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by

JOHN E. PICKERING, COLONEL, USAF
School of Aviation Medicine,USAF

EXPERIMENTAL OBSERVATIONS FOLLOWING CHRONIC EXPOSURES TO IONIZING RADIATION

SUMMARY

Experimental evidence on the effects of low dose rate chronic radiation exposures as determined from the research program of the School of Aviation Medicine has not as yet produced demonstrable detrimental biological damage at dose levels below 200 roentgens. There has been no significant decrease in life span, no incidence of leukemia, nor formation of mature cataracts.

Within the limited dose fractionation studies conducted during the therapeutic administration of x-radiation on select cancer patients there is no evidence to suggest a psychomotor performance decrement, nor did the clinical symptoms of the acute radiation syndrome cause alarming effects among those patients studied.

In the studies involving rats exposed every day of their life for the period of one year there was an increase in life expectancy under environmental conditions of 5° and 25° C. Mice experiments designed to study protraction and fractionation of dose have not yet demonstrated a significant decrease in life expectancy for those doses below 200 roentgens.

As these experiments continue with respect to long term survival perhaps more definitive statements can be made.

EXPERIMENTAL OBSERVATIONS FOLLOWING CHRONIC EXPOSURES TO IONIZING RADIATION

INTRODUCTION

Exposure to ionizing radiations, when in sufficient doses, can produce in man certain rather specific and well-defined responses. Data obtained from among the peoples of Hiroshima and Nagasaki, the few accidental exposures to Atomic Energy Commission personnel, the recent exposures in Yugoslavia, and extensive laboratory experiments reflect the typical acute radiation responses but not the latent effects from prolonged exposures to low levels of radiation. In this regard, the effects may not be manifest immediately but rather only after a prolonged period of time; hence, extreme care must be exercised in suggesting maximum permissible levels of exposure.

Among the more immediate effects are the decrease in white blood cells soon after radiation exposure; on or near the 5th post-radiation day, erythema; at 15 days, epilation with a subsequent regrowth of hair which is often gray in color; and frequently at 30 days, a desquamation and pigment proliferation (1). Lens opacities frequently appear after several months especially after exposure to fast neutrons (1) (see Fig. 1). Late somatic effects from relatively large, near-fatal doses of radiation appear as mature cataracts, in certain instances as leukemias, and in shortening of the life span. For the most part, however, sublethal doses -- less than 460 to 600 r (the acute lethal dose for half of a given population) but greater than 150 r -- are required to clearly produce these radiation effects.

So far, consideration has been focused on acute exposures to near lethal levels, but what of the much smaller doses given intermittently over

relatively long periods of time? Experimental data do not substantiate the typical acute radiation responses; certainly there is an absence of erythema, epilation, lens opacification (see Fig. 2), and desquamation. The drop in white blood cell count is much less severe; there is, however, a loss in cellularity in the bone marrow, but both of these responses disappear when radiation is removed and repair is allowed to ensue. This is true even when the dose ultimately accumulates numerically to much greater than the so-called LD_{50}^{30} dose (2) (see Fig. 3)

Even though the acute dose schedules discussed and the even greater protracted doses do not yet demonstrate irreversible biological damage, it is indeed true that these doses may have harmful biological consequences which are more subtle. Such emphasis has been placed on possible effects such as increased susceptibility to bone cancer and leukemia, a shortened life span, and harmful mutations that the public has become deeply concerned about them. All genetic information currently available leads to the conclusion that the increase in genetic mutations is proportional to the total dose (3). If this be true, a radiation dose of 2X must be presumed to be twice as harmful as a radiation dose of 1X; but we still do not know the amount of harm being doubled. Nevertheless, most mutations are harmful and since we have no way of establishing the doubling mutation rate in man except from other species, best estimates indicate that a doubling human mutation rate, after an accumulated dose during a generation, is in the range of 30 to 80 r. This is by far the smallest number yet defined in the development of dose vs. irreversible detrimental effects.

So far as life span is concerned, much evidence points to the fact that large doses of radiation significantly shorten longevity; on the other hand,

very meager data on low doses for very long exposure do not show significant reduction in life span. The several mathematical models which permit extrapolation down to very low doses and suggest that life is shortened a few days to a week per roentgen, have been examined recently in light of the available date. In fact, Mole (4) points out that from the very, very few points in chronic exposure to low weekly doses -- 10 r -- three different curves fit the data near equally well and one of them leads to the conclusion that there is a threshold at 1 to 2 r per day below which no shortening of life exists. Other experiments demonstrate that exposure to small doses of radiation increases life expectancy. Warren, in a survey of deaths of 82,441 physicians reported between 1930 and 1954, found that radiologists die on the average 5.2 years earlier than other physicians. Furthermore, nonradiology specialists known to be exposed in a limited way to radiation also show a definite shortening of life but less than that of a radiologist. One might then conclude that exposure to ionizing radiation is the predisposing factor in this shortening of life (5). Lewis (6) in re-evaluating the above data concludes that when properly age-corrected the radiologists' longevity is somewhat greater than that of the other groups. This clearly demonstrates that information as to what small doses of radiation will do to a complex organism like the human is still far from definitive (7).

It is now generally agreed that an increased incidence of leukemia can follow acute or chronic exposures to ionizing radiation. By the end of 1956, hematological studies in Hiroshima showed that an increased incidence of leukemia was related to the distance from the A-Bomb hypocenter and to the occurrence of the acute radiation symptoms. Furthermore, an elevated case incidence in 1950 has shown no conclusive evidence of decline as yet (8,9).

In 1950 leukemia killed 3.9/100,000 of our total population over 20 years of age, while from 1950 to 1954 120 physicians died of leukemia, an average annual rate of 11.2/100,000. The death rate for all physicians was about 3 times that of the adult population. As would be expected, leukemia shows a higher percentage among radiologists. Once again, however, it is difficult to establish a linear dose-response relationship. Evidence strongly suggests a threshold dose or, if you will, a "minimally effective" dose (10) of 200 r below which no detectable increase in leukemia incidence has been noted.

Radiation, as we know it today, can produce biologically detrimental responses. It is quite clear, however, that so-called threshold doses or, better, minimally effective doses do occur for every end point of concern with the greatest question surrounding possible genetic effects.

A careful comparison of many human exposures from among Japanese survivors, Marshall Islanders, and groups of cancer patients receiving therapeutic x-radiation reveals certain points in common (see Fig. 5). The one point of interest here suggests an individual sensitivity to ionizing radiation. Although there is, in general, a marked variability, in one specific instance, large numbers of persons were exposed under almost identical conditions and these data lead to the conclusion that extremes in susceptibility differ by a factor of about 2. For example, among people exposed to 200 r, the most sensitive would develop a clinical picture of the same severity as that exhibited by the most radioresistant person exposed to a dose of 400 r (11).

INFRA HUMAN PRIMATE STUDIES - SCHOOL OF AVIATION MEDICINE, 1952 - 1959

Long term radiation effects studies resulting from low dose rate mixed neutron/gamma fractionated exposures were begun in 1952. Evidence at this

early time suggested concern for effects on cataract production, shortening of life span, increased incidence in leukemia, temporary sterility and genetic effects. Small primates were chosen because of their relatively long life span and physiological similarities to man. Three dose rates, approximately $\frac{1}{4}$ rad/hr, 1 rad/hr, and 4 rad/hr of 8 or 16 hours duration were delivered at seven day intervals for 16 or 8 consecutive exposure periods so that total doses were approximately 30, 120, and 500 rad.

Ophthalmological examinations of these animals to date have revealed no significant abnormalities, although there are some slight changes (see Fig. 2). The 30 rad group showed a slight rise in WBC following exposure, but no significant change in lymphocyte counts. At 120 rad a slight rise in WBC was noted following the 8th week of radiation with a parallel rise in lymphocytes at the same time. The highest dose group at 8 weeks showed a definite rise in WBC. Bone marrow aspiration showed no significant change. This experiment was complicated by the necessity of underwater exposures, consequently three additional experiments were instituted using a synthetic simulated reactor of Po Be neutrons and Co^{60} gamma rays in such a way that the exposures could be made in free air. Eight groups of small primates were exposed at approximately 0, $\frac{1}{4}$, $\frac{1}{2}$ and 1 rad/hr for 16 hours duration at 4 and 12 day intervals for 20 or 40 total exposures with a neutron to gamma ration of 1 to 10. This resulted in total doses of 0, 78, 156, 316, and 616 rad. To date there is some slight evidence of ocular abnormalities in the highest dose group which can be attributable to ionizing radiation, however they will probably not develop into cataracts (see Fig. 2). From the psychomotor performance studies it was learned that there was no deterioration in the ability to perform tests which evaluate cognitive functions, motor learning function,

and sensory functions after having been exposed to radiation. At three years past radiation there is, however, a slight loss in visual acuity in the highest dose as determined by the closed circle test - a one degree opening cannot be discriminated from a closed circle. Hematologically there was a slight drop in white blood cell count with some loss of cellularity in the bone marrow. Both of these responses disappeared when the radiation was completed and repair allowed to ensue (see Fig. 3).

The bone marrow studies in this experiment, when compared to the earlier experiment, may imply that there may not be an additive or synergistic biological effect resulting from combinations of neutrons and gammas. Therefore, a third experiment has been implemented duplicating the dose and dose rate schedules using neutrons in one case and gamma rays in the other -- 16 hour duration and on a 4 day exposure interval. Data to date indicates small doses of whole body radiation produces a significant reduction of the total leukocyte count with the degree of reduction related to total dose. Furthermore, there is some recovery following the completion of the radiation schedule. To date nothing can be concluded concerning shortening of life span or incidence of leukemia, at these dose levels only prolonged observations will disclose or deny these factors.

HUMAN THERAPEUTIC AND EXPERIMENTAL DATA, M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE, AND THE SCHOOL OF AVIATION MEDICINE, 1951 - 1958

It has been established that chemotherapy, for a transitory period only, may relieve pain and cause subjective improvement in cases of incurable generalized tumors, quite frequently even those of low radiosensitivity. Because of its less severe side effects, whole-body x-irradiation has been suggested as a superior method for the palliative treatment of such patients. Is whole-body

x-irradiation, here, an effective procedure? If so, how high is the dose that can or must be administered to obtain beneficial results?

To answer these questions, a long-term study was initiated in 1951 and continued until 1956. From the beginning it was realized that significant clinical benefit could be expected, if at all, only at a dose level bordering the clinical threshold dose or clinical tolerance dose, beyond which serious complications might occur. Paucity of knowledge about this important range necessitated cautious exploration beginning at rather low doses. In the range from 15 to 25 r, whole-body roentgen therapy commonly has been used in the management of leukemias; on the basis of this experience, similar small doses were applied first to other, less radiosensitive, generalized tumors. With additional experience gained from careful observation of the patients, the dose was raised in later cases in steps of 25 r. The exploratory phases of the inquiry comprised 233 patients exposed to doses ranging from 15 to 200 r; the final phase consisted of a series of 30 patients who received 200 r. The nature of this study necessitated extensive general, clinical, and laboratory surveillance of the irradiated persons to detect promptly any harmful effect induced by the treatment.

In the first therapeutic study three exposure levels were available; 15, 25, and 50 r, as measured in air. Each dose level was reached either by a single exposure or by five equal fractional exposures separated by an interval of 1 hour. Each subject was given formal test instructions and practice periods on the three testing devices, Complex Coordination, Two-Hand Coordination, and Rotary Pursuit. The data considered do not contain the slightest hint that psychomotor performance was affected by the independent variables

under investigation. It is possible, of course, that protracted observation might have revealed important differences, particularly in subsequent rates of progress, but this possibility is generally denied by the second study.

Nine exposure levels, ranging from 0 through 200 r in 25-r steps, were sampled in the second study. Each subject received his prescribed exposure in a single session.

With the possible exception of the 200 r dose, there is no evidence that exposure to ionizing radiation has affected the psychomotor skills in question. Whether this exception is a true radiation effect is debatable (see Fig. 4). It could just as well have been a disease effect, for we must presume that the prescribed exposure intensity bore some relationship to the severity of the disease (12).

Clinical observations in the first study 15 to 75 r revealed that treatment was tolerated well in all cases. Three years later 30% of the patients were known to be living. Such a survival rate based on clinical experience is not believed to be significantly greater than that expected without whole-body radiation as an adjuvant. In the 100 r group there were some hematologic changes, a significant drop in lymphocytes occurred after the second post-irradiation day. And in the 125 to 175 r groups definite hematologic changes occurred during the initial 2 week period, significant drops in both lymphocytes and leukocytes occurred at 4 and 7 days, respectively. At 200 r it was concluded that: a) anorexia and vomiting only occasionally reached such a degree as to compromise satisfactory nutrition of the patients, b) a definite transitory amelioration of the disease was produced in 3 cases and a questionable improvement in several others, c) the bleeding tendency was increased in some of the patients; however, it did not cause alarming accidents,

and d) whole-body irradiation did not affect at all the life span of the patients when compared to a similar untreated group of cancer patients (13).

RAT STUDIES - UNIVERSITY OF WASHINGTON AND THE SCHOOL OF AVIATION MEDICINE 1956 - 1959

Rats living at 25° and 5° C. were exposed to total body irradiation -- Co^{60} -- at 0.1 r/hr for 8 hours daily from 4 months to 16 months of age. Irradiated animals at both temperatures had an increased life expectancy, and at 25° C. irradiated animals had a higher resting oxygen consumption.

The following generalizations seem warranted after histologic examination of rat tissues obtained from chronically irradiated and nonirradiated animals raised at 5° and 25° C.

1. There was no histologic evidence of irradiation injury in sections of the adrenal, the bone marrow, the ear (pinnae), the eyes, the kidney, the liver, the lung, the lymph nodes, the peripheral blood, the pituitary, the prostate, the spleen, the tail, the testis, the thyroid, and the tongue of rats receiving 0.84 r daily for one year.

2. The testis was markedly atrophic in rats raised at 5° C. This observation is not readily explained (14).

BURRO EXPERIMENTS - UNIVERSITY OF TENNESSEE, AEC FARM, AND THE SCHOOL OF AVIATION MEDICINE - 1952 - 1959

A total band of 59 burros exposed 6-8 years ago to Ta-182 gamma rays are being maintained to study the latent effects of ionizing radiation. Of particular interest is a group of 20 that received 25 r/day for a total dose of 350 r. Typical hematological changes occurred following exposure but in general recovery during the first post-radiation year revealed blood values within normal ranges. There are corneal opacities in both control and irradiated

animals with no statistical significance. Bone marrow smears also do not reveal significant changes attributable to radiation.

MICE DATA - UNIVERSITY OF CHICAGO USAF RADIATION LABORATORY AND SCHOOL OF AVIATION MEDICINE - 1956 - 1959

An extensive mouse program to study the effects of longevity from fractionation and protraction of gamma and neutron irradiation was instituted at the University of Chicago approximately 2½ years ago. Although the data is not yet conclusive and requires additional mathematical analysis, some preliminary observations can be made.

The basic gamma experiment involved three different dose rates of 1/3, 1 and 3 rep per hour at 1 day, 3 day or 9 day intervals (fractionation) with exposures lasting for 18, 54, and 162 days (protraction), and permitted dose ranges to extend from 0 rep, the control group, thru 10, 31, 94, 283, 850, 2,551 and 7,654 rep. In the gamma experiment, analysis of variance indicates that there is no significant difference between the survival time of 50% of the mice which received their dose over 54 days and those in which the dose was protracted for 162 days. Furthermore, it was observed that the 9 day cycling fractionation produced a significantly greater decrease in mean survival time than the 1 and 3 day fractionations. The 9 day fractionation appears to be more effective than the 1 day or 3 day cycling patterns in causing mortality. For those mice which received doses of less than 283 rep there is not a consistant dose dependent difference in the distributionof mortality from that of the control mice.

In the corollary neutron fractionation experiment dose rates of 1/15, 1/5 and 3/5 rep per hour were delivered in the same 1, 3 and 9 day cycles with the identical number of exposure doses - 18, 54 or 162, doses of 0, 19, 57,

170 and 510 rep were obtained. In general, the survival time of those mice which received 510 rep in the 3 day fractionation pattern were considerably shorter than that of the mice receiving 510 rep in the 1 and 9 day patterns. Furthermore, a survival time of the mice in the 9 day pattern is shorter than that of the mice in the 1 day pattern. Analysis of variance indicates that there is no significant difference between the survival time of 50% of the mice irradiated for 18 days and 54 days and that of the mice in which the exposure was protracted for 162 days. It is also indicated that the 3 day fractionation pattern does not produce a significantly greater decrease in the immediate survival time than does the 9 day fractionation pattern.

These studies and their analysis are being continued and indeed indicate extensive work must be done before any theory can be formulated on predictability of the longevity response.

RADIATION CATARACT EXPERIMENTS
B. ACUTE (PHASE III)

RADIATION TYPE AND SOURCE	DATE OF EXPOSURE	TOTAL DOSE	EARLIEST LENS OPACITIES (MONTHS)	DEGREE OF OPACIFICATION (OCT 1955)	TIME POST-RAD	POSSIBLE FUTURE PROGRESSION
FAST NEUTRONS (A) 14 MEV COCKROFT-WALTON ACCELERATOR	15 JAN 1953	250	13	2-3+	5 YRS	ARRESTED
		75	16-1/2	<1+	5 YRS	"
		21				IMPROBABLE
		6				"
		1.75				"
		.75				"
(B) "	4 NOV 1953	850	6-1/2	4+(MATURE 20 MONTHS)		
		250	14	2-3+	4 YRS	ARRESTED
		75	19-1/2	1+	4 YRS	IMPROBABLE
(C) "	26 MAY 1955	150		1+	30 MO	IMPROBABLE
		50				
		15				
THERMAL NEUTRONS LASL	23 JUL 1953	7500	DIED IN 16 WEEKS			
		2500	9-1/2	4+(MATURE 30 MONTHS)	53 MO	
		825	14-3/4	2+	53 MO	ARRESTED
GAMMA 12 MEV AUSTIN, CO^{60}	30 MAR 1954	3000	9-10 MO	4+(MATURE 30 MONTHS)		
		2000	9-10 MO	4+(MATURE 30 MONTHS)	45 MO	
		1000	9-10 MO	3+ 30 MO	45 MO	PROBABLE
		500	22 MO	<1+ 30 MO	45 MO	IMPROBABLE
		250				

Figure / 8

RADIATION CATARACT EXPERIMENTS
A. CHRONIC (PHASE II)

RADIATION TYPE AND SOURCE	DATE OF EXPOSURE	TOTAL DOSE			EARLIEST LENS OPACITIES (MONTHS)	DEGREE OF OPACIFICATION	TIME POST-RAD	POSSIBLE FUTURE PROGRESSION
		GAMMA	NEUTRON	RATIO				
REACTOR SOURCE (PHASE I)	OCT 52	0	0					
		25	0.74	1/34				
OAK RIDGE		107	3.0	1/36				
		493	11.8	1/42	30	<1+	5YRS	ARRESTED
SYNTHETIC SOURCE PoBe AND Co^{60} (PHASE II)	APR 54	0	0					
		70	8.2	1/9				
RADIOBIOLOGICAL LABORATORY-USAF		*140	16.4	1/9				
		**140	16.4	1/9				
		*284	32.5	1/9				
		**280	32.5	1/9				
		557	62.0	1/9	9	<1+	45 MOS	ARRESTED

*EXPOSURE INTERVAL EVERY 4 DAYS FOR 40 EXPOSURES
**EXPOSURE INTERVAL EVERY 12 DAYS FOR 20 EXPOSURES

Figure 2

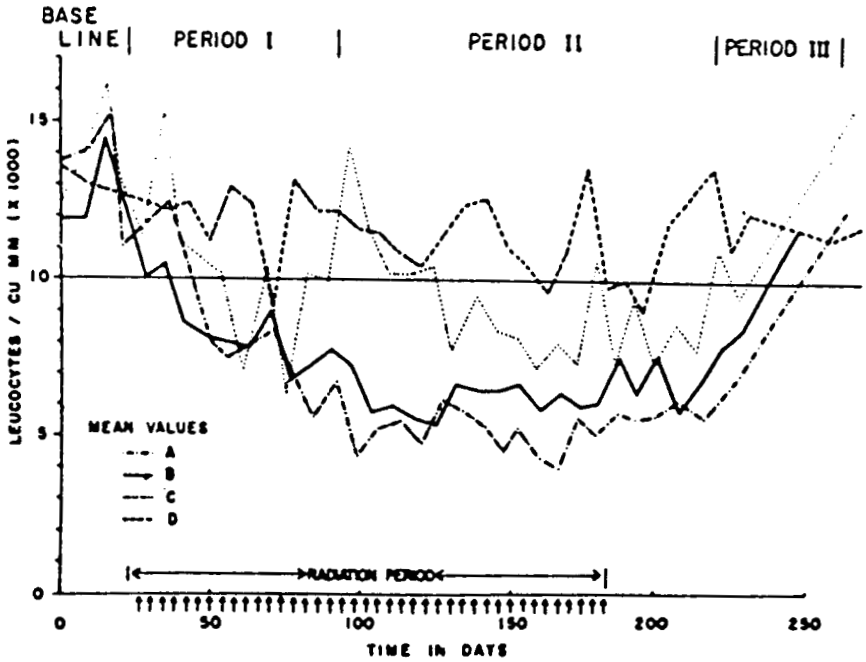
BASE LINE
PERIOD I
PERIOD II
PERIOD III
LEUCOCYTES / CU MM (X 1000)
15
10
5
0
MEAN VALUES
A
B
C
D
RADIATION PERIOD
0
50
100
150
200
250
TIME IN DAYS

Figure 3

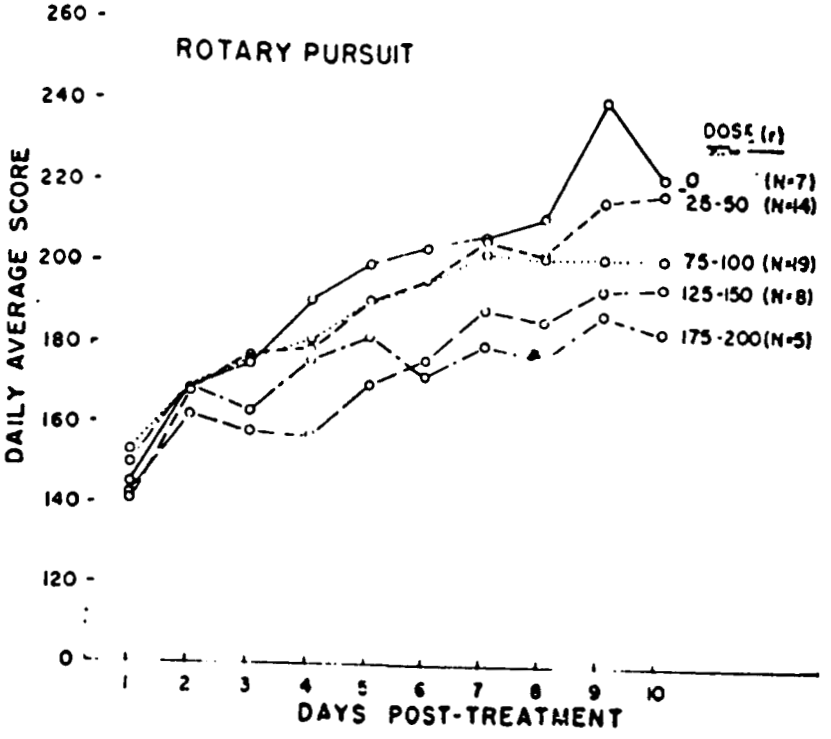
ROTARY PURSUIT
DAILY AVERAGE SCORE
260
240
220
200
180
160
140
120
0
1
2
3
4
5
6
7
8
9
10
DAYS POST-TREATMENT
DOSE (r)
0 (N=7)
25-50 (N=14)
75-100 (N=19)
125-150 (N=8)
175-200(N=5)

Figure 4

REFERENCES

1. Pickering, J. E., D. V. L. Brown, R. B. Payne, and F. S. Vogel. Aircraft Nuclear Propulsion Biomedical Research Program, Report No. 3, Sept. 1955.

2. Pickering, J. E., et al. Proceedings of The Fifth Meeting of the Medical Advisory Group Aircraft Nuclear Propulsion Program, 1956.

3. Biological Effects of Atomic Radiation Summary Reports. National Research Council, National Academy of Sciences, Washington, D. C., 1956.

4. Mole, R. H. Shortening of life by chronic irradiation: Experimental facts. Nature, 1957, 180, 456-460.

5. Warren, Shields. Longevity and causes of death from irradiation in physicians. J. A. M. A. 162:464-468 (29 Sept. 1956).

6. Lewis, E. B. Leukemia and ionizing radiation. Science, 1957, 125, 965-972.

7. Teller, E., and A. L. Latter. Our Nuclear Future--Facts, Dangers and Opportunities, pp. 116-125. New York: Criterion Books, 1958.

8. Wald, Niel. Blood picture of Hiroshima A-bomb survivors. Acta haemat. Japan. 20 (3): Supp. 152-159 (1957).

9. Wald, Niel. Leukemia in Hiroshima atomic bomb survivors. Science 127:699-700 (28 Mar. 1958).

10. Hazards of the medical uses of radiation. Am. J. Roentgenol. 80:696-706 (Oct. 1958).

11. Gerstner, H. B. Acute radiation syndrome in man: Military and Civil Defense Aspects. U. S. Armed Forces M. J. 9:313-354 (Mar. 1958).

12. Payne, R. B. Effects of Ionizing Radiation Upon Human Psychomotor Skills. School of Aviation Medicine Report No. 59-29, December 1958.

13. Miller, L. S., G. H. Fletcher, and H. B. Gerstner. Systemic and Clinical Effects Induced in 263 Cancer Patients by Whole-Body X-Irradiation With Nominal AirDoses of 15 to 200 r. School of Aviation Medicine Report No. 57-92, May 1957.

14. Carlson, L. D., W. J. Scheyer, B. H. Jackson. The Combined Effects of Ionizing Radiation and Low Temperature on the Metabolism, Longevity, and Soft Tissue of the White Rat. School of Aviation Medicine Report No. 57-78, March 1957.