomy) 1 week before or 1 month after irradiation.

† Whole body exposed to 250-kvp x-radiation at 5-6 weeks of age.

‡ Whole body exposed to 250-kvp x-radiation at 10 weeks of age.

or may somehow be a favored site for growth of neoplastic myeloid cells must not be overlooked. In short, the importance of the spleen in the development of granulocytic leukemia should probably be compared with that of the thymus in the development of lymphomas.

The effects of sham-splenectomy before irradiation on the incidence of both myeloid leukemia and lymphoma resemble the action of cortisone (60) and are for this reason possibly attributable to surgical stress. Why a similar effect on lymphoma induction was not observed with splenectomy itself cannot be explained; however, splenectomy does not affect the development of lymphomas in AKR mice (52) or in irradiated C57BL mice (26).

Other physiologic factors

In addition to the influences already mentioned, the activity of the adrenal cortex affects the induction of lymphoid tumors in mice, hypercorticism inhibiting and hypocorticism enhancing lymphoma formation (cf. 61). Other hormones have also been reported to influence the growth of leukemic cells, but the significance of their effects is equivocal (33, 36, 61).

EFFECTS OF EXTRANEOUS AGENTS

Turpentine

Because of its leukocytosis-promoting activity, turpentine was administered in conjunction with radiation to determine whether stimulation of granulopoiesis would enhance the induction of myeloid leukemia. Preliminary studies disclosed that myeloid hyperplasia in the marrow and spleen were maximal 7 to 9 days after intramuscular injection of turpentine. Hence, to irradiate the animal at the peak of heightened granulopoietic activity, irradiation was carried out one week after injection. In addition, animals were irradiated immediately before injection of turpentine so that the marrow would be stimulated in the irradiated state.

The results of this experiment (table VII) suggest that injection of turpentine before irradiation does not affect the induction of granulocytic leukemia, but the induction of lymphoma is enhanced, possibly through stress. Turpentine given after irradiation, however, augments the induction of granulocytic leukemia without affecting lymphoma formation. Although this enhancement is not of high statistical significance, the increased incidence of granulocytic leukemia greatly exceeded that noted in any previous experiment.

The relation between the enhancing action of turpentine in myeloid leukemogensis and the role of "promoting" agents in chemical carcinogenesis warrants further investigation. It is conceivable that the action of turpentine combined with the effects of homeostatic repair mechanisms to overstimulate proliferation of

TABLE VII

*Action of turpentine on leukemia induction by x-rays in RF male mice**

X-ray dose and material injected†	Number of mice	Mean age at death (mo.)	Leukemia incidence‡ (%)	
			Myeloid	Thymic lymphoma
0 r - saline	67	19.7	9 (±4)	2 (±1)
0 r - turpentine	59	18.7	6 (±4)	6 (±4)
300 r - saline	65	14.2	59 (±10)	8 (±3)
300 r - turpentine	68	12.8	73 (±10)	6 (±3)
Turpentine - 300 r	69	14.1	57 (±12)	16 (±5)

* A. C. Upton and F. F. Wolff (unpublished data).

† Whole body exposed to 250-kvp x-radiation at 10 weeks of age. Turpentine, 0.1 ml., or an equal volume of saline injected intramuscularly 1 week before or 1 hour after irradiation.

‡ Incidence adjusted (cf. 35) to correct for intercurrent mortality not attributable to leukemia.

myelopoietic cells. Neoplasia of these cells might therefore arise through the same mechanism as that postulated to induce lymphomas in the thymus (28).

Effects of filtrates

The pioneer work of Gross (19) and the confirmatory observations that not only lymphomas but an increasing variety of other neoplasms may be induced by filterable agents (12) raise the possibility that radiocarcinogenesis may involve the action of viruses or related factors.

To determine whether irradiation increases susceptibility to the leukemogenic action of cell-free filtrates of leukemic tissue, adult mice of the RF strain were injected with filtrates prepared from AKR mice bearing transplanted lymphomas. Because of the observations of Schwartz et al. (57), filtrates of brain tissue were used. In each of two experiments (table VIII), the injection of filtrates from leukemic AKR mice enhanced the induction of thymic lymphomas, whereas the injection of filtrates from normal mice did not do so. Furthermore, nonirradiated adults were resistant to this effect. Irradiation in adult life therefore seems to enhance the susceptibility of mice that are otherwise susceptible (13) only in infancy. The decreased incidence of granulocytic leukemia

TABLE VIII

*Enhancement of lymphoma formation in irradiated RF mice by inoculation with filtrates of lymphomatous tissue**

X-ray dose (r)	Filtrate injected†	Number of mice‡	Leukemia incidence§ (%)			
			Myeloid leukemia	Lymphoma		
				Thymic	Nonthymic	Total
0	None	67	4	0	4	4
0	Normal brain	45	2	0	2	2
0	Lymphomatous brain	54	2	0	10	10
450	Tyrode's solution	84	27	4	5	9
450	Normal brain	48	32	6	4	10
450	Lymphomatous brain and lymphoid tissue	84	20	11	21	32
450	Lymphomatous brain	83	12	22	19	41

* A. C. Upton and F. F. Wolff (unpublished data).

† Tissue homogenates from three AKR donors pooled in Tyrode's solution at 5° C. and then centrifuged for 30 minutes at 1,200 x g. centrifugate filtered through Seitz No. 0 03 filter with *Escherichia coli* under a negative pressure of 9 mm. of Hg. 0.1 ml. of filtrate (*Escherichia coli*-free) inoculated intravenously into each recipient within 1 hour after irradiation.

‡ Mice 10 weeks old at irradiation.

§ Analysis at 15 months after inoculation.

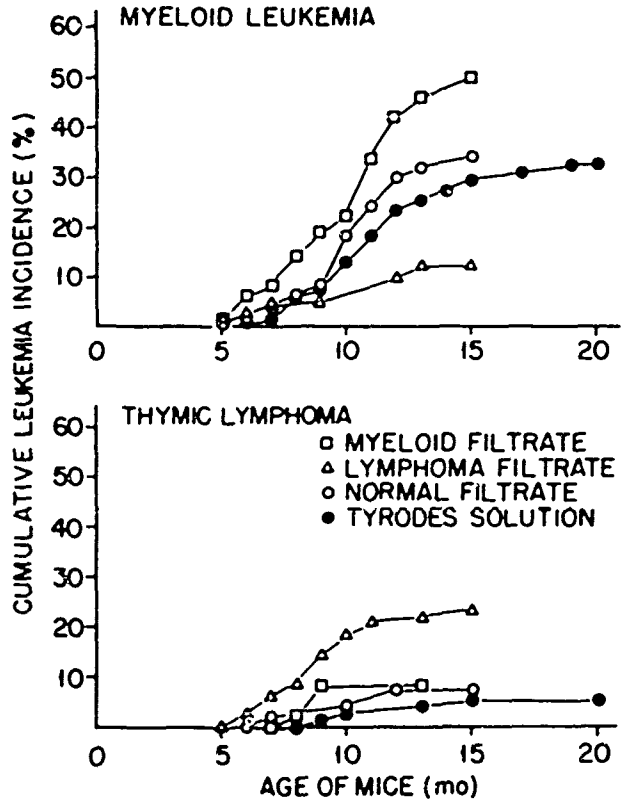

FIGURE 6

Incidence of leukemia in RF male mice exposed to 450 r of x-rays at 10 weeks of age followed by intravenous inoculation of cell-free tissue filtrates. The donor materials are as follows: O pooled normal AKR brain (table VIII), Δ pooled lymphomatous AKR brain (table VIII), □ pooled brain from irradiated RF mice developing granulocytic leukemia (49 mice in treatment group), ● Tyrode's solution (84 mice in treatment group) (A. C. Upton and F. F. Wolff, unpublished data).

in animals of this group (fig. 6), is ascribed to heavy intercurrent mortality of these mice from lymphomas.

To ascertain whether filterable leukemogenic agents are also present in radiation-induced leukemia, we are examining the tissues of irradiated mice developing granulocytic leukemias and lymphomas for such agent.. As yet we have no conclusive data, but preliminary results of our initial experiments strongly suggest that leukemogenic filtrates may be obtained from irradiated mice with granulocytic leukemia (fig. 6).

It is noteworthy that the one filtrate obtained from mice with granulocytic leukemia that has been tested thus far enhanced the induction of granulocytic leukemia only and did not significantly affect the incidence of lymphomas. Specificity was also noted with the filtrates obtained from lymphomatous AKR mice (table VIII), and preliminary results suggest specificity for filtrates obtained from irradiated RF mice developing thymic lymphomas. The failure of these filtrates to induce neoplasms different from those of the donor type contrasts with the observations of Gross (20), Stewart et al. (59), Latarjet and De Jaco (39) and others. It does not, however, indicate any real conflict, because the oncogenic effects of the filterable agents reported thus far have varied widely, depending on such factors as the strain of the donor and recipient,

methods of preparation of the filtrate, number of transplant generations of the donor neoplasm prior to filtration, serial passages of the agent through brain tissue, and cultivation of the agent in vitro. Whether the specificity of the leukomogenic effects of the two types of filtrates we have observed to date indicates the existence of two distinctly different types of agents remains to be determined.

Whether the agents are either free desoxyribonucleic acid (24) or nucleoprotein (40), or of both types, it is not clear where they come from, how radiation affects their production, what role they play in neoplasia, or how consistently they are present in radiation-induced tumors. Until further information is available, any one or a combination of three conceivable mechanisms may be postulated: (1) The agents are oncogenic viruses of low infectivity, which invade the animal from its environment after depression of its immunologic defenses by irradiation; this would presumably occur only with relatively large doses of radiation. (2) The agents exist in the host prior to irradiation as temperate or latent proviruses and are activated to a tumorigenic state by radiation; if this process is comparable to the induction of lysogenicity in bacteria, it might occur in response to minute doses of radiation (51). (3) The agents are fortuitously synthesized by radiation, through disturbance of normal nucleic acid formation (23). Elucidation of this question will require a better understanding of viruses and of the fundamental effects of radiation on the cell.

SUMMARY

The induction of leukemia by ionizing radiation is influenced by many variables, including radiation intensity, radiation dose, fraction of the body irradiated, genetic differences in susceptibility, age at irradiation, sex, and other physiologic factors.

The influence of these variables on the induction of leukemia varies with the hematologic type of leukemia induced.

Irradiation increases the susceptibility of adult mice to filterable leukemogenic agents that, administered after irradiation, enhance the development of leukemia.

The author is grateful to Dr. A. W. Kimball of the Mathematics Panel for statistical analysis of data.

REFERENCES

1. Andreason, E., and J. Ottesen. Acta physiol. scandinav. 10:258 (1945).

2. Arvy, L. Sang 16:198 (1944).

3. Barnes, W. A., and I. E. Sisman. Am. J. Cancer 37:1 (1939).

4. Brown, M. B., H. S. Kaplan, P. P. Weymouth, and J. Paull. Science 117:693 (1953).

5. Brues, A. M., and G. A. Sacher. *In* Nickson, J. J. (ed.) Symposium on Radiobiology, p. 441. New York: John Wiley and Sons, Inc., 1952.

6. Bungeler, W. Z. Pathol. 44:202 (1932).

7. Cole, L. J., P. C. Nowell, and M. E. Ellis. J. Nat Cancer Inst. 17:435 (1956).

8. Congdon, C. C. Blood 12.746 (1957).

9. Dixon, F. J., J. C. Roberts, and W. O. Weigle. J. Exper. Med. 105:417 (1957).

10. Dunn, T. B. J. Nat. Cancer Inst. 14:1281 (1954).

11. Ehrhart, H., and W. Stich. Klin. Wchnschr. 35:504 (1957).

12. Furth, J. *In* Ciba Foundation Symposium on Mechanisms of Carcinogenesis, London, 24-26 June 1958.

13. Furth, J., R. F. Buffett, M. Banasiewicz-Rodriguez, and A. C. Upton. Proc. Soc. Exper. Biol. & Med. 93:165 (1956).

14. Furth, J., and E. Lorenz. *In* Hollaender, A. (ed.) Radiation biology, vol. 1, p. 1145. New York: McGraw-Hill Book Co., 1954.

15. Furth, J., and J. L. Tullis. Cancer Res. 16:5 (1956).

16. Furth, J., and A. C. Upton. Acta radiol. Suppl. 116:469 (1954).

17. Furth, J., A. C. Upton, K. W. Christenberry, W. H. Benedict, and J. Moshmann. Radiology 63:562 (1954).

18. Glucksmann, A., L. F. Lamerton, and W. V. Mayneord. *In* Raven, R. W. (ed.) Cancer, vol. 1, p. 497. London: Butterworths Scientific Publications, 1957.

19. Gross, L. Proc. Soc. Exper. Biol. & Med. 76:27 (1951).

20. Gross, L. Proc. Soc. Exper. Biol. & Med. 83:414 (1953).

21. Gross, L. Acta haemat. 13:13 (1955).

22. Gross, L. Proc. Soc. Exper. Biol. & Med. 88:64 (1955).

23. Haddow, A. *In* Homburger, F., and W. H. Fishman (eds.) The physiopathology of cancer, p. 475. New York: Hoeber, 1953.

24. Hays, E. F., N. S. Simmons, and W. S. Beck. Nature, London 180:1419 (1957).

25. Kaplan, H. S. J. Nat. Cancer Inst. 9:55 (1948).

26. Kaplan, H. S. J. Nat. Cancer Inst. 11.83 (1950).

27. Kaplan, H. S. Acta Unio. internat. contra cancrum 7:849 (1952).

28. Kaplan, H. S. Cancer Res. 14:535 (1954).

29. Kaplan, H. S., and M. B. Brown. J. Nat. Cancer Inst. 13:185 (1952).

30. Kaplan, H. S., and M. B. Brown. Cancer Res. 12:441 (1952).

31. Kaplan, H. S., and M. B. Brown. Science 119:439 (1954).

32. Kaplan, H. S., M. B. Brown, and J. Paull. J. Nat. Cancer Inst. 14:303 (1953).

33. Kaplan, H. S., C. S. Nagareda, and M. B. Brown. *In* Pincus, G. (ed.) Recent progress in hormone research, vol. 10, p. 293. New York: Academic Press, Inc., 1954.

34. Kaplan, H. S., B. B. Hirsch, and M. B. Brown. Cancer Res. 16:434 (1956).

35. Kimball, A. W. Bull. Int. Statistical Inst. (In press)

36. Kirschbaum, A. Cancer Res. 17:432 (1957).

37. Kirschbaum, A., and A. G. Liebelt. Cancer Res. 15:689 (1955).

38. Kirschbaum, A., and H. Mixer. J. Lab. & Clin. Med. 32:720 (1947).

39. Latarjet, R., and M. De Jaco. C. R. Acad. Sci., Paris 246:499 (1958).

40. Latarjet, R., N. Rebeyrotte, and E. Moustacchi. C. R. Acad. Sci., Paris 246:853 (1958).

41. Law, L. W., and J. H. Miller. J. Nat. Cancer Inst. 11:253 (1950).

42. Law, L. W., and J. H. Miller. J. Nat. Cancer Inst. 11:425 (1950).

43. Law, L. W., and M. Potter. Proc. Nat. Acad. Sci. 42:160 (1956).

44. Law, L .W., and M. Potter. J. Nat. Cancer Inst. 20:489 (1958).

45. Lignac, G. O. E. Klin. Wchnschr. 12:109 (1933).

46. Lorenz, E., C. C. Congdon, and D. Uphoff. J. Nat. Cancer Inst. 14:291 (1953).

47. Lorenz, E., J. W. Hollcroft, E. Miller, C. C. Congdon, and R. Schweisthal. J. Nat. Cancer Inst. 15:1049 (1955).

48. Makinodan, T., I. C. Shekarchi, and C. C. Congdon. J. Immunol. 79:281 (1957).

49. Makinodan, T., N. Gengozian, and I. C. Shekarchi. J. Nat. Cancer Inst. 20:591 (1958).

50. March, H. C. Am. J. M. Sc. 220:282 (1950).

51. Marcovich, H. Nature, London 174:796 (1954).

52. McEndy, D. P., M. C. Boon, and J. Furth. Cancer Res. 4:377 (1944).

53. Metcalf, D. Brit. J. Cancer 10:442 (1956).

54. Mole, R. H. *In* Mitchell, J. S., B. E. Holmes, and C. L. Smith (eds.) Progress in radiobiology, p. 468. Edinburgh: Oliver and Boyd, 1956.

55. Morton, J. J., and G. B. Mider. Science 87:327 (1938).

56. Schwartz, E. E., and A. C. Upton. Blood. (In press)

57. Schwartz, S. O., H. M. Schoolman, P. B. Szanto, and W. Spurrier. Cancer Res. 17:218 (1957).

58. Silberberg, M., and R. Silberberg. Cancer Res. 15:291 (1955).

59. Stewart, S. E., B. E. Eddy, A. M. Gochenour, N. G. Borgese, and G. E. Grubbs. Virology 3:380 (1957).

60. Upton, A. C., and J. Furth. Blood 9:636 (1954).

61. Upton, A. C., and J. Furth. *In* Proceedings of the Third National Cancer Conference, p. 312. Philadelphia: J. B. Lippincott Co., 1957.

62. Upton, A. C., J. Furth, and K. W. Christenberry. Cancer Res. 14:682 (1954).

63. Upton, A. C., F. F. Wolff, J. Furth, and A. W. Kimball. Cancer Res. (In press)

64. Woolley, G. W., and M. C. Small. Ann. New York Acad. Sc. 68:533 (1957).