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MEDICINE, HEALTH & SAFETY
3 RADIATION BIOLOGY

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March 15, 1949

A. L. Holland, Jr., M.D.
Medical Advisor
Atomic Energy Commission
Oak Ridge, Tennessee

Dear Dr. Holland:

Transmitted herewith is copy number 123A of a report entitled "Tabulation of Available Data Relative to Radiation Biology."

I hope that you will review this material and bring it with you to the committee meeting to be held in Washington on Sunday, April 3, 1949. It is particularly hoped that you will come prepared to approve the section on Acute Exposure IX, "Estimated Results to Humans Exposed to Filtered 200-1000 Kvp X-rays Measured in Air," pages 34 and 35.

I wish again to call your attention to my letter of February 24, 1949, in which I requested that you forward to me special research problems not now in progress, but which you feel would be of value to NEPA.

Very Sincerely yours,

Andrew H. Dowdy

Andrew H. Dowdy, M.D.
Chairman, NEPA Advisory Committee
on Radiation Tolerance of
Military Personnel

[redacted]

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HEALTH AND BIOLOGY

(1) Motion made to accept report & note added that dosage ~~rates~~ of Los Alamos be subject to revision except table IV

TABULATION OF AVAILABLE DATA RELATIVE TO RADIATION BIOLOGY

Submitted by

Andrew H. Dowdy, M. D.

COMPILED FOR N E P A

1 9 4 9

Consultant Contract AT-04-1-GEN-60

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Report Submitted: February 1, 1949
Report Issued: March 15, 1949

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TABULATION OF AVAILABLE DATA RELATIVE TO
RADIATION BIOLOGY

COMPILED FOR N E P A

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Table I

HISTOGENETIC AND GENETIC EFFECT

Species	Reference	Type Radiation	Application	Dose	Observed Results: Gene Mutation	Observed Results: Chromosome Breaks	Recovery	Remarks
Mice	LAMS (1) Report #808	X-ray	Acute	5r to 325r to epidermis			35r = 5 hr. 325r = 6 days	Mitotic reduction *5r = 60% reduction 325r = 100% reduction
Mice	"	"	"	35r to adrenal, lymph node, and jejunum				Gave 50% reduction
Grasshopper	Hollaender Oak Ridge	Gamma & X-ray	"	5r (neuroblast - studied)			Transient	Recognizable reduction in mitotic rate
Rat	Charles Rochester	250 KVP X-ray	"	100r		At least 9% increase		Probably 18%
Mice	"	"	Chronic 0.1-10r/day 6 days/wk		Dominant 0.4% per 100r			In sperm
Mice	"	"	"		Semi-sterility 0.3% per 100r			In sperm
Drosophila (fruit fly)	Stern and Spencer II-188-5524	X-ray	Acute Female irradiated	25r-1000r @ rate of 10r/min.	Sex-linked lethal			**Linear

* Control, no radiation: 168 mitoses per 100,000 cells.

** At 50r, the mutation frequency was double that of the control. Induced mutation rate = .0019% per r.

(1) Knowlton and Hempelmann, Science, 107: 625, 1948.

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Table II

EFFECT OF IRRADIATION UPON GONADS

Species	Reference	Type Radiation	Application	Observed Results	Dose	Recovery Period	Remarks
Dog	Boche, Rochester #5936	250) 1000) Kvp.	Total body 6 days/week	? Sperm reduction	0.1 r/day	Partial - 4 weeks post-irradiation	
"	"	"	"	"	0.5 r/day	" "	
"	"	"	"	Aspermic 50% after 9 mos.	1.0 r/day	Partial recovery 4 mos. post-irradiation	Animals irradiated for one year
"	"	"	"	"	3 r/day 6 r/day & 10 r/day	—	Approximately 50% aspermic after 100 R_x
Women	(1) Peck et al	? 200 Kvp.	Local to ovary fractional	Sterility	625 r (depth dose)	None	Permanent sterility
"	"	"	"	Sterility in 94%	500 r (depth dose)	"	" "
Man	LAMS #808	Critical limit	Acute total	Testicular damage	180 r		Evidence of testicular damage
"	LAMS #808	"	"	Testicular damage	108 r		Evidence of testicular damage (biopsy)

Note: One female dog became pregnant after 3 r x 440 R_x or 1320 r (6 pups - all normal)

Ref: (1) Peck, W. S., MacGreer, J. T., Kretzmar, M. R., Brown, W. F. Castration of Female by Irradiation. Radiology 34:1176, 1940

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Table III

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INCIDENCE OF LEUKEMIA

Species	Reference	Type Radiation	Application	Dose Min. Detect.	Dose Max. Detect.	Observed Results	Recovery	Remarks
Rats (#) Wistar Strain	Rochester Seminars	X-ray (250 KVP (1000 KVP	Chronic total body irradiation	0.1r/day 6 da./wk	10.0r/day 6 da./wk	0.1r/day 1% 0.5r/day 2% 1.0r/day 3% 10.0r/day 12%	—	Rats exposed for 2 years
Rats Wistar Strain	Rochester and Biochemical Research	Neutrons	Chronic total body irradiation	0.11N/day 6 da./wk	1.7N/day 6 da/wk	0.11N/day 4% 1.7 N/day 16%	—	Rats exposed for 1 year
Female Mice LAF_1	*G. Lorenz	Gamma Rays	Chronic total body, 8 hrs./day			Time to 10% incidence 0.0r/day 600 days 0.11r/day 700 days 1.1r/day 600 days 2.2r/day 600 days 4.4r/day 480 days 8.8r/day 360 days		Overall incidence about 45% in the first five groups; about 70% in the last group

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INCIDENCE OF LEUKEMIA - contd

Species	Reference	Type Radiation	Application	Dose Min. Detect.	Dose Max. Detect.	Observed Results	Recovery	Remarks
Physicians	Henshaw *(1)	Not given	—	—	—	0.53% Physicians 0.39% General population		1933-1944: Physicians dying of leukemia as compared to general population
Radiologists	Ulrich *(2)	Not given	—	—	—	3.9% Radiologists 0.44% Other physicians, not radiologists		

(#) In Wistar strain of rats, breeding colony, of 20,000 - 30,000 rats, no spontaneous leukemias were observed at Rochester between 1943 and 1947. -- A. H. Dowdy

*(1) Henshaw, P. S., Hawkins, J. W. Incidence of Leukemia in Physicians, J. N. Cancer Inst., 4:339-346, 1944.

*(2) Ulrich, Helmuth. The Incidence of Leukemia in Radiologists, New England J. of Med., 234: Jan., 1946.

Other References:

a. Furth, J. and Furth, O.B. Neoplastic Disease Produced in Mice by General Irradiation with X-rays. Incidence and Types of Neoplasm, Amer. J. Cancer, 28:54-65, 1936.

b. Carman, R. D. and Miller, A. Occupational Hazards of Radiologists with Special Reference to Changes in the Blood. Radiology, 3:408-419, 1924.

c. Evans, W. H. and Roberts, R. E. Splenomedullary Leukemia in X-ray Workers, with Discussion of Previously Discussed Cases. Lancet, 2:748-751, 1928.

d. Nielsen, J. Chronic Occupational Ray Poisoning: discussion based on case of leukemia in radium worker. Acta Rad., 13:385, 1932.

e. Warren, S. and Dunlap, C. F. Effects of Radiation on Normal Tissues. III. Effects of Radiation on Blood and Hemopoietic Tissues, including Spleen, Thymus, and Lymph Nodes. Arch. Path., 34:562-608, 1942.

f. Dublin and Spiegalman. Mortality of Medical Specialists. J.A.M.A., 137:1519, 1948.

g. Lorenz. Radiology, 49:274, 1947.

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Table IV

HAEMATOLOGICAL EFFECTS OTHER THAN LEUKEMIA

Species	Reference	Type Radiation	Application	Dose Amt.	Dose Accum.	Observed Results	Recovery Period	Remarks
Dog	Rochester Seminar	X-ray (250 KVP (1000 KVP	Chr. total body 6 days/wk	10r/day-960r	Accumulated	Rbc drop, at accumulated dose 960r	—	
"	"	"	"	10r/day-960r	"	Hb drop, at accumulated dose 960r		
"	"	"	"	3r/day-282r	"	Reticulocytes drop		
"	"	"	"	6r/day-564r	"	Platelet) Total Wbc) drop Absolute) Neutrophils)		
"	"	"	"	3r/day-282r	"	Absolute Lymphocytes drop		
Rabbit	"	"	"	10r/day-960r	"	Rbc drop		
"	"	"	"	10r/day-720r	"	Platelet drop		
"	"	"	"	10r/day-240r-300r	"	Total Wbc) Absolute) Neutrophils) drop Absolute) Lymphocytes)		
Monkey	"	"	"	10r/day-60r-120r	"	Total Whites) Absolute) Neutrophils) drop Absolute) Lymphocytes)		
Dog	Biochemical Foundation	Fast Neutrons	Chr. total body irradiation 6 days/wk	1.7N/day-385N	"	Rbc drop		
"	"	"	"	1.7N/day-26.5N	"	Platelet drop		
"	"	"	"	1.7N/day-25.0N	"	Total Wbc) Absolute) drop Neutrophils)		

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HAEMATOLOGICAL EFFECTS OTHER THAN LEUKEMIA - contd

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Table IV
-contd-

Species	Reference	Type Radiation	Application	Dose Amt.	Dose Accum.	Observed Results	Recovery Period	Remarks
Dog	Biochemical Foundation	Fast Neutrons	Chr. total body irradiation 6 days/wk	1.7N/day-45N	Accumulated	Absolute Lymphocytes drop		
Rabbit	"	"	"	1.7N/day-325N	"	Rbc and Hb drop		
"	"	"	"	1.7N/day-50N	"	Total Wbc drop		
"	"	"	"	1.7N/day-75N	"	Absolute Neutrophils drop		
"	"	"	"	1.7N/day-25N	"	Absolute Lymphocytes drop		
Rat	"	"	"	1.7N/day-60N	"	Rbc drop		
"	"	"	"	1.7N/day-15N	"	Total Wbc) Absolute) drop Lymphocytes)		
"	"	"	"	1.7N/day-25N	"	Absolute Neutrophils drop		
Rabbit	Hogen and Sacher CH-3754	X-ray	Acute total body	50-150 r	"	Detectable effects upon haematological elements		

Note: Analysis of original data incomplete. Results indicated above are tentative.

Note: In special Los Alamos Report #808, Knowlton reports studies on 10 workers exposed during the course of their work and studied for 77 weeks and compared with 24 non-exposed workers over the same period of time. The average accumulated exposure was 16 r; the average drop in total Wbc. was 12-13%; absolute neutrophils drop was 10-11%; and the absolute lymphocyte drop was 16-17%, as compared to a 3% lymphocyte drop in unexposed personnel. Neutrophil control 0%. Total Wbc. of controls 0-1% drop.

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Table IV-A

ACUTE TOTAL BODY IRRADIATION OF RATS WITH 250 K V P

HAEMATOLOGICAL EFFECTS (DOWDY)

Blood Element	Dose in r	Occurrence, hours post-irradiation	Extent of Depression	Duration of Depression	Recovery, hours post-irradiation	Duration of Recovery	Hours post-irradiation to recovery and per cent recovery
R B C	Min. detectable 300 r	225 hours	16%	225 hours	450 hours	150 hours	600 hours 100%
	Max. depression 600 r	240 "	66%	210 "	450 "	150 "	600 hours 68%
Hb.	Min. detectable 300 r	243 "	16%	208 "	450 "	150 "	600 hours 100%
	Max. depression 600 r	245 "	70%	205 "	450 "	150 "	600 hours 70%
Reticulocytes	Min. detectable 100 r	75 "	36.8%	0 ± "	75 "	0 ± "	75 hours 193%
	Max. depression 600 r	75 "	100%	203 "	277 "	165 "	442 hours 145%
Platelets	Min. detectable 100 r	225 "	20%	0 ± "	225 "	—	600 hours 100%
	Max. depression 700 r	225 "	90%	225 "	450 "	>600 "	600 hours 30%
Absolute Neutrophils	Min. detectable 100 r	75 "	15%	82 "	157 "	60 "	217 hours 129%
	Max. depression 600 r	75 "	100%	215 "	285 "	200 "	485 hours 100%
Absolute Lymphocytes	Min. detectable 25 r	16 "	15%	4 "	20 "	5 ± "	25 hours 107%
	Max. depression 500 r	23 "	100%	225 "	225 "	375 "	600 hours incomplete

Note: (1) It is difficult to determine the point where minimal detectable effects are real; therefore, considerable error. (Dowdy)

(2) Error in picking maximal depression is substantial as several hundred roentgen may be required to depress the count from 90% to 100%. Furthermore, recovery times and per cent recovery times are obtained from surviving animals only. (Dowdy)

(Stearner, reported by Brues) "Blood response of rats given 100 r total body x-ray shows a fall in lymphocytes of 70% to 75% of control count with recovery in about 10 days. No effect noted on heterophils. At 25 r, rat lymphocytes fall 30% at one day and are recovered at 20 days."

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Table V

EMBRYOLOGICAL EFFECTS OF IRRADIATION

Species	Reference	Criteria Organ or System	Type Radiation	Application	Dose in r	Results	Remarks
Rat Wistar	Wilson Rochester Project	Resorption Rate growth	Not stated, thought to be 120 Kvp.	Local through operative wound to one uterine horn	50	Negative first 72 hours	Radiation given 10 days post-conception
Rat	"	Resorption	"	"	100	+ - 72 hrs.	"
Rat	"	Reduction wt. of fetus	"	"	100	+ 72 hrs.	"
Rat	"	Eyes malformed Lens malformed	"	"	100	+ 72 hrs.	Also G.U. tract and heart retarded
Rat	"	Resorption Decreased wt. fetus Eye deformity	"	"	200	Resorption + + Reduction + + (wt) Eyes + + +	
Chinook Salmon	Donaldson	L.D. 50 - 125 days Abnormal eye development	200 Kvp	Total body	1000		Eyed embryos irradiated
Mouse	*Hollaender	Changes resembling gene mutation. Oligodactylism	250 Kvp	Total body irradiation of mother	200-500		2-17 days gravid mice

*Hollaender states that preliminary data indicate that 100 r gives similar striking changes.

Note: All these data are preliminary and incomplete.

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Table VI

N - r RATIO

Species	Reference	Criteria Organ or System	Type Radiation	Application	Remarks
Mice	Evans & Failla	Haemogram	Fast Neutrons	Total body, acute	1 N = 8 r
Mice	"	Haemogram Survival time	80 r/day 10 N/day	Total body, fractional	1 N = 8 r (approx.)
Mice	Evans, T. C. (1)	Mortality Haematology Gonads Lens of Eye	1.4 N/day	Total body, fractional	1 N = 12-15 r
Rat	Rochester and Biochemical	Mortality	Fast Neutrons X-ray	Total body, chronic	1 N = 8-21 r
Rabbit	"	"	"	"	1 N = 12-16 r
Dog	"	"	"	"	1 N = 6-14 r
Mice	Zirkle (2) Roper Riley Stapleton CH-2571	"	Fast Neutrons Gamma rays	Total body, acute	Fast neutrons and gamma rays completely additive (acute radiation)
Mice & Rabbits	" CH-3839	"	"	"	1 n = 5-12½ r or gamma rays (1 n = 2.5 reps)

(1) Evans, T. C. Effects of Small Daily Doses of Neutrons on Mice, Radiology, 50:811-833, 1948

Note: Mitchell (Brit. J. Radiology, 20:368, 1947) found 1 rep of neutrons equivalent to 32 ± 8.6 r of gammas when the doses were delivered in one or two days.

Table VII

MORTALITY TABLE

Species	Reference	Application	Type Radiation	L.D. 50 Dose Time
Guinea Pig	Ellinger (4) Henshaw (5)	Total body	200 KVP	200 r
Dog	Cole et al. (6)	"	200 KVP	300 r
Dog	Rochester expt. #5980	"	1000 KVP	335 r
Mouse	Ellinger (4)	"	200 KVP	400 r
Mouse C3H	Henshaw (5)	"	200 KVP	450 r
Mouse LAF	Henshaw (5)	"	200 KVP	600 r
Monkey	Rochester Report #5980	"	250 KVP	500 r
Rat	Cole et al. (6)	"	200 KVP	590 r
Rat Wistar	Rochester Report #5980	"	250 KVP	650 r
Hampster	Rochester Report #5980	"	250 KVP	700 r
Rabbit	Hagen et al.(7)	"	200 KVP	790 r
Man				

(4) Ellinger, F. Radiology, 44:125-142, 1945.

(5) Henshaw, P. S. J. Natl. Cancer Inst., 4:485-501, 1944.

(6) Cole, K. S. et al., Metallurgical Laboratory, University of Chicago, 1944.

(7) Hagen, Jacobsen, Murray and Lear, Metallurgical Laboratory University of Chicago, 1944.

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Table VIII

MORTALITY CHRONIC X-RADIATION 3 r – 10 r PER DAY

Species	Sex	Reference	Type Radiation	Application	r per day	Total r received at death	Remarks
Dog # 1	F	Boche Rochester #5939	1000 KVP	Total body 6 days/wk	10.0 r	1200	
" # 2	F	"	"	"	"	3110	
" # 3	F	"	"	"	"	1340	
" # 4	F	"	"	"	"	2540	
" # 5	M	"	"	"	"	3590	
" # 6	M	"	"	"	"	1240	10 dogs or 50%
" # 7	M	"	"	"	"	1830	3 dogs were alive at 5000 r (2 M and 1 F) dead at accumu-
" # 8	M	"	250 KVP	"	"	1300	lated dose of
" # 9	F	"	"	"	"	1320	1440 r
" #10	F	"	"	"	"	1110	
" #11	M	"	"	"	"	1270	
" #12	F	"	"	"	"	1440	
" #13	M	"	"	"	"	1070	
" #14	M	"	"	"	"	2660	
" #15	M	"	"	"	"	1150	
" #16	M	"	"	"	"	1870	1 F alive at 5000 r
" #17	M	"	1000 KVP	"	3.0 r	1199	2 M and 2 F living at 1500 r
" #18	M	"	250 KVP	"	"	1305	3 F living at 1500 r
" #19	F	"	1000 KVP	"	6.0 r	2940	
" #20	M	"	"	"	"	2304	
" #21	M	"	"	"	"	2064	
" #22	M	"	"	"	"	2214	1 F alive at 3000 r
" #23	F	"	250 KVP	"	"	1908	3 M and 1 F alive at 3000 r

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Table IX

Species	Reference	Type Radiation	Application	Observed Result	Accumulated Dose at Half Survival in r	Remarks
Rat	Boche 11-188-5936	X-rays 250 and 1000 KV	Within 10-15 min. per dose	Mean Death Time		
			0	85.8 weeks	0	
			0.10/day, 6/week	81.7 "	48	
			0.5 " "	76.7 "	230	
			1.0 " "	76.9 "	460	
			10.0 " "	58.3 "	3500	
Rat	"	"	" "	Factor related to life-span decrease		
				2.4×10^{-4}		
Dog	"	"	" "	2.1×10^{-4}		
Rabbit	"	"	" "	1.1×10^{-4}		
Mouse	Henshaw's data	X-rays 200 KV	*	2.0×10^{-4}		
Mouse	Lorenz et al. Radiology, 49:274, 1947	Gamma Rays	0.0 /8 hr/day	690 days half survival		
			0.115 " "	780 " " "		
			1.1 " "	690 " " "	760	
			2.2 " "	630 " " "	1390	
			4.4 " "	600 " " "	2640	
			8.8 " "	500 " " "	4400	
Guinea Pig	"	"	0.0 " "	75% survival (1100 days)		
			1.1 " "	1100 day half survival	1200	
			2.2 " "	960 " " "	2100	
			4.4 " "	540 " " "	2400	
			8.8 " "	150 " " "	2300	
Mice C3H	Henshaw's data given by Boche #5936	X-rays 200 KV	0 r per week	45.8 weeks, Mean Death Time		
			*25 " "	36.8 " " " "	920	
			50 " "	34.6 " " " "	1730	
			75 " "	27.1 " " " "	2032	L.D. 50 = 450 r
			100 " "	23.9 " " " "	2390	
			125 " "	19.2 " " " "	2400	

*Dosages are in equal fractions
5x/wk., i.e. 5rx5, etc.

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Table X

EFFECT OF RADIATION HUMAN CASES

Case	Age	Reference	Type Radiation	Application	Lymphocytes	Neutrophils	Other	Remarks
1.	53	CH-3868	400 KVP	Total body acute 60 r	+ reduction	± reduction	None	Ca epiglottis. Reduced lymphocytes for 157 days.
2.	75	"	"	"	+ rise followed by + reduction	+ rise followed by + fall	+ platelet fall 28th-71st day	Ca tonsillar pillar and fossa. Lymphocyte fall persisted 151 days.
3.	59	"	"	"	+ fall	+ fall	None	Ca epiglottis.
4.	72	"	"	"	± reduction	None	None	Ca right breast. Lymphocyte fall transient.
5.	57	"	"	Total body acute 27 r	No effect	Sl. increase	None	Ca epiglottis.
6.	61	"	"	Total body acute 120 r	+ reduction	± temporary reduction	Platelets reduced at 24-48 hours	Ca larynx. Lymphocytic reduction not marked.
7.	65	"	"	"	+ reduction most marked 35th day	± rise	+ decrease in Rbc. and Wbc.	Ca larynx.
8.	54	"	"	"	+ reduction	± rise	± rise in platelets 2nd-14th day	Ca epiglottis (1) Change not impressive
9.	73	"	200 KVP	Fractional total body 502 r Nov 26-Dec 20	++++ Starting after 2nd R_x	++++ Starting after 2nd R_x	Nausea & vomiting 1, 2, 6th R_x	Ca hand with metastasis. 3750 cc. transfusion 26th and 30th day.
10.	67	"	"	Fractional total body 300 r in 33 days	+++	+++	+ depression bone marrow	Chr. rheumatoid arthritis.
11.	25	"	"	87.5 r total body. In 8 daily treatments	+ reduction	+ reduction	Rbc. and Wbc. + reduction	Arthritis.
12. 13. 15.	35 23 23	" " "	" " "	7 r total body q. day for 3 days	None	None	None	None (Total 3 cases)

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Table X
-contd-

EFFECT OF RADIATION HUMAN CASES - contd

Case	Age	Reference	Type Radiation	Application	Lymphocytes	Neutrophils	Other	Remarks
-	-	Rochester	1000 KVP	Estimated 25 r total body from overhead tube	None	None	None	Dose estimated at mid-torso.
1.	-	LAMS #808	Critical limit	Total body Estimated 290 r	++++ reduction	++++ reduction	Epilation, anemia, thrombocytopenia, gross testis damage	Death 25th day. (2) Aplastic bone marrow.
2.	-	"	"	Estimated 18 r	No reduction	No reduction	Normal	Still normal 10 mos. post-irradiation.
3.	-	"	"	" 880 r	++++ reduction	++++ reduction	Nausea, vomiting, gastric distress	Death 9th day.
4.	-	"	"	" 180 r	+++ reduction	+++ reduction	Epilation, vomiting, weakness	Evidence of testicular damage.
5.	-	"	"	" 108 r	+++ reduction	+++ reduction	Nausea, vomiting, fatigue, epilation, testicular atrophy	(Biopsy) Evidence of testicular damage.
6.	-	"	"	" 86 r	Normal	Normal	Normal	Normal 2 years post-exposure.
7.	-	"	"	" 65 r	+ reduction	+ reduction		Normal 15 mos. post-exposure.
8.	-	"	"	" 22 r	Normal	Normal	Normal	Normal
9.	-	"	"	" 18 r	+ reduction	Normal		Normal
10.	-	"	"	" 14 r	Normal	Normal	Normal	Normal

Note: (1) No radiation nausea observed in cases receiving 60 or 120 r acute doses.
(2) Of the Los Alamos cases, all but case 9. and case 10. revealed increase in refractile bodies in the lymphocytes.

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Table X-A

EFFECT OF TOTAL BODY IRRADIATION

HUMAN CASES

Submitted by Dr. R. S. Stone

Cases 1-29 CH-3863
Cases 30-32 UCRL-41

Case	Age	Type of Radiation	Application: Elapsed Days	Application: Daily Dose	Application: Total Dose	Lymphocytes: During R_x	Lymphocytes: After R_x	Neutrophils: During R_x	Neutrophils: After R_x	Other such as RBC, etc.	Remarks
1.	23	200 KV	27	15	321	Fluctuate from ++++ increase to ++++ decrease	25 days after + decrease 60 days after + decrease	++++ Fluctuations	4 days after ++++ decrease 60 days after ++++ increase		Poor subject. Hodgkins Disease with fluctuating blood counts. Followed 48 days.
2.	33	200 KV	58	50	394	Fluctuate from ++++ increase to ++++ decrease		+ decrease			Poor follow-up (cooperation poor) Followed 130 days.
3.	58	200 KV	24	10 or 20	295	Fluctuate from ++++ increase to ++++ decrease	++++ increase	++ decrease + increase	++ decrease		Recovery of count in 90 days for PMN - by end of treatment for lymphocytes. Followed 154 days.
4.	61	100 KV 200 KV	89	30	367						No good because too much local treatment and not enough blood counts.
5.	29	100 KVx10 200 KVx18	59	10	291	Fluctuate from + increase to +++ decrease	++ decrease at end of R_x gradual return to normal in 180 days	Fluctuate mostly up to +++	Low in 50 days +++ decrease recovery	Hgb & RBC + decrease during R_x	++ fluctuation in PMN for 600 days. Otherwise complete recovery. Followed 834 days.
6.	64	200 KV	25	10 or 20	244	Down to ++++ decrease		Fluctuate from + increase to ++++ decrease			Followed only 36 days and received local x-ray therapy during that time.
7.	36	100 KVx23 200 KVx3	35	10 or 15	295	Down to +++ decrease		Fluctuate from ++++ increase to ++++ decrease			Followed 36 days

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Table X-A
-contd-

EFFECT OF TOTAL BODY IRRADIATION HUMAN CASES - contd

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Cases 1-29 CH-3863
Cases 30-32 UCRL-41

Case	Age	Type of Radiation	Application: Elapsed Days	Application: Daily Dose	Application: Total Dose	Lymphocytes: During R_x	Lymphocytes: After R_x	Neutrophils: During R_x	Neutrophils: After R_x	Other such as RBC, etc.	Remarks
8.	46	200 KV	22	15	302	Down to ++++ decrease	Low level continued	Fluctuating increase to ++++	++++ decrease. Lowest level 18th day after end of R_x		In 32 days followed after R_x. PMN and lymphocytes did not recover. Followed 74 days.
9.	66	200 KV	16	20	300	Decrease to ++++	Did not return to pre-R_x level until 315th day	Fluctuate from ++ increase to ++++ decrease	Low of 630 22 days after end of R_x		Lymphocytes and PMN continued low most of the time.
10.	51	200 KV	16	20	300	Fluctuating but frequently ++++ decrease	Low of 620 9 days after end of R_x	Fluctuate from ++ increase to ++ decrease	Low of 805 on 30th day after R_x. Recovery by 60th day		Lymphocytes returned to normal by 43rd day after R_x. PMN returned to normal by 60th day. Lymphocytes and PMN frequently low. Followed 1946 days.
11.	63	200 KV	17	20	300	Fluctuating mainly down to ++++ decrease max.	Recovery 56 days after end of R_x	Fluctuate from ++ increase to ++ decrease	Recovery by 55, but tended to fluctuate at low level		Lymphocytes generally low for about 2 years, but tend to be higher. Polys tended to be low for 2 years. Followed 1650 days.
12.	47	200 KV	17	20	313	Always down Greatest decrease +++	Not complete recovery in 46 days	Fluctuate mostly + up	Fluctuate mostly below normal		Not sterilized in 46 days. Reports from other Physician showed "normal" blood 10 months after R_x. Followed 46 days.
13.	66	200 KV	15	20	258	Always decreased ++ to +++	Remained down	Fluctuate less than + either up or down	++ decrease in 10 days		Lymphocytes did not return to 3500 level. Polys remained lower after R_x. Followed 784 days.
14.	38	1000 KV	5	20	100	Always decreased + or ++	Rapid Recovery	Fluctuate Most increase	Mostly down + or ++		Lymphocytes tended to fluctuate below pre-R_x level. Polys " " " " pre-R_x level. Followed 79 days.

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Table X-A
-contd-

EFFECT OF TOTAL BODY IRRADIATION HUMAN CASES - contd

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Cases 1-29 CH-3863
Cases 30-32 UCRL-41

Case	Age	Type of Radiation	Application: Elapsed Days	Application: Daily Dose	Application: Total Dose	Lymphocytes: During R_x	Lymphocytes: After R_x	Neutrophils: During R_x	Neutrophils: After R_x	Other such as RBC, etc.	Remarks
15.	74	1000 KV	6	20	100	Little change	+ decrease for 3 days	Up to a + decrease	Slightly low		Relatively little effect on polys and lymphocytes. Followed 88 days.
16.	66	1000 KV	6	20	100	Mostly + decrease	Normal	Mostly slight to + decrease	Down to a ++ decrease		Total WBC and polys lower - but more normal " after treatment. Lymphocytes normal. Followed 615 days.
17.	38	1000 KV	7	20	120	++ decrease by last day	Immediate recovery	Normal fluctuation	Normal fluctuation		Practically no change. Followed 37 days.
18.	55	1000 KV	5	20	100	++ decrease	Recovery by 39th day	Normal or slight increase	Normal fluctuation		At 1 yr. and 2 yr. intervals the polys and lymphocytes + total WBC were more normal than before R_x. Followed 100 days and then on the 386th and 655th.
19.	55	1000 KV	17	20	283	+ total + decrease	Low of 880 90 days after finish of R_x	Marked fluctuations	Continued fluctuations		Lymphocytes below pre-treatment level almost constantly. Polys varied about the same during and after R_x. Followed 1071 days.
20.	36	1000 KV	17	20	300	Fluctuating downward to ++ decrease at end	++++ decrease on 4th day after R_x	Marked fluctuation mostly down ++ decrease	+++ decrease on 4th day after R_x		Patient a drifter who did not return. Followed only 21 days.
21.	42	1000 KV	21	20	292	Gradual downward to +++ decrease	Below 1000 for 431 days	Fluctuating but mostly slight decrease to + decrease	Low of +++ decrease on 25th post R_x day		Lymphocytes never back to normal, but above 1200 after 755th day. Followed 1210 days.

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Table X-A
-contd-

EFFECT OF TOTAL BODY IRRADIATION HUMAN CASES - contd

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Cases 1-29 CH-3863
Cases 30-32 UCRL-41

Case	Age	Type of Radiation	Application: Elapsed Days	Application: Daily Dose	Application: Total Dose	Lymphocytes: During R_x	Lymphocytes: After R_x	Neutrophils: During R_x	Neutrophils: After R_x	Other such as RBC, etc	Remarks
22.	33	1000 KV	18	20	300	++ increase followed by slight decrease	Low of 600 on 23rd day post-R_x	Slightly downward trend	+++ decrease by 23rd day post-R_x		Lymphocytes returned to pre-R_x level by 321st post-R_x day. Polys soon returned to normal levels. Followed 1344 days.
23.	48	1000 KV	19	20	302	++ increase followed by ++ decrease	Low of 160 on 8th day post-R_x	Slight fluctuation up and down	Generally downward. Low on 33rd day post-R_x		Lymphocytes continued below 1000 all through post-R_x period. Polys gradually returned to normal levels. Followed 421 days.
24.	25	1000 KV	7	20	120	++ decrease by end of R_x	Low of +++ decrease on 35th day post-R_x	+ decrease during R_x	++ decrease on 35th day post-R_x		Lymphocytes back to normal by 49th day. Polys recovered by 49th day, but low thereafter. Followed 615 days.
25.	32	1000 KV	2	20	40						Complicated by previous x-ray. Followed only 2 days.
26.	64	1000 KV 200 KV	38 26 4	10	299	+ decrease during R_x near end	++ decrease on 30th day post-R_x	+ fluctuation up and down	Above pre-R_x level		Lymphocytes recovered by 44th day post-R_x. Polys seldom below pre-R_x level. In normal range at all times. Followed 351 days.
27.	45	1000 KV 200 KV	40 27 3	10	301	Gradual fluctuating decrease to +++ at end of R_x	Gradual increase to normal by 62nd day post-R_x	Occasional + decrease	On 29th post-R_x day ++ decrease		Lymphocytes stayed at or above pre-R_x level after 62nd post-R_x day. Polys tended to stay near pre-R_x level. Followed 585 days.

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Table X-A
-contd-

EFFECT OF TOTAL BODY IRRADIATION HUMAN CASES – contd

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Cases 1-29 CH-3863
Cases 30-32 UCRL-41

Case	Age	Type of Radiation	Application: Elapsed Days	Application: Daily Dose	Application: Total Dose	Lymphocytes: During R_x	Lymphocytes: After R_x	Neutrophils: During R_x	Neutrophils: After R_x	Other such as RBC, etc.	Remarks
28.	52	1000 KV 200 KV	91 17 41	5	298	Occasional + decrease	On 5th post-R_x day ++ decrease	Occasional + decrease	Fluctuating around normal		Lymphocytes and polys near normal level. Followed 913 days.
29.	68	1000 KV 200 KV	68 15 37	5	278	Fluctuating down to +++ decrease near end of R_x	+++ decrease 2 days after R_x	Occasional ++ decrease generally downward	++ decrease 2 days after last R_x generally upward		Lymphocytes did not recover to pre-R_x value. Polys only once reached pre-R_x value. Followed 351 days.
30.	59	100 KV	36	10	298	Occasional ++ decrease Tends to fluctuate more near end	Around ++ decrease for 54 days	Fluctuate from + decrease to ++ increase	Tend to fluctuate considerably		Lymphocytes rose to +++ increase and stayed above pre-R_x values. Polys tend to be normal or slightly low. Followed 771 days.
31.	58	100 KV	36	10	299	Fluctuate from + increase to + decrease	++ decrease 2 days after R_x	Fluctuate from + increase to + decrease	Fluctuate around Pre-R_x value		Lymphocytes tend to higher values. Polys vary around pre-R_x value. Followed 716 days.
32.	58.	100 KV	19	20	303	++ decrease but fluctuate up	Slowly upward	Tend to be low even before R_x and during R_x			Lymphocytes recover by 107 post-R_x day. Polys tend to stay on same low value as before R_x. Followed 674 days.

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Table X-B

COMPARISON OF RADIATION EFFECT BY TOTAL DOSE

26 CASES

Submitted by Dr. R. S. Stone

	1.		2.		3.		4.		5.		18 Patients	
	200 & 100 Kv 300r 2 pts.		200 Kv 300r 9 pts.		1000 & 200 Kv 300r 2 pts.		1000 Kv 100r 6 pts.		1000 Kv 300r 7 pts.		Total of numbers 2, 3, & 5	
	sig +	sig −	sig +	sig −	sig +	sig −	sig +	sig −	sig +	sig −	sig +	sig −
Conclusion of treatment course	−	−	−	1 pt	−	1 pt	−	1 pt	−	−	−	2 pts
	−	−	−	−	−	−	−	−	−	−	−	−
	−	−	1 pt	−	−	1 pt	−	1 pt	1 pt	1 pt	2 pts	2 pts
	−	−	2 pts	3 pts	−	2 pts	−	1 pt	1 pt	1 pt	3 pts	6 pts
	−	−	1 pt	6 pts	−	2 pts	1 pt	4 pts	−	6 pts	1 pt	14 pts
	−	−	6 pts	−	−	−	2 pts	−	1 pt	−	7 pts	−
30 days after conclusion of treatment	1 pt. only		8 pts. only						6 pts. only		16 Patients	
	−	−	−	1 pt	−	1 pt	−	1 pt	2 pts	1 pt	2 pts	3 pts
	−	−	−	1 pt	−	1 pt	−	−	−	−	−	2 pts
	−	−	−	4 pts	−	1 pt	1 pt	2 pts	−	4 pts	−	9 pts
	−	−	−	5 pts	−	1 pt	1 pt	1 pt	−	3 pts	−	9 pts
	−	−	−	3 pts	−	2 pts	1 pt	4 pts	−	5 pts	−	10 pts
	−	−	4 pts	−	−	−	−	−	−	−	4 pts	−
60 days after conclusion of treatment			7 pts. only				4 pts. only				15 Patients	
	−	−	−	1 pt	−	1 pt	−	1 pt	−	−	−	2 pts
	−	−	−	1 pt	−	−	−	1 pt	−	−	−	1 pt
	−	1 pt	1 pt	2 pts	−	−	−	−	1 pt	3 pts	2 pts	5 pts
	−	1 pt	1 pt	3 pts	−	−	−	1 pt	1 pt	1 pt	2 pts	4 pts
	−	1 pt	1 pt	1 pt	−	1 pt	1 pt	1 pt	−	5 pts	1 pt	7 pts
	−	−	5 pts	1 pt	−	−	−	−	1 pt	−	6 pts	1 pt

Summary of results on 26 of the patients treated to total of 100 r (6 pts.); 300 r (20 pts.), with daily doses of 5 r, 10 r, 15 r, and 20 r.

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Submitted By R. [illegible] Stone

Table X-C

TECHNIQUES EMPLOYED FOR TOTAL IRRADIATION

Name and Year	K.V.P.	M.A.	Filtration	cm t.s.d.	Field Size	No. of Field	Location of Field	r/R_x	Min/R_x	Frequency of R_x	Remarks
1923 Chaoul & Lange			1 mm Cu	40-45	¼ of torso	4	Upper & lower torso - A. & P.	~60		About every 2 days	60-70% S.E.D. to each field in 8 weeks
1927 Teschendorf	180		0.5 mm Zn 2.0 mm Al	150	½ of body	2	A. & P.	~10	30-45	About two times a week	
1931 Teschendorf	170	6		180-200	½ of body	2	A. & P.	~12	6-10	Usually 5-8 day interval	
1931 Groedel & Lossen					Small	28	Covered body	84-360		4-5 fields a day	Not body irradiation, really
1931 Sluys	200			150	¼ of torso	4	Upper & lower torso - A. & P.	25 - 50		Daily -- 1 field	Total-- 200-2400 r
1932 Heublein	185	3	2 mm Cu	548 & 732	Body	1	Body	1.26 r/h	20 hrs. out of 24	Up to 187 hours	
1932 Ardent & Gloor	170	3	.5 mm Cu .5 mm Zn		Body			60-120			
1936 Squalitzer	170	3	0.5 mm Zn 1.0 mm Al	150	Body	2	A. & P.	~25	~20	1 r a day 6 days - rest 6 days	Usually 2 courses of irradiation. Shields eyes, genitalia-
1936 O'Brien	200	5	1.0 mm Cu 1.0 mm Al	300	Body	1	Body	~10	40		

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Table X-C
-contd-

TECHNIQUES EMPLOYED FOR TOTAL IRRADIATION - contd

Name and Year	K.V.P.	M.A.	Filtration	cm t.s.d.	Field Size	No. of Field	Location of Field	r/R_x	Min/R_x	Frequency of R_x	Remarks
Hunter 1936	200	4	0.5 mm Cu 4.0 mm Celluloid	215	Body	1	Body	20	60	Daily	(Polycythemia vera) 600 r in 35 days
Hunter 1936	200	6	same	215	Body	1	Body	54	60	Daily	(Polycythemia vera) 1102 r in 30 days
Sanderson 1936	200	4,6	0.5 mm Cu	225	Body	2	A. & P.	24, 42	60	Daily	(Polycythemia vera) 70-600 r given
Mallet 1939				340	Body	1	Body	5-20		2 times a week	
Craver & Medinger 1942	185	1	5.5 mm Cu	300	Body	1	Body	0.86	r/hour	Continuous	100 r - 300 r usually
Dale 1931			0.5 mm Zn 2.0 mm Al	100	Body	2	A. & P.	12-18	12-18	Daily - 5 d to 5 weeks	Head, neck, & genitalia shielded. 1/10 - 3/5 S.E.D. total per series.
Mallet 1946	200		0.5 mm Cu 2.0 mm Al	150-300	20x10 to Body	Vary	Body	25	30	4-5 R_x/week	Stop if WBC below 2500, RBC below 2.5. 500-1200 r/field series

PRIVACY ACT MATERIAL REMOVED

Table X-D

SUMMARY

POLYCYTHEMIC AND LEUKEMIC PATIENTS LIVING 1 YEAR OR MORE

Submitted by Dr. Shields Warren
New England Deaconess Hospital, Boston

	In One Year 10,000 u.c. P^{32}	In One Year 10,000-20,000 u.c. P^{32}	In One Year 20,000 u.c. P^{32}	TOTAL
+ hurt by radiation	0	2	1	3
- not hurt by radiation	18	12	5	35
TOTAL	18	14	6	38

10,000 U.C. P^{32}	Case No.	
1. - 4,750 u.c.	6	HODGKIN'S DISEASE
2. - 4,645 u.c.	10	MONOCYTIC LEUKEMIA
3. - 4,680 u.c.	16	HODGKIN'S DISEASE
4. - 8,385 u.c.	27	TERMINAL LYMPHATIC LEUKEMIA
5. - 8,663 u.c.	30	MYELOMA
6. - 5,130 u.c.	37	ACUTE LYMPHATIC LEUKEMIA
7. - 5,982 u.c.	38	HODGKIN'S DISEASE
8. - 6,140 u.c.	45	POLYCYTHEMIA
9. - 2,280 u.c.	57	POLYCYTHEMIA
10. - 7,800 u.c.	64	TERMINAL CHRONIC MYELOGENOUS LEUKEMIA

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Table X-D
-Contd-

10,000 U.C. P^{32}	Case No.	
11. - 7,720 u.c.	77	LYMPHOSARCOMA
12. - 7,800 u.c.	79	POLYCYTHEMIA VERA
13. - 9,000 u.c.	83	LEUKEMIA
14. - 7,000 u.c.	88	POLYCYTHEMIA VERA
15. - 8,000 u.c.	89	POLYCYTHEMIA
16. - 5,500 u.c.	92	MYELOGENOUS LEUKEMIA
17. - 4,000 u.c.	98	POLYCYTHEMIA
18. - 6,700 u.c.	99	MULTIPLE MYELOMA

10,000 - 20,000 U.C. P^{32}		
1. - 10,038 u.c.	3	SUBACUTE LYMPHATIC LEUKEMIA
2. - 16,955 u.c.	7	CHRONIC MYELOGENOUS LEUKEMIA
3. + 15,770 u.c.	26	TERMINAL CHRONIC LYMPHATIC LEUKEMIA
4. + 13,110 u.c.	28	SUBACUTE CHRONIC LYMPHATIC LEUKEMIA
5. - 12,528 u.c.	31	CHRONIC LYMPHATIC LEUKEMIA
6. - 18,615 u.c.	3	MYELOGENOUS LEUKEMIA
7. - 19,664 u.c.	34	CHRONIC MYELOGENOUS LEUKEMIA

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PRIVACY ACT MATERIAL REMOVED

Table X-D
-Contd-

10,000 - 20,000 U.C. P^{32}	Case No.	
8. - 12,857 u.c.	39	
9. - 13,680 u.c.	47	MULTIPLE MYELOMA - GROUP A
10. - 15,615 + u.c.	65	CHRONIC LYMPHATIC LEUKEMIA
11. - 15,700 u.c.	86	LYMPHOID LEUKEMIA
12. - 12,300 u.c.	87	POLYCYTHEMIA VERA
13. - 16,000 u.c.	95	MYELOGENOUS LEUKEMIA
14. - 14,500 u.c.	96	MYELOGENOUS LEUKEMIA

20,000 U.C. P^{32}		
1. - 25,440 u.c.	60	CHRONIC MYELOGENOUS LEUKEMIA
2. - 20,080 u.c.	63	CHRONIC LYMPHATIC LEUKEMIA
3. - 27,872 u.c.	66	CHRONIC MYELOGENOUS LEUKEMIA
4. + 24,150 u.c.	72	CHRONIC MYELOGENOUS LEUKEMIA
5. - 21,000 u.c.	74	CHRONIC MYELOGENOUS LEUKEMIA
6. - 25,900 u.c.	93	MYELOGENOUS LEUKEMIA

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Table XI

CHEMICAL ASPECTS 1/

Species	Reference	Type Irradiation	Application	Dose r 2/	Observed Result	Remarks
Enzymes & other naturally occurring organic compounds	Many Authors			See Footnote 3/	Produce chemical changes	Biological significance unknown apart from possible genetic effects
	Barren MDDC-484	X-rays	Acute	100 r	Inhibited respiration in spleen slices 10%; testes 31%	
Rat	Barron et al MDDC-1241	"	"	50-500 r	Inhibited uptake of glucose by intestine over 2-4 hours	
Dog	Prosser et al Radiology 49, 299, (1947)	"	"	200 r	Blood clotting increased 2-4 times	
Dog	Allen et al J. Exp. Med. 87, 71 (1948)	"	"	450 r	Heparin-like substance found in blood	Later similar observations have been made in rabbits at 800 r and apparently in man
Rat	Kohn & Robinett ORNL 116	"	"		Heparin not found	By administering Heparin the LD 50 was reduced from 550 r to 350 r
Rat	Prosser et al ibid	"	"	200 & 100 r	SCN space increased by 2% for a few days	Dogs required 400 r. Water intake and urine output disturbed with mid-lethal doses
Dog	"	"	"	100 r	Increased sedimentation rate of erythrocytes	

1/ The examples given illustrate various types of chemical approach to the radiation problem. Many of the observations still require confirmation.

2/ The doses given are not usually minimum doses.

3/ The dose to produce effects depends on the purity of the compound, its dilution, and the number of molecules changed per ion pair.

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Table XI
-contd-

Species	Reference	Type Irradiation	Application	Dose r 2/	Observed Result	Remarks
Mouse?	Dougherty & White End. 39, 370 (1946)	X-rays	Acute	200 r	Adrenal cholesterol dropped from 60-65 mg.% to 10 mg.%	Such a change in cholesterol is interpreted as paralleling an increased hormone secretion.
Rat	Patt et al CH-3830 P59 (1948)	"	"	200-650 r	Drop in adrenal cholesterol 2-6 hours	Fall prevented by prior adrenal cortical extract injections.
"	Patt et al ANL-4163 P 86 (1948)	"	"	650 r	Total cholesterol in gland doubled 5 days after irr. Weight of gland also increased at that time.	
Mouse	Dougherty & White	"	"	10 r	Decrease in plasma gamma globulin	3 hours after irradiation
Rabbit	Craddock & Lawrence MDDC-1698	"	"	250 r	Antibody production markedly decreased if antigen injection started after irr., not if started 4 days previously	
Fern Spores	Zirkle	"	"		Ammonia or carbon dioxide modified the sensitivity	
Yeast	Anderson	"	"		The sensitivity varied depending on the presence or absence of oxygen	
Rat 1 day old	Evans	"	"		Less damage at low temperatures or with respiration or circulation stopped	
Dog	Rekers & Field Science 107, 16, 1948	"	"	350 r	Fewer dogs treated with rutin died from this dose than in an untreated series	Rats are reported to be unaffected
Male Mouse	Gardner et al End. 32, 116, (1943)	"	"	550 r	Prior injection of estradiol benzoate decreased the radiosensitivity	

RESTRICTED

S U M M A R Y

I. Genetics (Table I)

A. Mice

The genetic hazard in mice is approximately 1% of bad sperm per 100 r. This value apparently excludes recessives and dominants or chromosome mutations with small effects. (Donald Charles). See Appendix, page v, paragraph 3.

B. Drosophila

1. 50 r doubled mutation frequency of control group.

2. Induced sex-linked lethal mutation in Drosophila in single exposure of 25 r - 1000 r is linear and equal to 0.0019% per r. (Spencer and Stern)

II. Histogenetic (cytogenetic) (Table I)

A. Rats

1. Chromosome breaks in intestine and lymph nodes are at least 9% per 100 r (probably 18%). (Charles)

B. Mice

1. Inhibition of mitotic activity in mouse epidermis is 100% with 35 r and 60% with 5 r. (Knowlton & Hempelmann, quoted by Langham)

2. Neuroblast of grasshopper. The mitotic rate at 8 r drops to approximately 1/2 and at 64 r to zero. Recovery within a few hours. (Hollaender)

III. Gonads (Table II)

A. Dogs

1. 1.0 r/day, 6 days/week results in temporary aspermia at 9 mos. in 50% of males. Partial recovery 4 mos. post-irradiation after 1 year continuous irradiation.

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III. Gonads - continued (Table II)

A. Dogs

2. 3.0 r/day, 6 days/week to accumulated total of 1320 r - female conceived and delivered 6 normal pups. (Boche)

B. Homo sapiens

1. 130 r produced testicular damage in male.

2. 108 r produced severe testicular damage. (LAMS #808)

3. 625 r (fractional) to ovary produced permanent sterility.

4. 500 r (fractional) to ovary produced permanent sterility in 94%. (Peck et al.)

IV. Leukemia (Table III)

A. Rats

1. 0.1; 0.5; 1.0 and 10.0 r/day, 6 days/week (x-rays) produced leukemia in 1.0%; 2.0%; 3.0% and 12.0%, respectively. (Rochester)

2. 0.11N and 1.7N/day, 6 days/week produced 4.0% and 16.0%, respectively. (Biochemical)

B. Physicians

1. Incidence in physicians is 0.53% as contrasted to 0.39% in general population. (Henshaw)

2. Incidence in radiologists is 3.9% as contrasted to 0.44% in physicians other than radiologists. (Ulrich)

V. Haematology (acute radiation) (Tables IV; IV-A)

A. Rats

1. 25 - 100 r results in transient lymphopenias down to 30%. (Brues & Dowdy)

2. 100 r results in appreciable transient reduction in reticulocytes, platelets, and neutrophils. (Dowdy)

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V. Haematology (acute radiation) cont'd. (Tables IV; IV-A)

A. Rats

3. 300 r results in approximately 16% temporary reduction in Rbc. and Hb. (Dowdy)

B. Humans, acute (Table X)

1. 60 - 120 r produce inconsistent mild to moderate lymphopenias which in some instances last 164 days. (CH-3868, LAMS #808)

2. 18 r and above results in increased number of refractile bodies in the lymphocytes. (LAMS #808)

3. 60 - 120 r produce inconsistent mild reduction in neutrophils. (CH-3868, LAMS #808)

4. 108 and 180 r produce marked depression of lymphocytes and neutrophils. (LAMS #808)

C. Humans,* semi-acute (Tables X; X-A; X-B: X-C; X-D)

1. 87.5 r (in 8 R_x over 9 days) resulted in reduction (delayed -- 80-120 days) Hb, platelets, and lymphocytes. (CH-3868)

2. 300 r (in 22 R_x over 33 days) marked lymphopenia, neutropenia, and slight bone marrow depression. (CH-3868)

3. 502 r (in 6 R_x over 30 days) produced profound lymphopenia, neutropenia, with transfusion required. (CH-3868)

D. Animals, chronic (Table IV)

1. 1 r/day, 6 days/week for 1 - 2 years produced no unequivocal alteration in peripheral blood picture. Probably at critical level, however. (Dowdy)

2. 3 r/day, 6 days/week (dog), first detectable blood change in reticulocytes and lymphocytes at accumulated dose of 282 r. (Dowdy)

*(1) C. W. Wildon; Radiology, Vol. 46, p. 364, 1946
(2) Supplement to beta Radiologica, 1946-48

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V. Haematology

D. Animals, chronic - contd. (Table IV)

1.7 N/day, 6 days/week (dog), accumulated doses of 25 N - 50 N, first change in platelets, lymphocytes, and neutrophils. (Dowdy)

10 r/day, 6 days/week (dog), accumulated dose 60 - 120 r, reduction in lymphocytes and neutrophils. (Dowdy)

10 r/day, 6 days/week (dog), accumulated dose 960 r, first drop in Rbc. and Hb. (Dowdy)

1.7 N/day, 6 days/week (dog), accumulated dose 385 N, Rbc. drop. (Dowdy)

VI. Embryology (Table V)

A. Rats

1. 50 r to 10 day gravid uterus--no effect.

2. 100 r to 10 day gravid uterus--results in increased reabsorption, reduced fetal weight, eye and lens abnormalities, and in some instances other developmental processes. (Wilson)

3. 200 r (whole body radiation) to 9 - 12 day gravid uterus resulted in pronounced effects characteristic of embryo age. 100 r suggests similar effects.
(Russell, quoted by Hollaender)

VII. N - r Ratio (based on mortality) (Table VI)

A. Acute: 1 N $\Leftrightarrow$ 5 - 12.5 r

B. Chronic: 1 N $\Leftrightarrow$ 6 - 21 r

VIII. Mortality (Tables VII; VIII; IX)

A. Acute, L.D. 50

1. In warm-blooded mammals, the spread is from 200 r to 790 r. (Table VII)

B. Chronic (dog)

1. 10 r/day, 6 days/week. 50% mortality at accumulated dose of 1440 r.
   3 dogs survived 5000 r.

2. 6 r/day, 6 days/week. 50% mortality at accumulated dose of 2940 r.
   5 dogs survived 3000 r.

3. 3 r/day, 6 days/week. 7 out of 9 were surviving at 1500 r.

C. Chronic (rat, mouse, guinea pig)

1. 10 r/day, 6 days/week (rat). 50% survival at accumulated dose of 3500 r.

2. 8.8 r/8-hour day (mouse). 50% survival at accumulated dose of 4400 r. Guinea pig, 50% survival at accumulated dose of 2300 r.

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Acute* Exposure (X) Estimated Results to Humans Exposed to Filtered, 200-1000 KVP X-Rays, Measured in Air

the estimates given below apply to normal individuals. It should be borne in mind that

A. 25 r and below; no detectable clinical effects.

1. From animal experiments it would appear that if man behaves like the mouse and drosophila, there will be, due to radiation, a genetic effect which is much smaller than the spontaneous rate of mutations. In other words, the combined result of the spontaneous and the radiation-induced genetic abnormalities would be slightly increased but much less than double the spontaneous rate alone.

2. Delayed effects* possible but highly improbable.

B. 50 r; slight, transient reductions in lymphocytes and neutrophils. No other clinically detectable effects.

1. Incidence of radiation-induced genetic abnormalities is expected to be approximately the same or smaller than the spontaneously occurring abnormalities.

2. Delayed effects possible but serious effects on the average individual very improbable.

C. 100 r; at this level, nausea and fatigue may be a problem. Reductions in lymphocytes and neutrophils with delayed recovery. Above 125-150 r, vomiting may become a problem.

1. Incidence of radiation-induced genetic abnormalities, which are quantitatively proportional to the dose, will probably still be comparable to or somewhat greater than those occurring spontaneously.

2. Delayed effects, in summation, would be expected to shorten the life expectancy of man on the average by not more than about 1% from all causes, assuming that limited observations on animals can be extrapolated to man.

* received within 24 hrs.

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D 200 r; at this level, fatalities, 2-6 weeks after exposures, might occur in a small proportion of the irradiated individuals. Nausea, vomiting, and fatigue will probably occur in most persons within 24 hours. Definite depression of practically all blood elements, reduced vitality, in most cases with a convalescent period of 3 to 6 months. Temporary sterility in some cases and possibly permanent ~~sterility in rare instances~~;

1. Incidence of radiation-induced genetic abnormalities will be expected to be at least twice as frequent as the spontaneously occurring abnormalities.

2. Delayed effects--that these would be of major consequence in a small percentage of individuals would seem very probable.

E. 400 r; it would be expected that virtually everyone would be immediately incapacitated by such an amount of radiation, and many would never recover completely. ~~Some~~ Some deaths would occur in 2 to 6 weeks.

* The expression, "delayed effects", as used here, refers to any harmful effects on the recipient of the radiation, and attributable to radiation, manifested at any time subsequent to the period when acute reactions may occur.

APPENDIX

GENERAL BACKGROUND

Submitted by Dr. Donald Charles

1. A human sperm contains 24 chromosomes. Each chromosome contains a "string" of some hundreds of genes.

2. A human egg contains a similar set of chromosomes and genes.

3. So in the nucleus of a fertilized egg there are 48 chromosomes altogether - 24 kinds, each in duplicate - and perhaps 10,000 kinds of genes also each in duplicate.

4. Each gene has two main types of action:
   a. each catalyses some particular chemical process, given the proper materials;
   b. each reduplicates itself at, or some time before, each cell division. (In this latter action the bonds between genes in the same chromosome also reduplicate.)

5. So each new cell of a developing embryo is equipped with 24 pairs of chromosomes with their associated genes.

6. Some genes come into action at or shortly after fertilization. They operate in a "field" of limited complexity, i.e., the cytoplasmic differences already existing in the fertilized egg. Their activity probably increases the regional differences and permits other genes in turn to come into play.

7. In general different batteries of genes come into action at different times, in different cells or tissues, and for varying intervals - determined by when and where the materials for their operation become available. Some genes perhaps remain inactive until long after birth.

8. Most, if not all, genes are very slightly unstable. Among for example a million descendants by reduplication from a single original gene perhaps one or a few will have a somewhat different structure.

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9. Once a gene has undergone such a change (mutation) it reduplicates the changed structure thereafter, except for the occurrence of further mutations.

10. Mutation probably decreases the catalytic activity of genes. So a mutant gene M' acts in the same process as the normal gene M from which it arose, but less effectively.

11. A child who inherits a mutant M' from one parent and the normal gene M from the other parent may or may not show effects of the mutant.

    a. If MM cells are able to do more of the specific M-catalysis than is necessary, MM' cells may be able to do enough so that the presence of M' is not indicated by any deviation from normal structure or function. The mutant M' is said to be <u>recessive</u>.

    b. If MM cells do just enough of the M-catalysis, MM' will not. Some embryonic process will deviate from its normal course and some detail of structure or function will become abnormal, though not necessarily harmful. A mutant of this sort is said to be <u>dominant</u>.

12. Radiation-induced mutants, like the spontaneous, may be either recessive or dominant.

13. In man the potentially dangerous mutants are the dominants, and the recessives in that one pair of chromosomes which determines sex.

14. A third class of potentially dangerous inheritable changes can be induced by radiation: <u>chromosome mutations</u>. A piece may be broken off one chromosome and attached to another. A section may be inverted in situ. Chromosomes may exchange sections.

15. Thus in a sperm which has been exposed to radiation any one or more of many thousands of genetic changes <u>may</u> occur: any of the thousands of genes may mutate and chromosomes may break and re-attach at any of the thousands of bonds between genes.

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[redacted]

16. Since any one of these changes has a very low probability at moderate exposure, the majority of exposed sperm will not undergo any mutation. In the minority which are affected one gene will mutate in one sperm, a different gene in another sperm, in still a third cell there will be a chromosome mutation, and so on.

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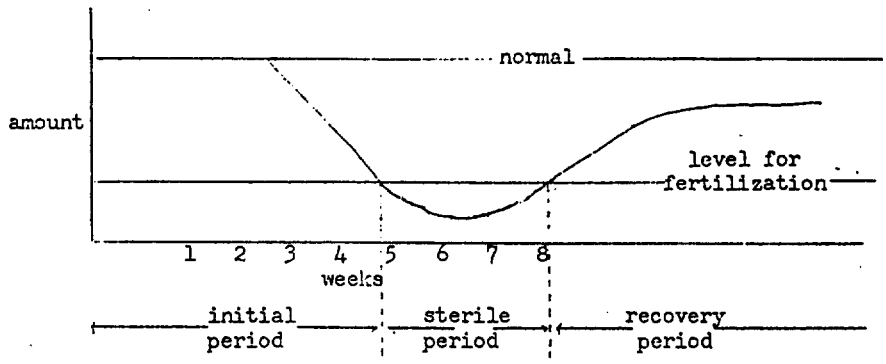
[redacted]

GENETIC CHANGES IN HUMAN SPERM AND EGGS, CAUSED BY
A SINGLE EXPOSURE OF 300r OR LESS

Submitted by Dr. Donald Charles

Until data from Hiroshima and Nagasaki are studied, we can only assume that radiation would affect reproduction and heredity in humans much as it does in other animals. Unfortunately it is just the range from 50 to 300r about which we know least, even in mice and rats, so far as genetic effects are concerned. Pre-war experiments were done chiefly at 400r and above; Manhattan work has been mainly on chronic exposures of 10r and less. So the following statements rest on a double extrapolation: from low or high exposure to intermediate, and from other mammals to man.

1. In exposed males, the amount of sperm available for ejaculation would vary with time after exposure roughly as follows:



How far the count drops and when the recovery begins both depend on the number of roentgens received. The sterile period might last 1-2 weeks at 200r and 3 weeks at 300r.

2. Eggs fertilized by sperm released in the initial period have poor prospects. (a) About 10% would die for each 100r the father had received. Most of these eggs would die before implantation, and so cause the mother little trouble. But perhaps one-third of them would implant, die later and be resorbed as embryos or be still-born. (b) Among the live-born children there would be roughly 0.5% with detectible structural abnormalities for each 100r the father had received. (c) Among these

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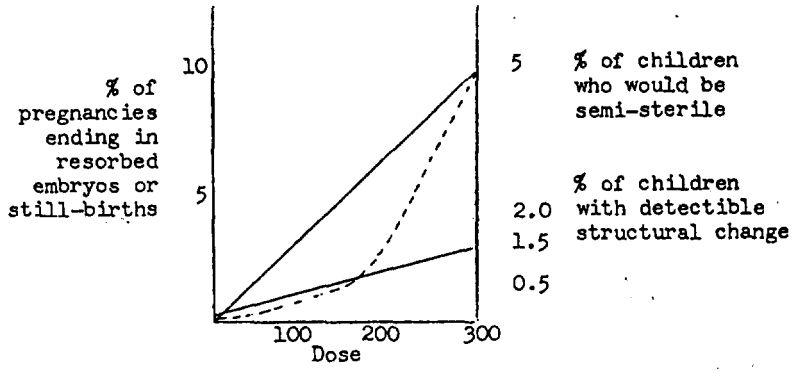
children there would also be some who, as adults, would themselves be permanently semi-sterile: half of their children (grandchildren of the exposed male) would die in utero. The proportion so affected varies with roughly the square of the dose and is represented in the following graph.



3. Eggs fertilized by sperm released in the recovery period have fair prospects. Of the three effects shown in the previous graph

deaths in utero (top curve) would be reduced by perhaps half;

semi-sterility in children would be nearly absent;

structural changes would persist in the same frequency.

Thus at 300r only about 6-7% of recovery-period pregnancies would be affected, in contrast to 16-17% of initial period pregnancies. And of the 6-7% affected, perhaps 3% would be early resorptions, so that the over-all genetic hazard <u>after</u> the initial period might be about 1% per 100r.

4. The reason for the difference between initial and recovery periods is as follows. (a) The initial period sperm were in the testis ducts at the time of exposure. The recovery period sperm were formed, after the exposure, from "stem cells" in the testis. (b) Radiation produces chromosome breaks in both mature sperm and stem cells. The broken ends may stay so, or may recombine in various ways. (c) The affected sperm are able to fertilize eggs but, in the divisions which follow fertilization, the rearranged chromosomes are not distributed normally so that some cells get too much or too little chromosome material and the embryo dies. (d) The affected stem cells go through a cell division in forming sperm. Only those cells without major chromosome change give rise to sperm which

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are viable. This division then acts to filter out many of the chromosome abnormalities from recovery period sperm.

5. We have at present no basis for estimating the frequency of genetic changes in the eggs produced by exposed women. But it would probably be of the same order of magnitude as in sperm, and worse in the first egg released after exposure than in subsequent eggs.

6. All of the genetic exposure effects are, so far as we know, identical with changes that occur in the absence of radiation. The exposure simply increases the proportion of eggs or sperm in which they happen. Furthermore faulty parent nutrition, disease, etc., may produce similar end effects on embryos. Therefore, not all still-born or abnormal children of Hiroshima or Nagasaki parents after May 1946 can be blamed on radiation effects. What proportion must be so credited could only be determined if we had adequate pre-blast vital statistics.

Experimental Procedure

1. The general plan of the work is indicated by the following table.

Pure strains bred in Jackson Laboratory

"dba" "C57" "Bagg albino" x "Swiss albino"

albino hybrids

Crosses made at Rochester

dba ♂ x 4 C57 ♀♀

(rayed daily)

F_1 ♂♂ + F_1 ♀♀ x albino hybrids

(autopsied, not bred) (bred four times, then autopsied)

"F_2" litters testing fertility, and genetic significance of any abnormalities, of the F_1 ♀♀ ; ordinarily discarded a few days after birth.

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2. Gene and chromosome mutations which occurred in the sperm of exposed and control males were detected as follows:

If the sperm contained a	The effect in an offspring formed from that sperm was
dominant gene mutation	deviation from normal structure or function
recessive gene mutation in the sex chromosome (transmitted to F_1 ♀♀, not F_1 ♂♂)	none in F_1; but half of the sons of F_1 ♀♀ are affected
chromosome mutation (transmitted to F_1 ♂♂ or ♀♀ ; studied only in ♀♀)	reduced fertility

3. In brief, the procedure was to hunt among the offspring of exposed and control male mice for

   a. sons and daughters with some abnormality of structure or function;

   b. daughters producing definitely fewer than normal offspring in four litters;

   c. daughters producing only half as many sons as daughters (i.e., daughters receiving sex-chromosome recessive mutants with lethal effects).

4. The procedure was complicated by two main factors:

   a. all of the effects of mutant genes or chromosomes may be duplicated by developmental and post-natal accidents quite independent of heredity.

   b. the effects of mutant genes range from large and conspicuous down to very slight and difficult to detect.

5. So the procedure involved a double sifting: first, each F_1 mouse had to be classified as normal or abnormal (with respect to the three criteria in item 3 above); second, those classified as abnormal had to be tested to determine whether the abnormality was hereditary or not. The latter discrimination is possible because the hereditary abnormalities are transmitted by the individual carrying them to half of its offspring.

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Results

1. The essential results are shown in graph 1. The leftmost point shows the proportion of sperm, from control males, in which there was a mutant gene or chromosome. The next point to the right shows the proportion of mutant-bearing sperm from males receiving 0.1 r/day. This point is plotted above that point on the dose scale which represents the average total roentgens received by those sperm from which the offspring of 0.1 r males had been formed. The remaining points represent corresponding data for sperm of males exposed to 0.5, 1.0 and 10.0 r/day.

2. The slope of graph 1 is the probability per roentgen that a mutation (of the magnitude and types we studied) will occur: the value is 6.4×10^{-5} per r. Thus of a million sperm exposed to 30r about 1900 undergo mutation in one or another gene or chromosome. If one of the unaffected sperm happens to be used in fertilization no harm has been done; if one of the affected, the result will be one of the abnormalities listed above.

3. The mutation hazard indicated by graph 1 is lower than the true value because of defects in our procedure. Abnormalities found in F_1 ♂♂ were not tested by breeding, nor were all defects in F_1 ♀♀ because of space and time limitations. Among the untested abnormalities should be some due to dominant gene mutations. Since any particular mutation is not likely to have occurred more than a few times in the experiment the missed mutants should be among those aberrations which were not found more than a few times altogether. So in graph 2 are plotted, as in graph 1, the proportions of sperm from which were formed F_1 mice showing some type of structural abnormality that appeared altogether four or fewer times among the 11,000 F_1 mice examined. The increase in proportion with increasing dose can only mean genetic effects of the radiation at a rate of about 4.2×10^{-5} per roentgen.

4. Adding the two values together gives an overall mutation hazard of 1.1×10^{-4} per r. This value still excludes recessives and dominants or chromosome mutations with small effects.

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5. The total mutation rate is distributed roughly as follows among the several classes of mutations:

dominants with structural effects	40%
recessive lethals in sex chromosome	10% ?
chromosome mutations	50%

6. Two major uncertainties remain:

   a. Is the x-ray mutation rate in man as high as in mice?

   b. What proportion of the mutants we have found would be serious if they occurred in man?

   Obviously neither question can be answered. With respect to the first, we might better work on the conservative assumption that the mutation rate will not be lower in man than in mouse. On the second, it might be wise to take a similar attitude. Certainly in the creature whose genetics we know best, Drosophila, nearly every mutant gene has deleterious effects. We may first notice the presence of a mutant by an alteration of some minor morphological detail, like eye color, but on further study we find that superficial change to be accompanied by a greater or less reduction of general vigor or of life span.

7. If we take this view we are forced to wonder whether a human exposure of 0.1 r/day is acceptable. It means an increase of 1% in the hazard of transmitting a new mutant gene for each 100r a parent has received at time of conception.

(Note: the values given in paragraphs 2-4 above have since been revised to about 5.7, 2.0 and 7.7×10^{-5} per r.)

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Induced Mutation Rate

How often do genetic changes occur in x-rayed reproductive cells? Available figures are few and not very accurate, except for sex-linked lethals in Drosophila. In the following table values which are not underlined have been obtained by extrapolation from experimental results; numbers in parentheses are note and literature references.

Percent of Sperm Affected

	Gene Mutations lethal	Gene Mutations sub-lethal	Gene Mutations marginal	Chromosome Mutations
One 10r dose:				
Drosophila	0.11	0.06	0.42	0.004
Mouse	-	0.04 ±	-	(0.01-0.07 (1) (0.1 (2)
Tradescantia (pollen)	-	-	-	0.05-0.2 (3)
One 600r dose:				
Drosophila	6.6 (4)	3.6 (4)	25.2 (4)	1.8 (5)
Mouse	-	2.4+(6)	-	33 (7)
Tradescantia	-	-	-	90+ (8)

How does the induced mutation rate vary with dosage? Gene mutations seem to occur in direct proportion to total dose down at least to 25r (4,9,10) no matter how the dose is applied - continuously or intermittently, at low or high intensity (4). The evidence however is very limited: one class of mutations in one chromosome of one organism.

The frequency of chromosome mutations varies not only with total dose, but also with intensity and interval between doses. Here the evidence is still more remote from man, mainly from microscopic observation of x-rayed Tradescantia pollen, plus limited mouse and fruit fly data (3,5,8).

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Notes and References

1. Obtained by extrapolation from Snell's results (7) on the assumption that chromosome mutation rate is proportional to the 2 and 1.5 power of dose, respectively. The former would be more probable, according to (3), for 10r given in 17-18 minutes as in the Manhattan Department work, since Snell's 600r exposure was administered in 16.5 minutes. Extrapolation from Snell's results by Marinelli's formula (8) gives a value of about 0.02.

2. Report of Genetics Division, Mouse Section, Manhattan Department, at the Industrial Tolerance Conference on 23-24 January 1945.

3. Sax, K., 1941. Cold Spring Harbor Symposia on Quantitative Biology 9: 93-101.

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5. Bauer, H., M. Demerec and B. P. Kaufmann, 1938. Genetics 23: 610-630.

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7. Snell, G., 1935. Genetics 20: 545-567.

8. Marinelli, L. D., B. R. Nebel, N. Giles and D. R. Charles, 1942. American Journal of Botany 29: 866-874.

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[illegible]

Stone - Radiation of Humans:-

I 2 articles on problem.

Ethics governing service of prisoners: Feb 48

History & Ethics of use of Humans in medical Experiments. — Ivy — Science July 48

II: ① Voluntary Consent

② Danger of each exp. preceded by animal exps.

③ Preformed in Medical manner.

④ Request NME arranged for it & the info ~~all~~ & protocols be unclassified

[illegible]

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