A COMPARISON OF THE RELATIVE EFFECTIVENESS OF RADIATIONS OF DIFFERENT AVERAGE LINEAR ENERGY TRANSFER ON THE INDUCTION OF DOMINANT AND RECESSIVE LETHALS IN DROSOPHILA

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SINCE 1927 numerous investigators have subjected various plants and animals to radiations of different ion density to determine the relative biological effectiveness (RBE) of the different radiations. Usually it was found that the RBE increased as the linear energy transfer (LET—energy in electron volts dissipated per micron of tissue traversed by ionizing particles) or ion density of the radiation increased. In a few cases the reverse was observed and in others the biological effect was independent of the LET (for a review of these data, see ZIRKLE 1954).

Data from early Drosophila work produced conflicting opinions as to the biological effectiveness of radiations of different LET for the induction of the various genetic effects studied. It was reported that the less densely ionizing beta, gamma, and X-rays were equally effective in producing sex-linked recessive lethals (ZIMMER and TIMOFÉEFF-RESSOVSKY 1942; CATCHESIDE 1948) and translocations (MULLER 1940), and more effective than the more densely ionizing fast neutrons for the induction of recessive lethals (DEMPSTER 1941; GILES 1943; TIMOFÉEFF-RESSOVSKY and ZIMMER 1938; FANO 1944) and translocations (CATSCH *et al.* 1944).

On the other hand, it was reported that fast neutrons were more effective than the less densely ionizing radiations in the production of translocations (DEMPSTER 1941) and dominant lethals (DEMPSTER 1941; FANO 1944). ZIRKLE (1954), reporting the data of STAPLETON and ZIRKLE (1946) and ZIRKLE and PARRISH (1950), however, states that the RBE for the survival of Drosophila eggs after exposure to radiations that varied in average LET increased with increasing LET except that the most densely ionizing fast neutrons from uranium fission were less effective than cyclotron neutrons yet more effective than other radiations of lower average LET. Results of recently published data indicate that the RBE of different radiations for the induction of all genetic effects increases with increasing LET (BAKER and VON HALLE 1954; MICKEY 1954; MULLER 1954; LEWIS 1954; STONE *et al.* 1954; IVES *et al.* 1955; EDINGTON 1956). Since these differences in the RBE were explained to be the result of differences in the LET of the radia-

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tions used, it would appear that within the neutron energy range available, the RBE of neutrons of different average energy would also depend on the LET.

The purpose of this paper is to compare the RBE of fast neutrons of different LET spectra with radiations of lesser ion density for the induction of sex-linked recessive lethals and dominant lethals in Drosophila. These data show that the effectiveness of different radiations on the induction of the genetic effects studied depends on the LET even within the energy range of fast neutrons available for this investigation.

MATERIALS AND METHODS

Biological

For a more accurate comparison of the results reported in this paper with those of earlier work performed in this laboratory with different radiations on the induction of dominant lethals and sex-linked recessive lethals (hereafter called recessive lethals), the experimental techniques used were the same as those already described by BAKER and VON HALLE (1953) for dominant lethals and by EDINGTON (1956) for recessive lethals. These methods will be briefly described. For the detection of dominant lethals, Oregon-R males, two to four days old were exposed to several doses of fast neutrons or gamma rays and pair-mated immediately to Oregon-R virgin females. After a 24-hour mating, the males were discarded and the females were placed on a charcoal agar medium (with 250 units per ml of Squibb's Mycostatin added to prevent yeast growth) for a 24-hour egg-laying period. After 24 hours, the females were transferred to a fresh vial containing charcoal agar for an additional 24 hours, and the eggs laid in the first vial were counted. After a second 24-hour period, the proportion of eggs that had hatched was determined by a count of collapsed eggs. Similar 24 and 48-hour counts were made on the second set of eggs.

The induction of recessive lethals by 14-Mev fast neutrons was determined by the Muller-5 method (SPENCER and STERN 1948). Oregon-R males, two to four days old, were irradiated and mass mated immediately to Muller-5 virgin females. The parents were transferred to fresh culture bottles every two days for six days. Then the males were discarded, and the females were transferred to fresh culture bottles and allowed to lay for six additional days.

In all dominant and recessive lethal tests, controls were run simultaneously with the experimental series.

Physical

The physical methods employed for the X-ray, gamma-ray, and low-energy neutron irradiations have been described (EDINGTON 1956; SHEPPARD *et al.* 1957; GHORMLEY and HOCHANADEL 1951; KIRBY-SMITH and DANIELS 1953). The 14.1-Mev neutrons used in this experiment were produced by the $T(d,n)He^4$ nuclear reaction, which satisfies many desiderata for radiobiology with a neutron source. The cross section for this reaction is great enough that experiments can be performed with modest-sized positive ion accelerators; the emitted neutrons are monoenergetic; the reaction itself is free of significant gamma ray emission (Sawyer and Burkhardt 1955). A 250-kev Cockcroft-Walton accelerator (Bergstralh *et al.* 1953) with radiofrequency ion source (Moak *et al.* 1951) produced the neutrons by bombardment of a thick zirconium tritide target on a platinum backing (Massey 1957) with deuterons. Figure 1 illustrates details of the target assembly and irradiation setup. Intolerable local target temperatures were avoided by a thin (0.6 mm), rapidly flowing stream of tap water and by rotation of the target about a ball and socket joint not shown in Figure 1. Deuteron beam currents of several hundred microamperes produced average dose rates of about 800 rep per hour at the distance of the biological material. The flies were contained in plastic cups at 4.90 to 5.30 cm from the center of the target with the average distance about 5.15 cm. Perforated lids prevented anoxia for periods well in excess of the duration of irradiation. The cups were machined from nylon, which has been calculated to be the common plastic most nearly tissue equivalent for 14-Mev neutrons (Randolph 1957a), and their wall thickness of 2.5 mm insured secondary equilibrium for 14-Mev protons. From target discoloration, the over-all cross sections of the deuteron beam was roughly an equilateral triangle with 5 mm sides. Most of the ions, however, were within a central circular focal area of about 2 mm diameter. This central spot was thought to be located to within 2 mm. To

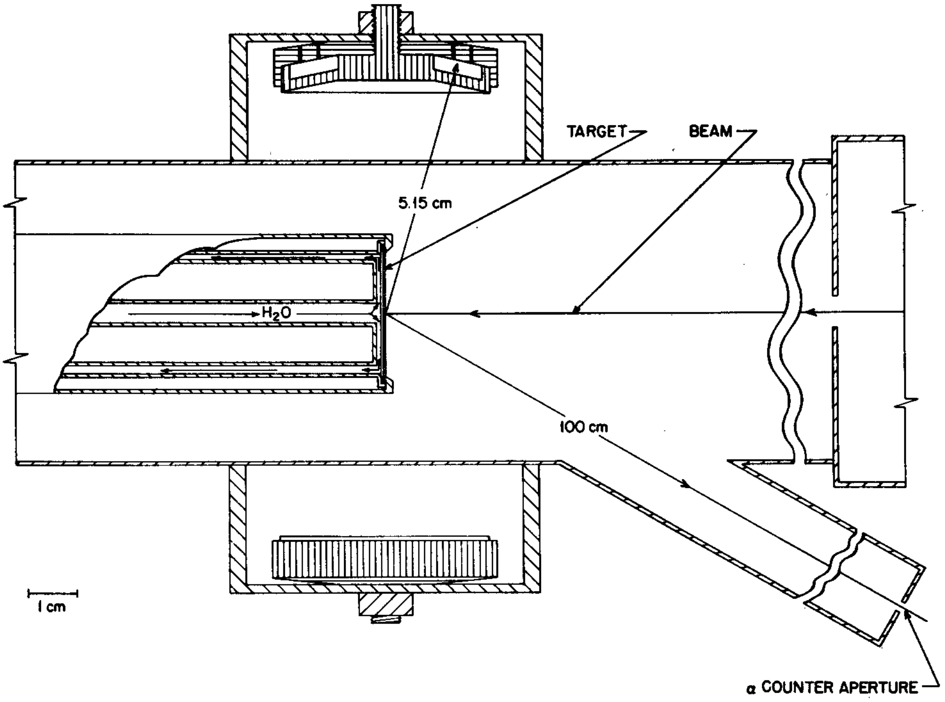

Figure 1.—Physical conditions for exposure of Drosophila to monochromatic 14-Mev fast neutrons.

minimize the possible error caused by miscentering of the beam, half of each dose was administered with the flies in one position and half with them on the diametrically opposite side of the target. Thus the effect of a 3 mm error in centering would be reduced to less than one percent at this distance. The accelerator room was air-conditioned with forced ventilation and temperature of 20° C.

The absolute dosimetry is based on intercomparisons of several independent systems of fast neutron dosimetry. The systems included: a small, homogeneous polystyrene-acetylene ion chamber (DARDEN and SHEPPARD 1951) with the Townsend method for measurement of ionization with a vibrating reed electrometer (Applied Physics Corporation Model 30-C) as a null detector, a Hurst absolute fast neutron detector (HURST *et al.* 1954), and conversion to dose (RANDOLPH 1957a) from absolute fast neutron flux determinations obtained by: (1) a proportional counter for measurement of the companion alpha particles of the $T(d,n)He^4$ reaction and (2) a long counter with flat neutron response up to 14 Mev (GRAVES *et al.* 1955) calibrated versus a known Po-Be neutron source. Intercomparisons of these methods agreed to within ten percent, which was the same general magnitude as the expected errors in absolute values by any one system. Hence the average values were thought to be correct to within ten percent. The gamma ray contamination, which was caused by neutron interactions at the walls of the room and near the target, was determined to be less than five percent of the total dose by a special ion-chamber proportional counter, when used as an ion chamber, measured total dose; and as a proportional counter, measured only fast neutron dose by electronic discrimination against gamma radiation.

For a determination of the doses, the elemental composition of Drosophila sperm was assumed equivalent to that of wet tissue. In our experiments for 14-Mev neutrons, where most of the ionizing particles originate from nuclear interactions throughout the flies or in the nylon (tissue equivalent) cups, this assumption seems justified. The same general argument holds for the conditions of our X and gamma irradiations.

RESULTS

The data obtained in each of the radiation runs reported in this paper, with the exception of the dominant lethal experiment with gamma rays that consisted of a single experiment at each dose, were tested for homogeneity by the χ^2 method at each dose level. The variation observed in the recessive lethal tests was that expected from random sampling of binomial populations; therefore, the average value for each dose with its standard error (S.E.) was tabulated in Table 1. The dominant lethal results, however, were heterogeneous; consequently, the results of each individual experiment at each dose were listed separately in Table 2 with the gamma-ray dominant lethal data and their standard errors.

Weighted regressions that best fit the experimental data for each genetic effect studied were calculated by the least-squares method. Since there was approximately five percent gamma contamination in the total dose from the neutron exposures, a simultaneous fitting similar to that used by RUSSELL *et al.* (1954)

was performed. It included a linear term (recessive lethals) and an exponential (dominant lethals) and accounted for the five percent gamma contamination (assumed to be no different from gamma rays emitted by a Co^{60} source). The linear equation, $y = 0.11 - 2.39\, D$ (where y is the predicted percentage and D the dose in kilorep), was found to fit the fast neutron recessive lethal data. The dominant lethal frequency-dose relation for gamma rays was best described by the exponential quadratic equation, $\ln y = \ln 97.17 - 0.144\, D - 0.021\, D^2$, and an exponential linear equation, $\ln y = \ln 97.49 - 0.48\, D$ (where y is in percentage survival and D is the dose in kilorep) gave the best fit to the monochromatic 14-Mev fast neutron data. Although the χ^2 values for goodness of fit of the experimental data for both gamma ray- and fast neutron-induced dominant lethals to their respective regression were high ($P = < 0.01$), there were no systematic departures from expectation.

Table 1

The percentage of sex-linked recessive lethals induced by monochromatic 14-Mev fast neutrons

Dose (rep)	Chromosomes tested	Number of lethals	Percentage lethals
0	3309	10	0.30±0.09
1000	3000	71	2.37±0.28
2000	2359	136	5.77±0.48
3000	1407	101	7.18±0.69
4000	1294	105	8.11±0.76
5000	747	97	12.99±1.23

Table 2

The percentage of egg hatch after exposure to Co^{60} gamma rays and 14-Mev fast neutrons

Gamma rays				14-Mev fast neutrons			
Dose (rep)	Eggs laid	Eggs hatched	Percentage egg hatch	Dose (rep)	Eggs laid	Eggs hatched	Percentage egg hatch
0	1294	1272	98.30±0.36	0	1591	1533	96.35±0.47
1000	1131	947	83.73±1.10		1209	1183	97.85±0.42
2000	1018	716	70.33±1.43		1424	1390	97.61±0.41
3000	987	509	51.57±0.60	1000	1344	816	60.71±1.33
4000	1093	405	37.05±1.46		392	249	63.52±2.43
5000	1146	311	27.13±1.31		1388	902	64.99±1.24
6000	796	182	22.86±1.49	2000	1813	689	38.00±1.14
					924	379	41.02±1.62
					1592	586	36.81±1.21
				3000	1297	289	22.28±1.16
					847	184	21.72±1.42
				4000	1290	176	13.64±0.96
					627	61	9.73±1.18
					1148	131	11.41±0.94
				5000	1031	96	9.31±0.91
					234	20	8.55±1.83

In Figure 2 the weighted linear regression for recessive lethals on dose for monoenergetic 14-Mev fast neutrons is plotted with the regressions for recessive lethals on dose for Co^{60} gamma rays, X-rays, and 1-Mev fast neutrons reported by EDINGTON (1956). The regressions for percentage egg hatch (1— dominant lethals) on dose for gamma rays and 14-Mev fast neutrons are plotted in Figure 3 with the regressions of egg hatch on dose for X-rays ($\ln y = \ln 95.03 - 0.17\,D - 0.04\,D^2$) and 1-Mev fast neutrons ($\ln y = \ln 97.0 - 0.88\,D$) reported by BAKER and VON HALLE (1953) and SHEPPARD *et al.* (1957), respectively. In both Figures 2 and 3, the data have been corrected for the unirradiated controls.

From both the recessive lethal and dominant lethal results, RBE values were calculated, with Co^{60} gamma rays as a base for comparisons. The RBE of the different radiations for the induction of recessive lethals is determined simply by a comparison of the slopes of the regressions for each radiation with that for gamma rays. With X-rays, however, the nonlinear frequency versus dose relation prevents such a comparison because the RBE is dose dependent. Since the logarithmic regressions for percentage hatch on dose are curvilinear for X and gamma rays and linear for both 1- and 14-Mev fast neutrons, no RBE comparison applicable for all levels of biological damage can be made. Consequently, the RBE values were obtained by comparison of the estimated doses of each radiation corresponding to 50 percent egg hatch. The RBE values for the induction of recessive and dominant lethals are tabulated in Table 3.

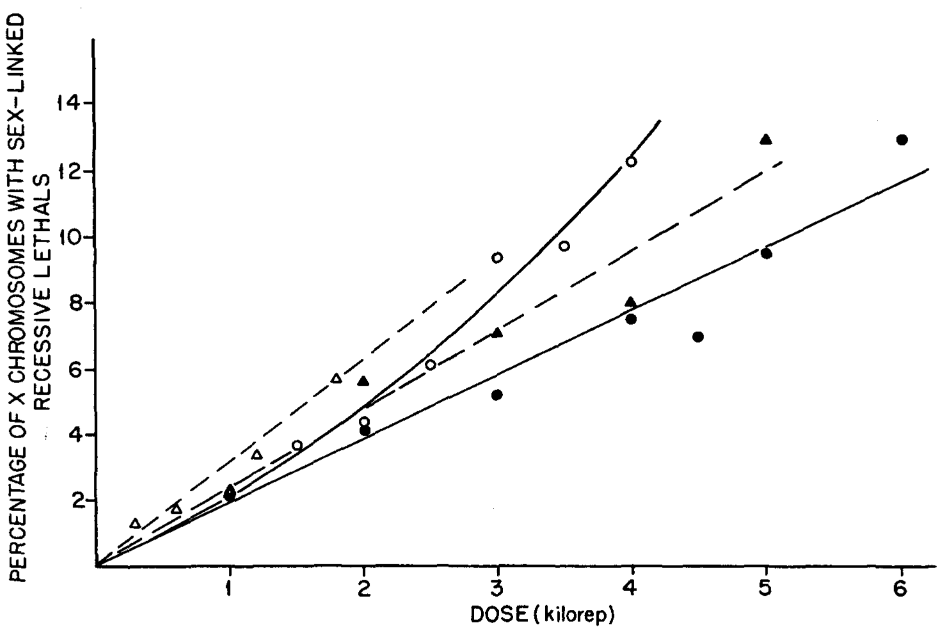

FIGURE 2.—The percentage of X chromosomes with recessive lethals induced by gamma rays (●), X-rays (○), 1-Mev (△), and 14-Mev fast neutrons (▲), in *Drosophila melanogaster*.

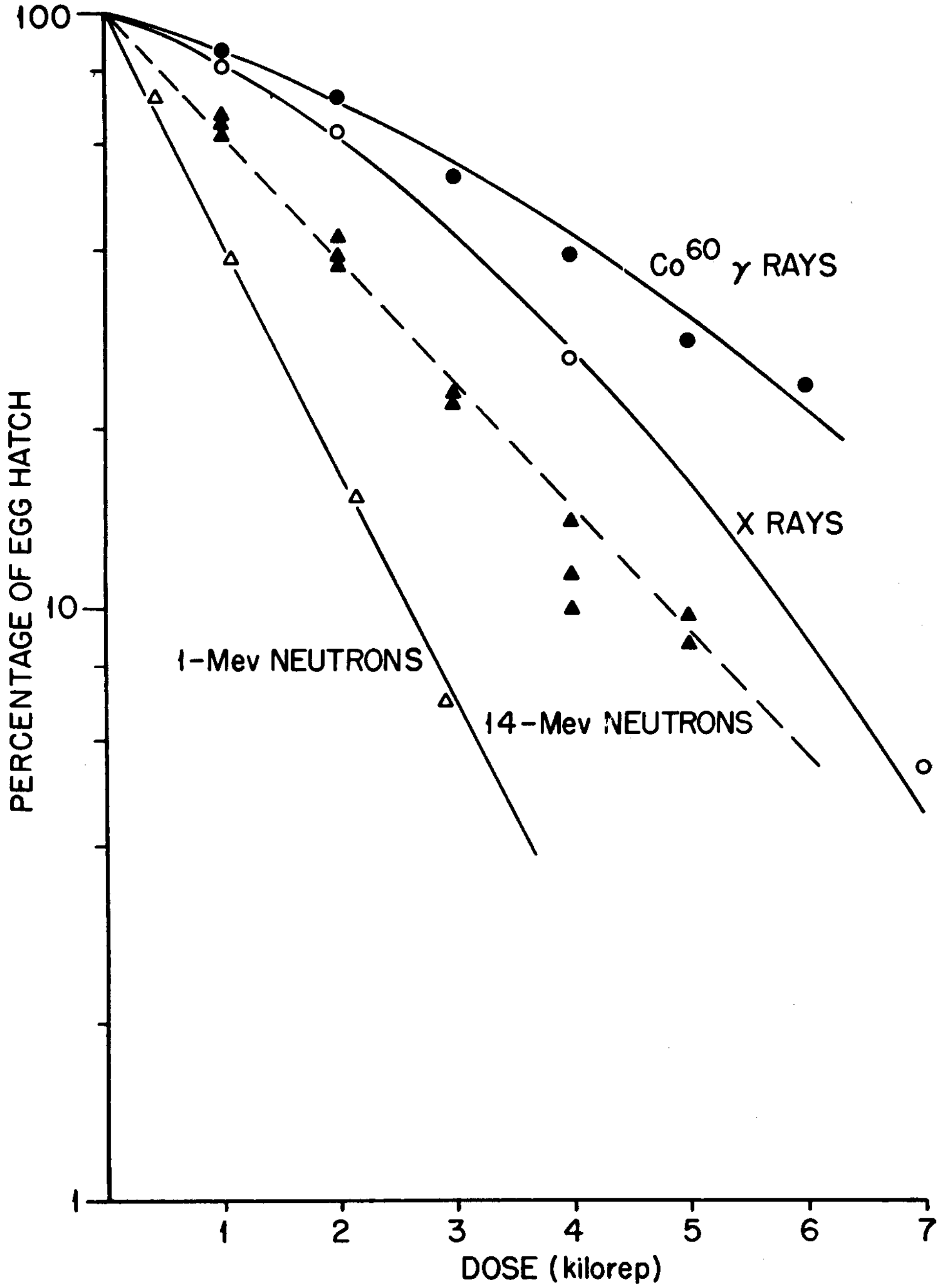

FIGURE 3.—The percentage of dominant lethals induced in sperm of Drosophila by gamma rays (●), X-rays (○), 1-Mev (△), and 14-Mev (▲) fast neutrons.

TABLE 3

The relative biological effectiveness of radiations of different average linear energy transfer on the induction of recessive lethals and dominant lethals

	LET (kev/μ)		RBE	
Radiation	Energy average	Track average	Recessive lethals	Dominant lethals (50% hatch)
Gamma rays	0.32	0.27	1.0	1.0
X-rays	2.2	1.8	varies with dose 1.1 at 1000 r; 1.4 at 4000 r	1.24
Fast neutrons				
14 Mev	75.0	12.0	1.23	2.27
1 Mev	67.0	46.0	1.62	4.23

DISCUSSION

The radiations used in the experiments discussed produce high-energy secondary ions (electrons in the photon irradiations, atomic nuclei in the neutron irradiations) that dissipating their energies by ionization and excitation, cause the biological effects observed as a result of a series of biochemical effects. The differences in effectiveness per unit dose of different ionizing radiations are thought to be caused primarily by differences in LET occuring in the irradiated material. Unfortunately, except for monoenergetic charged-particle irradiations of materials that are thin compared to the range of the particles, radiations produce a wide and complex spectrum of LET values throughout the irradiated material. Although mathematical or graphical description of LET spectra, which may be given, constitute the means for complete description of the LET spectra, the simplicity of single number characterizations of LET spectra seems more desirable for comparisons and interpretations of these studies than other more-detailed means.

Of several possible single-number, simply derived characterizations, we choose to consider only two here, although it may well be that no single number can adequately describe the LET spectra. One is what we call the "track average LET," which is that obtained when equal statistical weights are assigned to equal track lengths of all ionizing particles. This may be obtained from a division of the total energy of the ionizing particles by the total track length produced in the irradiated material. The other characterization, which we call the "energy average LET," is that average obtained when equal statistical weights are assigned to equal amounts of energy dissipated by the ionizing particles. This average is not so readily pictured as the result of elementary physical measurements of path length and energy, but might be, as BURCH and BIRD (1955) have mentioned, the natural physical average one would use. LEA (1955) and ZIRKLE (1954) used what we call the track average. BOAG (1954) has discussed both averages briefly. BURCH and BIRD (1955) and HURST *et al.* (1956) used the energy average. RANDOLPH (1957b) has given a mathematical definition of these averages.

The LET values given in Table 3 were calculated from various pieces of published data. The Co^{60} gamma-ray and the X-ray figures are based on JOHNS' review (JOHNS 1956) and the cyclotron neutron figures on an approximate estimate of the neutron spectrum by SHEPPARD *et al.* (1957). Because of differences in tube potential and filtration, the X-ray data are not strictly applicable to our work, but other uncertainties are thought to be more important. We have neglected the effect of delta rays, although BURCH and BIRD (1955) showed that this raises the energy average LET for X-rays and Co^{60} gamma rays to about 10 kev per μ and 7 kev per μ. Consideration of delta rays would reduce the track average values. We calculated our neutron LET values for first collisions in wet tissue (LEA 1955) of unit density surrounded by enough wet tissue to give secondary equilibrium. We started from BOAG'S (1954) distribution functions, extended his work to include heavy recoils with the help of SNYDER and NEUFELD'S evaluation (SNYDER and NEUFELD 1957) of stopping powers at low velocities near and below those at the Bragg peak of ionization, and, particularly for the 14-Mev neutrons, took into account the inelastic nuclear collision processes and angular distribution of elastically scattered neutrons (RANDOLPH 1957a). That the energy average is greater than the track average is most evident for the 14-Mev neutrons, in which 70 percent of the dose is contributed by recoil protons with energy average LET of about 15 kev per μ and 30 percent heavy particles with energy average LET of more than 200 kev per μ.

Throughout our LET calculations we have assumed that the number of electrons per unit volume of the biological material is negligibly different from that for water; whereas in these experiments the volumes of biological interest with high concentrations of nucleoproteins probably have 20 to 30 percent more electrons per unit volume. This consideration tends to increase all LET values by about the same factor, which has not been included in Table 3.

From comparisons of results of these investigations with those previously published from this laboratory, it is obvious that the relative effectiveness of the different radiations on the induction of the genetic effects studied is dependent on the average LET of the radiation used. If the track average is accepted as the proper representation of the average LET, then the RBE increases as the LET increases even within the neutron energy range studied. If, on the other hand, the energy average is the best estimate of the average LET, the RBE increases, passes through a maximum, and then decreases with increasing LET. This is true for both the recessive lethal and dominant lethal data; however, for recessive lethals the RBE-LET relation is not so clear cut because of the nonlinear frequency-dose relation for X-rays. Regardless of the method used for the determination of the average LET values, it is evident that the present RBE data is markedly different from the reported results of earlier investigations, especially for the induction of recessive lethals by radiations of different specific ion density.

Examination of the recessive lethal data reveals a close similarity in the relative effectiveness of X-rays and monochromatic 14-Mev fast neutrons. This observation is of especial interest when one attempts to explain the discrepancy between the present RBE results in Drosophila and those of the earlier genetic investigators. The results obtained by TIMOFÉEFF-RESSOVSKY and ZIMMER (1938) and ZIMMER and TIMOFÉEFF-RESSOVSKY (1938, 1942) will be used here for comparative purposes since the only adequate description in the early literature of the physical conditions of exposure was given in these publications.

SHEPPARD *et al.* (1957) have already pointed out that the average energy of the fast neutrons in the experiments of TIMOFÉEFF-RESSOVSKY and ZIMMER was probably much higher than the 3.9 Mev reported. Since this is true, the early neutron results should approach more closely the results obtained with 14-Mev instead of 1-Mev fast neutrons. Although there is some uncertainty about whether the flies were surrounded by sufficient tissue equivalent material in the early neutron experiments, we think it unlikely that the entire discrepancy observed in the RBE values of the present and earlier experiments is caused by differences in neutron dosimetry. It is, therefore, necessary that the biological techniques used be examined more closely. Although the mating techniques of the experiments are not entirely dissimilar, ZIMMER and TIMOFÉEFF-RESSOVSKY (1938) stated in the biological procedures of their neutron series, "Bestrahlt wurden 2 bis 3 Tage alt Drosophila melanogaster ♂♂, die etwa 48 Stunde nach Bestrahlung mit ClB ♀♀ gekreuzt wurden." This statement may be the answer to the problem at hand. It is now known from the work of BAKER and VON HALLE (1953) that the frequency of detectable genetic damage is significantly lower in the offspring of X-irradiated males that have been held with or without females for 24 or 48 hours. Although this is not true when fast neutrons of 1-Mev average energy are used (BAKER and VON HALLE 1954), unpublished evidence obtained in this laboratory shows that 14-Mev fast neutrons that have an average energy more nearly equivalent to the neutrons used by ZIMMER and TIMOFÉEFF-RESSOVSKY, behave in this respect as X-rays. Therefore, the biological results of the fast neutron irradiations of ZIMMER and TIMOFÉEFF-RESSOVSKY would be lower than if the males were mated immediately after exposure. If the fast neutron data of ZIMMER and TIMOFÉEFF-RESSOVSKY were compared with X-ray results observed from immediate mating after exposure, the resulting RBE would be erroneously high. If this were true, a corrected RBE of fast neutrons determined from the data of ZIMMER and TIMOFÉEFF-RESSOVSKY would be similar to the RBE reported by us.

It is interesting that in almost all investigations in which radiations of different average LET were compared for a determination of their relative effectiveness for the induction of dominant and recessive lethals, the RBE for the induction of dominant lethals (that almost certainly originate from chromosome breaks) for any given radiation was greater than that for recessive lethals. The values obtained in these experiments also indicate the RBE for dominant lethals is higher than that for recessive lethals and, as the average LET of the radiation increases, the discrepancy between the RBE for dominant lethal and recessive lethal induction becomes greater. This difference could be caused by increased dominant lethality induced by the more effective radiations, which would in turn preferentially siphon off potential recessive lethals that would arise as the result of break dependent deficiencies or chromosome aberrations. It is also possible that the different genetic events (point mutations, deficiencies, and lethals associated with chromosome changes) that express themselves as recessive lethals have different RBE values and the RBE observed for total recessive lethals is an average of the individual values.

SUMMARY

An investigation was made of the effects of monochromatic 14-Mev fast neutrons and Co^{60} gamma rays on the induction of dominant lethals and of 14-Mev neutrons on the production of sex-linked recessive lethals in Drosophila. These results were compared with those of other reports from this laboratory, in which radiations of different average LET were used. It was shown that the RBE of different radiations for the induction of both genetic effects studied is dependent on the LET of the radiation used.

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