EXPERIMENTAL STUDIES ON THE LATE EFFECTS OF NUCLEAR DETONATION

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A large population of genetically uniform mice, 6-12 weeks of age, was exposed to atomic detonation, and after recording the mortality rates during the first few weeks after exposure, the animals were transported to Oak Ridge for study of the delayed effects of irradiation. Radiations from atomic detonation were composed predominantly of high energy gamma rays, with a small component of fast and a still smaller flux of slow neutrons, the gamma to neutron ratio increasing with the distance from ground zero. Small numbers of mice were irradiated beneath lead shields, so as to receive predominantly neutron radiation.

Survival patterns, shown in Table 1, indicate that the $LD_{50}/30$ days was approximately 755 r, with little difference between males and females. At one year postirradiation the LD_{50} had dropped to 733 r for males and 716 r for females. Significant shortening of the life span resulted from doses well beneath the threshold for acute lethality. This reduction of longevity, appreciably greater in females, resulted from degenerative and neoplastic diseases induced or exaggerated by irradiation, as will be disclosed.

The first of the delayed effects noted was cataract, which appeared during the third month postirradiation. Within 90 days after exposure virtually all

irradiated mice had opacities detectable with the slit-lamp. The rate of progression of the opacities varied directly with the dose (Chart 1). Lens damage was more severe for a given dose of neutrons than for comparable doses of gamma rays; thus, in cataract induction approximately 100 rep of neutrons corresponded to about 650 r of gamma rays (RBE = 6.5).

Systematic studies of the eye disclosed a remarkable change of the iris consisting of progressive loss of iris tissue, as illustrated in Fig. 1. This process appears to be an abiotrophy apparently hereditary in this strain, as mild atrophy of the iris occurred in aging nonirradiated controls; like cataract, however, the degree of atrophy was significantly greater following irradiation, in proportion to the dose.

Greying of the fur was noted as early as 3 months' postirradiation, progressing with time as a function of the dose (Chart 2). It varied with different anatomical regions but in certain areas was sufficiently well correlated with the dose to constitute a simple, though only approximate, biological dosimeter.

The incidence of thymic lymphosarcoma was greatly elevated by irradiation, in proportion to the dose (Chart 3). The threshold for thymic lymphoma induction appears to be in the neighborhood of 500 r. The earliest cases were manifest in the fourth month, and the peak incidence occurred from 7 to 12 months after exposure. Contrary to experience with most strains of mice, thymic lymphomas were more common in males than in females.

In contrast to thymic lymphoid tumors, other forms of leukemia, including lymphomas, reticulum cell sarcomas, and rarely myeloid leukemias, occurred relatively late in life. These were less numerous in the irradiated mice than in the controls, but this may be attributable to differences in longevity alone (Chart 4). These will be illustrated and their relative frequency given.

Tumors of a variety of types have been encountered. Ovarian neoplasms were common at all dose levels and very rare among controls (Chart 5), as might be anticipated from earlier studies. Histologically they include lutecmas, granulosa cell tumors, tubular adenomas of germinal epithelium, cystadenomas, hemangiomas, and mixtures of these types. Their lower incidence at high dose levels is related to reduced longevity, as their latent period is relatively long (12-15 months).

An unanticipated finding was the relatively high incidence of pituitary tumors in irradiated mice. These were more common in females (Table 2), and their frequency was roughly proportional to the dose with the exception of doses above the LD_{60}. They appeared late in life, the peak incidence occurring 20-25 months' postirradiation. All thus far studied have been chromophobic. Experimental studies indicate that most of these secrete ACTH; a few, however, have given evidence of TSH-secretion.

Another unexpected and interesting neoplasm observed in the irradiated mice is adenoma of the Harderian, or posterior lacrymal, gland. This growth occurred more commonly at low dose levels (Table 3), probably because of its long latent period (15-17 months). It is a locally invasive neoplasm, often obliterating the orbit, surrounding skull, and adjacent soft tissue (Fig. 2). Thus far no such tumors have been observed in the controls.

The frequency of mammary gland tumors was increased by irradiation (Chart 6). The neoplasms occurring earliest were predominantly adenomas and adenocarcinomas, those developing late in life sarcomas. From earlier investigations a correlation between these neoplasms and tumors of the ovary

might be anticipated. A table correlating age, sex, and ovarian and breast tumor incidence will be given.

Tumors of the lung, liver, adrenal, kidney, etc., have been observed with regularity, but the incidence of these neoplasms has not yet been analyzed.

Fatal glomerular degeneration of the kidney occurred frequently at dose levels above 500 r (Chart 7). The lesion is interpreted, in the light of morphologic evidence (Fig. 3), as a degeneration of the glomerular capillary, somewhat resembling diabetic glomerulosclerosis. It culminates in nephrosclerosis and renal failure, often with generalized arteriosclerotic changes. The pathogenesis of this abnormality remains to be demonstrated; however, its relation to irradiation is indicated conclusively. Large doses of radiation have been reported to induce similar changes in the kidneys of man and other animals.

Degenerative changes in the adrenal gland were frequent among the irradiated animals; they will be discussed in relation to pituitary tumors.

TABLE 1. MORTALITY OF MICE EXPOSED TO ATOMIC DETONATION

Dose (r)	No. exposed and	Per Cent Mortality					
		Male			Female		
		30 days	1 yr.	30 mos.	30 days	1 yr.	30 mos.
812-932	880	91	94	100	94	97	100
759-785	440	61	74	99	60	74	100
711-733	440	30	41	100	29	47	100
631-687	440	7	20	96	11	34	100
491-556	440	5	16	86	2	19	99
367-424	440	*	*	*	*	*	*
287-318	440	3	8	69	3	11	92
192	220	3	8	64	3	7	82
0	620	0	5	60	3	3	66

*These figures are incomplete due to loss of mice during transportation from field laboratories.

TABLE 2. INCIDENCE OF PITUITARY TUMORS IN MICE EXPOSED TO ATOMIC DETONATION

Dose (r)	Female			Male		
	No. surviving 30 days	Pituitary Tumors at 25 months		No. surviving 30 days	Pituitary Tumors at 25 months	
		No.	%		No.	%
812-932	25	0	0	39	0	0
759-785	87	0	0	85	3	5
711-733	157	14	12	153	2	2
631-687	195	17	12	204	8	4
491-556	215	22	12	208	4	2
367-424	78*	7*	11*	108*	0*	0*
287-318	213	10	5	213	2	1
192	107	4	4	107	0	0
0	301	1	0.3	310	0	0

*These figures are incomplete due to loss of animals in transit from field laboratories.

TABLE 3. HARDERIAN GLAND TUMORS IN MICE EXPOSED TO ATOMIC DETONATION

Dose (r)	Harderian Gland Tumors at 30 Months Postirradiation			
	Female		Male	
	No.	%	No.	%
812-932	0	0	0	0
759-785	0	0	0	0
721-733	2	1.2	4	2.6
631-687	5	2.6	2	0.9
491-556	3	1.4	5	2.4
367-424	0*	0*	4*	3.7*
287-318	6	2.8	4	1.9
192	3	2.8	2	1.9
0	0	0	0	0

*These figures are incomplete due to loss of animals in transit from field laboratories.

Chart 1. Incidence of lenticular opacities in mice exposed to atomic detonation.

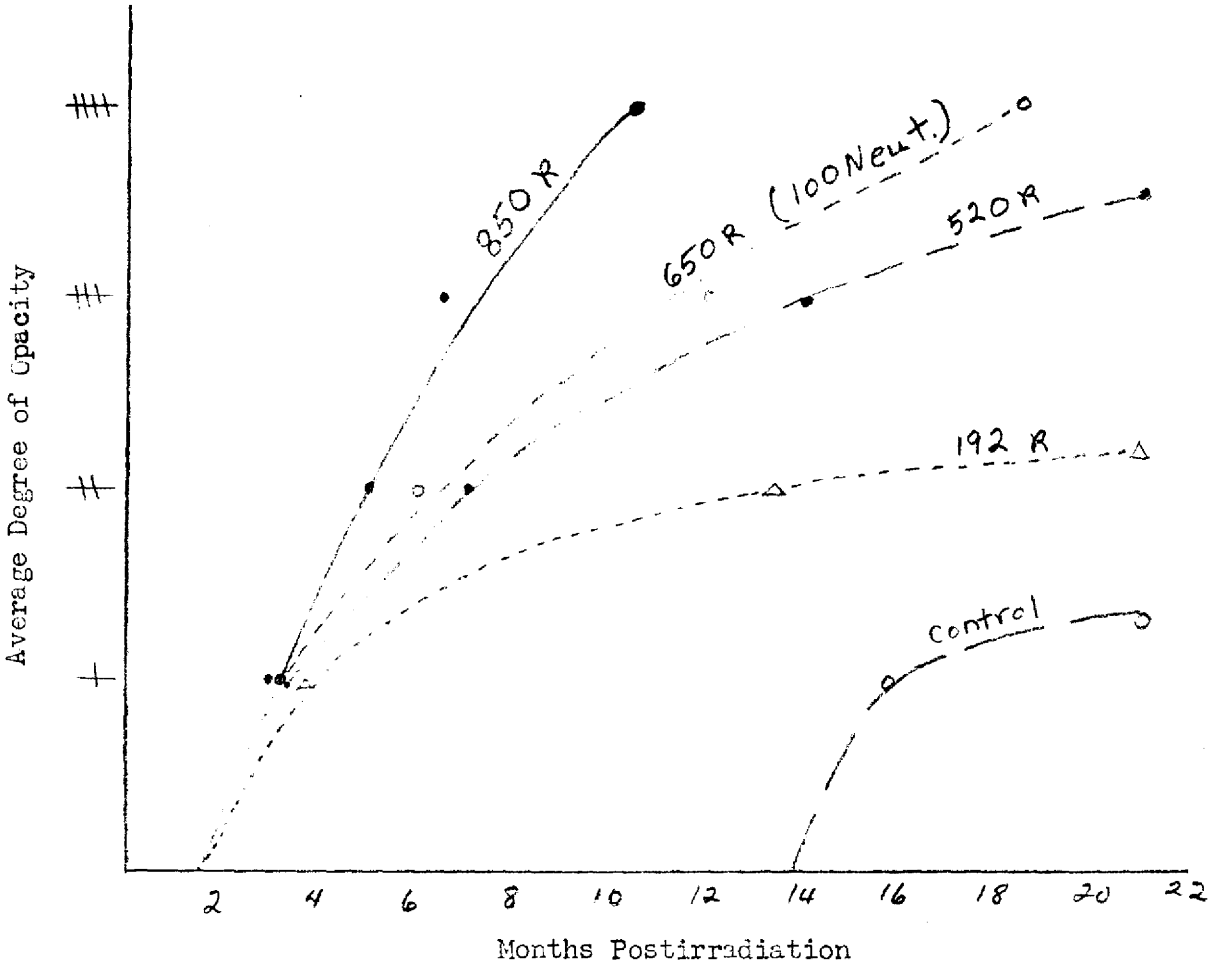


Chart 2. Depigmentation of fur of mice exposed to atomic detonation.

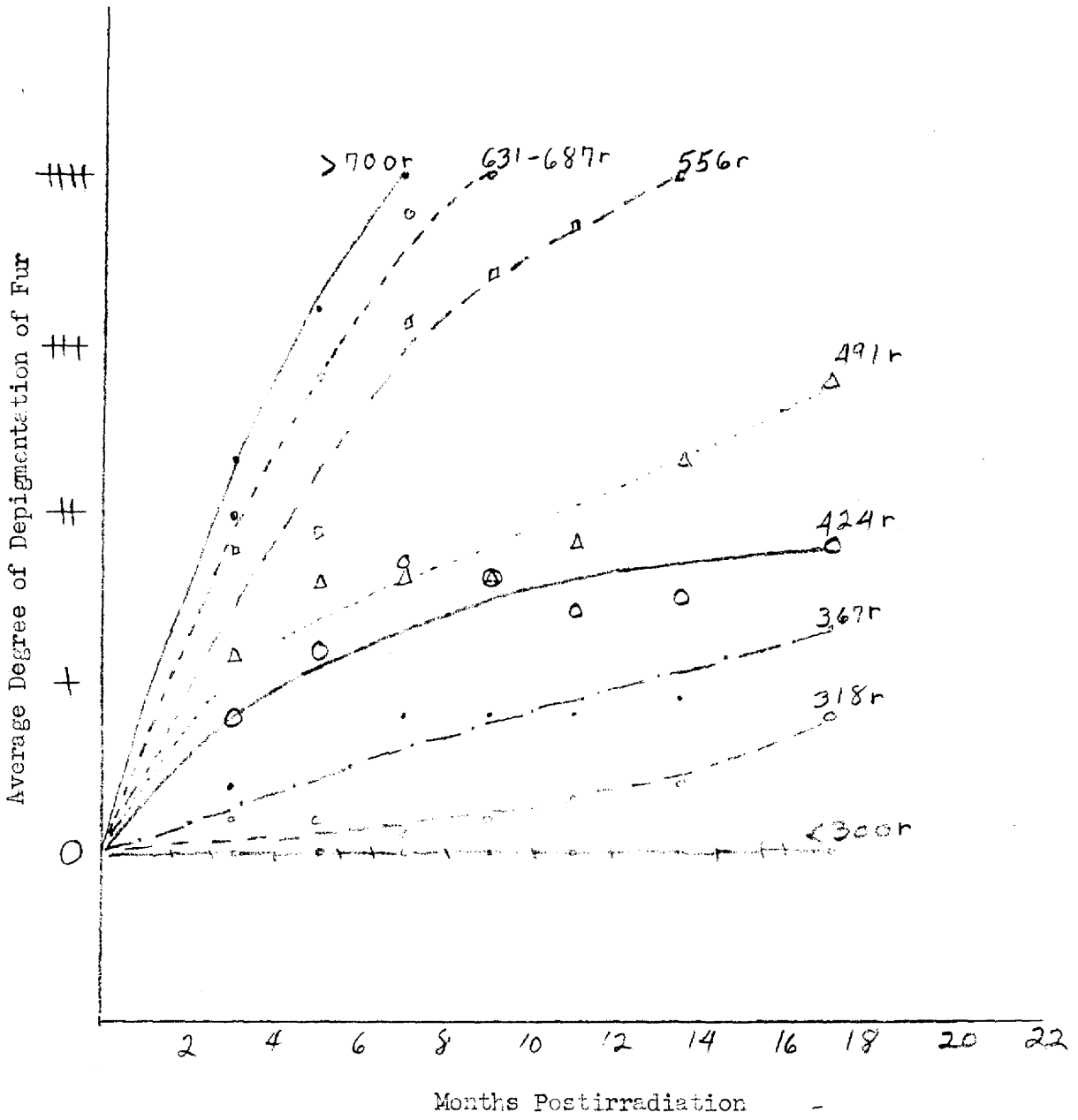


Chart 3. Incidence of thymic lymphoma in mice exposed to atomic detonation.

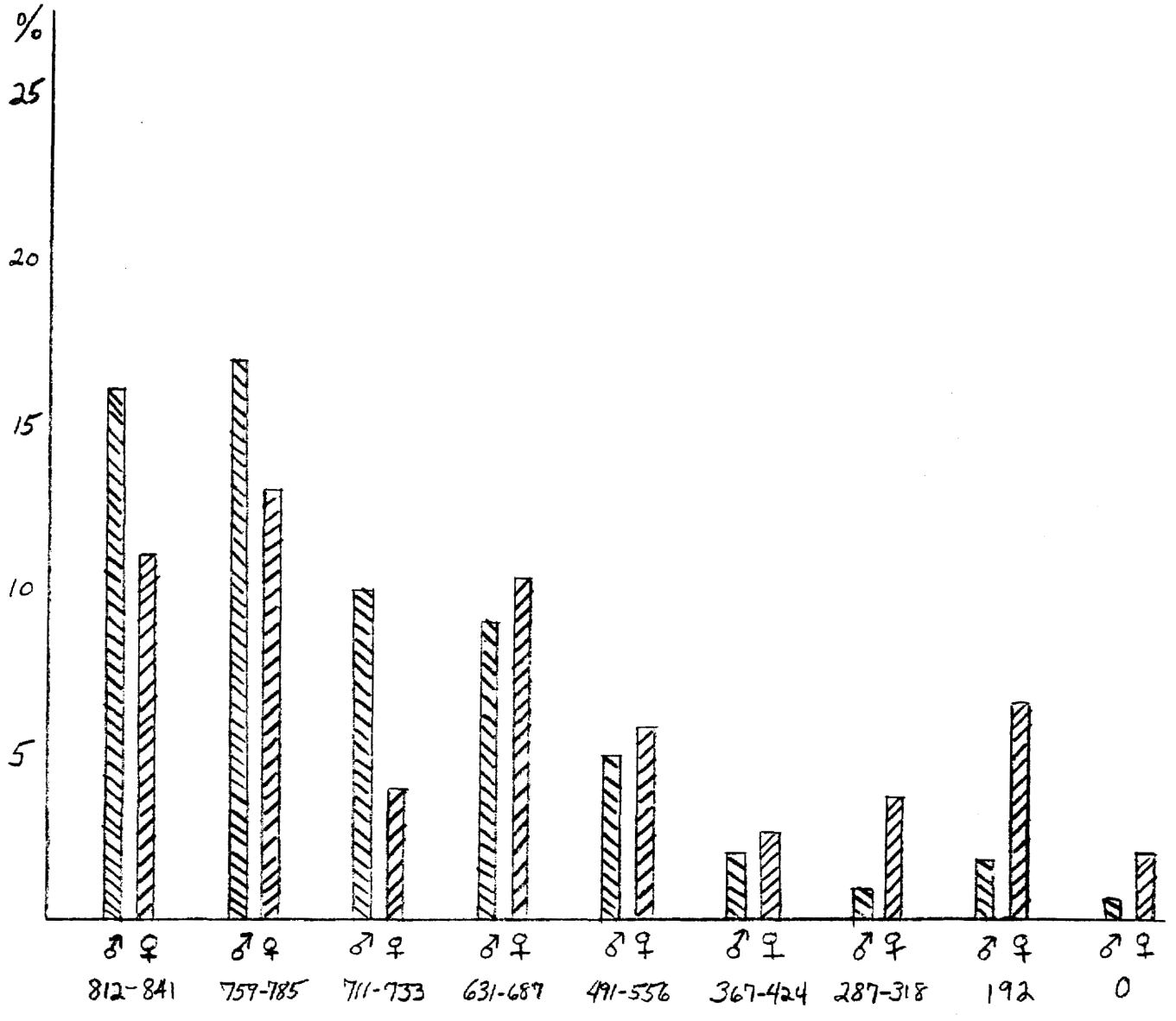


Chart 4. Incidence of non-thymic leukemia in mice exposed to atomic detonation.

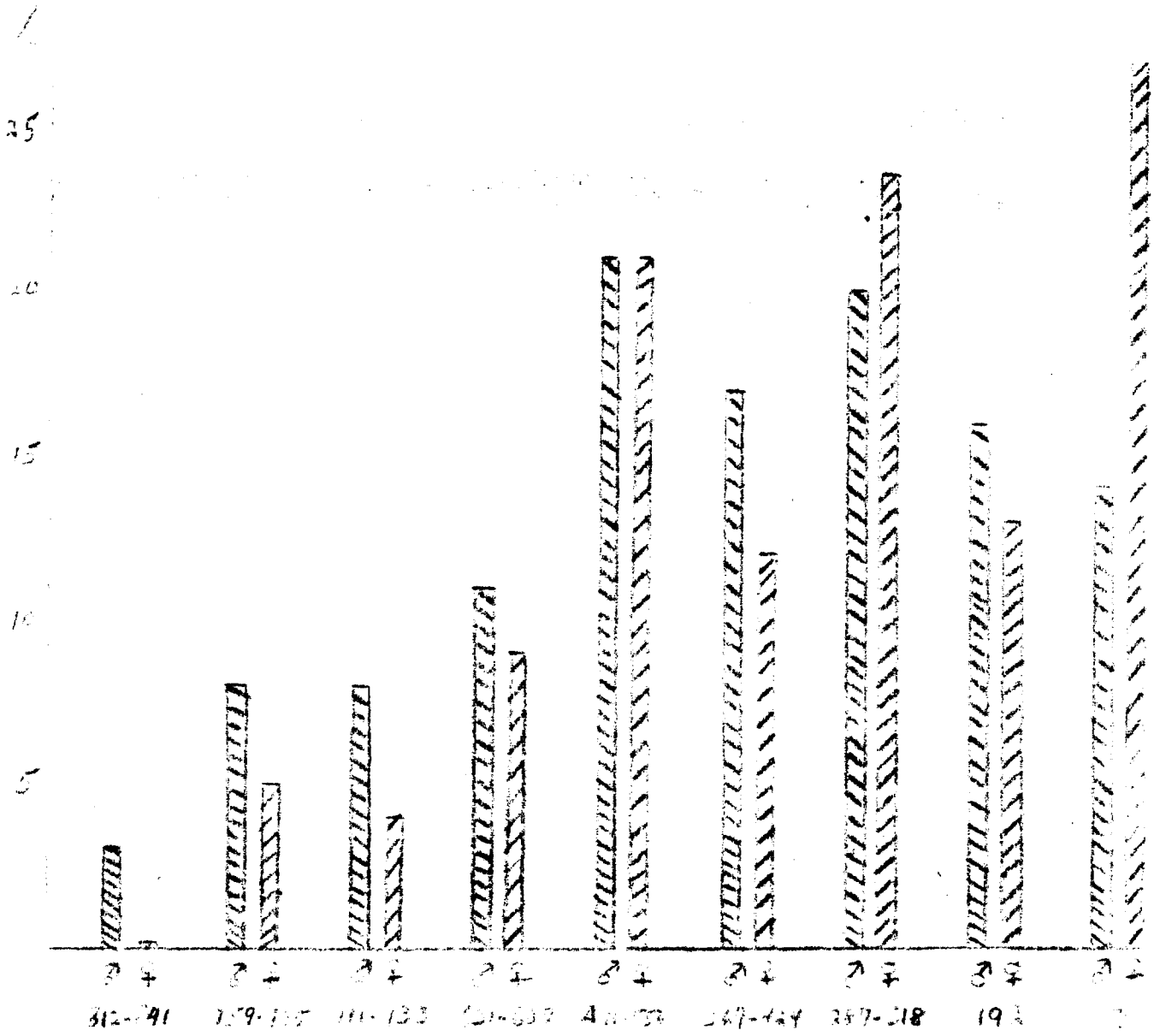


Chart 5. Incidence of ovarian tumors in mice exposed to atomic detonation.

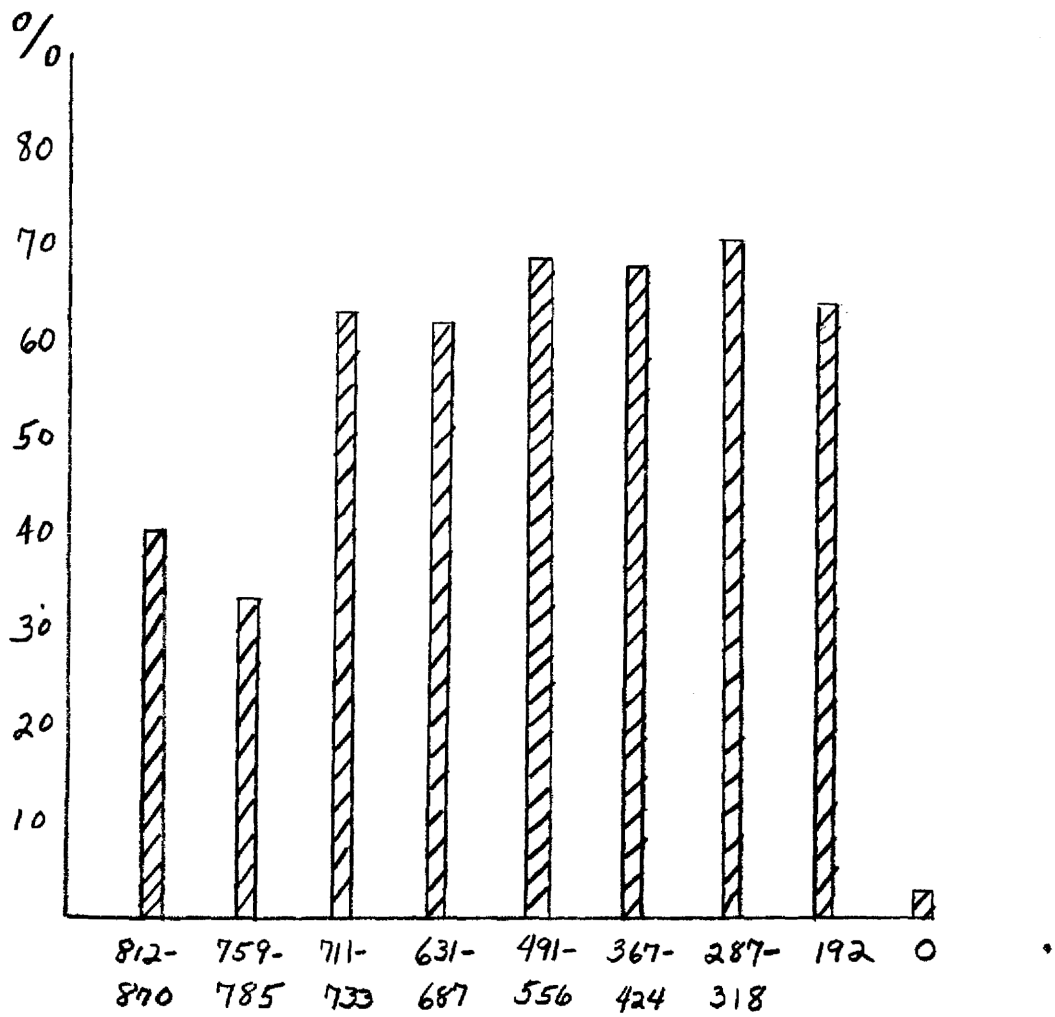
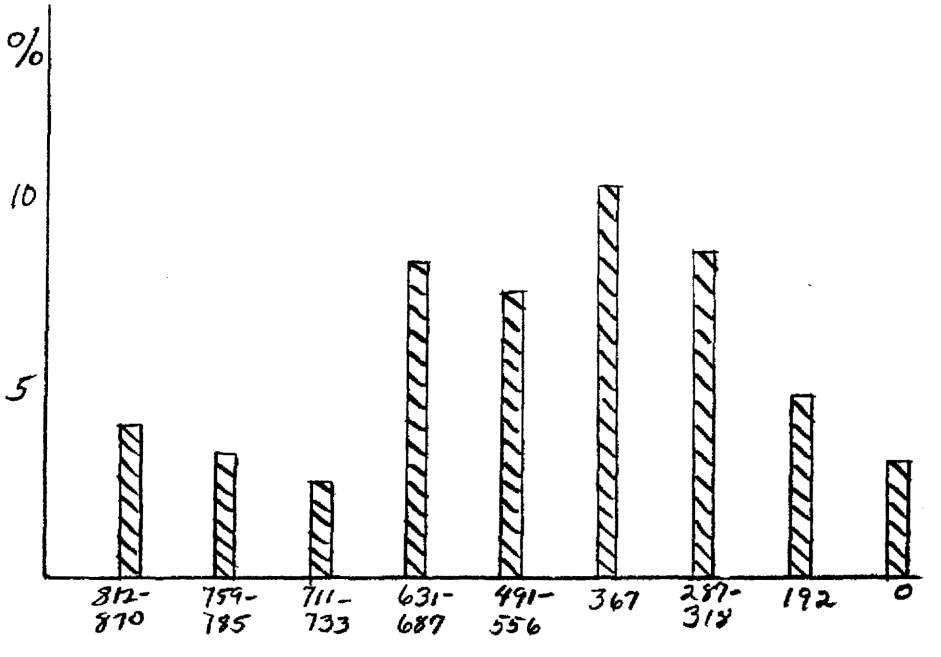


Chart 6. Incidence of mammary gland tumors in mice exposed to atomic detonation.



Dose of Radiation(r)

Chart 7. Incidence of glomerular degeneration in mice exposed to atomic detonation.