LEARNING ABILITY AND PHYSICAL WELL-BEING IN OFFSPRING FROM RAT POPULATIONS IRRADIATED OVER MANY GENERATIONS

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THE possibility that unfavorable changes in the genetic component of human intelligence may result from artificially induced increases in mutation rate has been discussed in a number of official reports (e.g. MEDICAL RESEARCH COUNCIL 1956, and UNITED NATIONS SCIENTIFIC COMMITTEE on the EFFECTS of ATOMIC RADIATION 1958). Although such harmful effects might be predicted on theoretical grounds, their probable magnitude is unknown. The most serious attempt to estimate the likely extent of the presumed change appeared in the report of the British Medical Research Council which was published in June of 1956 (MATHER 1956). However, even the best information available at the time was inappropriate, in that much of the reasoning had to be based on a double extrapolation, from fruitflies to man, and from bristle numbers on the flies to mental ability in man. Studies of radiation effects on variability of quantitative traits in mammals were lacking; and there had been none at all relating to any trait even remotely resembling human intelligence.

Direct tests for the presumed mutational erosion of mental performance in animals, although obviously laborious, seemed not only possible but considerably overdue. Such a study was therefore started at Chalk River in August of 1956, using rats and one of the conventional maze tests of learning ability.

Because there was no certainty of detecting any effect at all, the experiments were planned so as to employ the highest doses compatible with maintenance of the irradiated groups over a succession of generations, together with the shortest practicable generation cycles, that is, mating immediately following the irradiations. Thus, fertilizations were with germ cells exposed at stages especially sensitive to induced genetic change. The object was to accumulate in the germ plasm, by means of radiation exposures in each generation, the largest possible total genetic damage in the shortest possible time.

The emphasis proved to be expedient. Interpretation of the results might have been simplified had matings been carried out in the post-sterile period, but the numbers of years required to accumulate a given total exposure to the germ plasm would have had to be substantially extended, owing to the increased interval between the generations and the necessity of limiting the dose per generation to ensure that irradiated animals recovered their fertility. Such experiments will be needed eventually, but an extension of the present study beyond its current 8 year duration might well have been difficult to justify.

Early published results from this study have shown a decline in learning

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ability among offspring from lines that had been subjected to gonadal irradiations of the male parents in each of a number of successive generations (McGregor and Newcombe 1962). However, these early results were of borderline statistical significance in two experiments, while in a third no effect was shown. Since then the total number of animals maze tested has been doubled (from 464 to 923) and the number of generations of gonadal exposures has also been doubled in the largest of the experiments. As a result, it is now possible to describe with greater assurance what the effects are under the conditions of these particular experiments.

The earlier studies have also yielded, as by-products, evidence of harmful effects on physical well-being, congenital dwarfism, eye defects, and infant death all being more common among descendants of irradiated parents (McGregor and Newcombe 1961; McGregor, James and Newcombe 1960).

As the particularly laborious series of experiments relating to maze learning ability has now been completed, this seems an appropriate time not only to present the accumulated results but to consider the merits of approaches that make use of behavioral traits. Some attempt should also be made to apply the findings, despite their obvious limitations, to an assessment of the possible effects which similar exposures might have on intelligence in man, since it was this practical problem that prompted the work in the first place.

MATERIALS AND METHODS

The maze test: For the tests of learning ability a multiple-T elevated maze was chosen. Each unit of the maze resembled a yardstick supported horizontally at about waist height from the floor. Most of the 19 units were arranged so that the end of one joined the centre of the next at right angles to make a T; one end of the top of the T formed a blind alley and the other joined the center of the next unit to make a further T, and so on. In this way a continuous elevated path 1 inch wide led from a starting point, via fifteen 90-degree turns (ten right and five left in random sequence) and past 15 blind alleys, to a finishing point. The pattern of the maze and its characteristics have been described in detail in the earlier paper (McGregor and Newcombe 1962).

A complete test of the learning ability of an animal required 30 working days, i.e., six 5-day weeks in all. Food intake was restricted to two-thirds the normal amount in order to provide an incentive to search for food. Two of the 6 weeks were spent conditioning the animals to find food at short range on the narrow path, first at the end of a single straight unit on 4 successive days, and next at the end of a single T made up of two units, the food being on the right arm of the T for 3 days and on the left arm for another 3 days. Each animal was allowed ½ hour a day over the 10 days, eight animals being conditioned at the one time on separate units.

When placed on the complete maze, a conditioned animal tended to explore for food and, over the 20 days of the test proper, became increasingly proficient at finding the food placed at the end of the path. Entries into blind alleys diminished progressively, and so did the numbers of retraces, while less and less time was required by most of the animals to finish the run. Each animal was given a maximum of just 10 minutes a day to find the food on the complete maze, and only one animal was tested at a time.

A number of different sorts of score were kept during the studies, but the most reliable of these proved to be a count of the entries into blind alleys with all four paws on forward runs. In the case of animals that failed to complete a run within the allotted 10 minute period, the blind alleys that had not been reached were included in this error score so that it became, in essence, the opposite of a count of the number of blind alleys successfully bypassed. The total error scores for particular animals, summed over the series of 20 consecutive trials on the maze proper, served as the most useful measure of learning ability.

Precautions were taken to ensure that the animals were not guided by the scent of the food, or by that of their own trails on the maze. Food decoys were placed about the room, and halfway through the 20-day test the paths were scrubbed and then wiped down with alcohol and each unit of the maze turned through 180 degrees.

A few animals failed to show the usual tendency to explore, some crawling only a few paces, others sitting still and looking over the edges of the narrow path. Whether the inhibitions suffered by these so-called "sitters" were the product of fear or of a genuine lack of mental ability is not known, but such animals must be regarded as distinctly handicapped in learning to find food under the conditions of the test.

The total error scores accumulated by individual rats over the 20 trials on the maze ranged from about 20 to 300 with a mode around 30 to 40. Because the extreme skewness of this distribution precluded use of the usual statistical tests for significance of a difference between means, it was found convenient to convert the crude error scores into normalized scores that are distributed in a Gaussian fashion. Units of half a standard deviation were chosen, forming a scale from 0 to 11 on which the mean fell halfway between 5 and 6, the high numbers representing poor learning ability. The process of normalizing was carried out independently for each statistical test, and always on combined data for irradiated and control groups.

The maze testing alone, over the past 8 years, has required a number of thousands of hours. The total is probably at least two-thirds of the maximum of 3,643 hours that would have been required had all of the 923 animals taken their full allotted times.

The experiments: Five experiments have been carried out (see Table 1). Experiments 1, 2, and 3 were based on irradiated and control groups consisting at the start of 30 mating couples, while experiments 4 and 5 were larger than this. Induced sterility in the irradiated groups tended to reduce the numbers of animals available for matings in the later generations, and to limit the numbers of generations over which experiments could be continued. To counter this effect, the numbers of matings were substantially increased in experiment 2 from generation 5 onward, and in experiments 4 and 5 from the beginning. In the control groups, the numbers of matings were adjusted in each generation to be essentially the same as for the irradiated groups. For the combined experiments, a total of 2,984 matings were carried out, and 15,243 animals were reared (Table 2).

Gonads of males were irradiated just prior to mating at age 90 days, the exposures being repeated in each generation. A lead shield with opening 2¾ inches in diameter was used to protect the rest of the body. To ensure that the testes and the adjacent regions of the sperm ducts did not remain within the body cavity, and possibly within the shielded area, a cushion

TABLE 1

Summary of maze experiments

Experiment No.	Dose per generation (r)	No. of generations	Animals tested per generation*		Total animals surviving to end of tests	
			Control	Irradiated	Control	Irradiated
1	400†	3	16	16	48	47
2	600	12	24	24	244	246
3	800	4	16	16	64	63
4	1000	2	32	32	60	60
5	1000	3	16	16	47	44
Combined					463	460

* These include equal numbers of the two sexes.
† Both the maternal and the paternal gonads were irradiated in each generation.

TABLE 2

Numbers of matings, litters, and animals born, in irradiated and control groups

			Control			Irradiated		
Experiment No.	Dose per generation (r)	Generation	No. of matings	No. of litters born	No. of offspring	No. of matings	No. of litters born	No. of offspring
1	400	1	30	10	96	30	13	82
		2	27	17	180	25	20	115
		3	30	21	171	30	9	48
2	600	1	30	28	256	30	29	157
		2	30	23	206	30	15	64
		3	23	21	205	23	14	94
		4	36	33	347	36	30	159
		5	61	51	465	61	46	261
		6	99	75	741	99	78	554
		7	116	101	1073	114	95	553
		8	118	86	856	118	66	306
		9	110	74	692	110	65	352
		10	116	75	639	116	67	312
		11	110	60	679	110	44	263
		12	119	74	557	119	75	316
3	800	1	30	29	299	30	25	106
		2	30	22	184	30	17	61
		3	19	17	155	19	14	44
		4	20	16	155	19	9	37
4	1000	1	60	52	520	60	46	148
		2	51	50	534	51	30	84
5	1000	1	112	90	853	112	70	252
		2	97	74	752	98	29	81
		3	20	18	183	20	10	46
Combined			1494	1117	10748	1490	916	4495

on a special holder was pressed gently against the abdomen to bring the testes into the scrotum and keep them there during the exposure. This holder also did away with the need to anaesthetize animals in order to keep them in position during the exposure.

For just one of the experiments (No. 1), the gonads of female parents were also exposed. The method used was developed late in the study and involved operating on the animals under anaesthetic and exteriorizing the ovaries for long enough to permit them to be irradiated outside the body. The uterus and the rest of the body were shielded during the exposure.

The radiation exposures were administered at rates in the vicinity of 200r/minute, a 2 million volt X-ray machine being used initially, and a 300 kilovolt machine later in the study. Males were placed with their mates immediately following exposure and left with them for a period of 18 days.

Offspring from irradiated and control groups were maze tested at 90 days of age, equal numbers of males and females being used. A week on a full diet was allowed at the end of the maze testing, prior to irradiation of the male animals (then approximately 140 days old). The young were born a month later, when the parents were about 25 weeks old; thus, two generations could be reared and tested in a year.

The accumulated exposures to ancestors of maze tested animals, when averaged over all of the animals tested from the irradiated groups, amounted to 2587r (Table 3).

TABLE 3

Accumulated exposures to the germ plasms of maze tested animals

			Control	Irradiated		
Experiment No.	Dose per generation (r)	Generation	No. maze tested	No. maze tested	Accum. exposure (r)	Av. accum. exposure for all animals (r)
1	400*	1	16	15	800	
		2	16	16	1600	
		3	16	16	2400	1387
2	600	1	16	16	600	
		2	16	16	1200	
		3	16	16	1800	
		4	16	16	2400	
		5	14	15	3000	
		6	30	30	3600	
		7	29	30	4200	
		8	30	30	4800	
		9	30	30	5400	
		10	15	15	6000	
		11	16	16	6600	
		12	16	16	7200	3663
3	800	1	16	16	800	
		2	16	16	1600	
		3	16	16	2400	
		4	16	15	3200	1981
4	1000	1	30	30	1000	
		2	30	30	2000	1500
5	1000	1	15	14	1000	
		2	16	14	2000	
		3	16	16	3000	2045
Combined			463	460		2587

* Both male and female parents irradiated.

RESULTS—LEARNING ABILITY

Effects on modal and mean values: The effects of the irradiation in increasing the numbers of errors made by descendant animals throughout the tests is clearly seen in the pooled data from all generations and all experiments. The distribution of the total error scores for the irradiated groups is shifted upward by an amount approaching one unit on the normalized scale, and equivalent to somewhat under half of a standard deviation (Figure 1). This increase in modal value, as seen in the combined results, is the product of a trend that occurs consistently throughout all five experiments (Table 4).

Elevation of the mean error score as a result of the irradiations amounted to 0.75 units on the normalized scale and was equivalent to 0.38 of a standard deviation (Table 5). The difference is statistically highly significant (P is in the vicinity of one in a million).

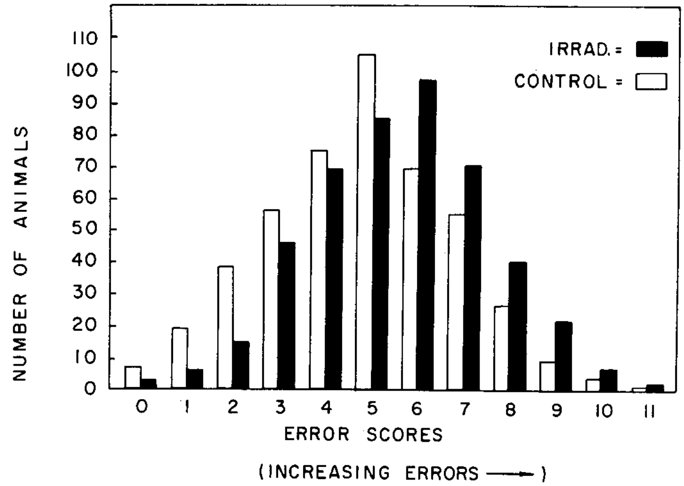

FIGURE 1.—Distributions of error scores for animals from irradiated and control groups. (Based on 463 and 461 animals from the two kinds of groups respectively.)

Effects on numbers of dull and bright animals: Differences are seen in the proportions of "dull" and "bright" animals. Dull animals may conveniently be taken as those with error scores that exceed the mean by more than one standard deviation, and bright animals as those with scores that were lower than the mean by the same amount. Each of these categories was represented by about 15 to 16 percent of the total animals.

The frequency of dull animals was increased by a factor of 1.71 in the irradiated as compared with the control groups (Table 6), and that of bright animals was reduced by a factor of 0.64 (Table 7). Both shifts are statistically significant, one at the 0.5 percent and the other at the 5 percent level.

TABLE 4

Frequency distribution of normalized error scores by experiments (combined data from all generations and both sexes)

Experiment No.	Dose per generation (r)	Error scores											
		0	1	2	3	4	5	6	7	8	9	10	11
Control groups													
1	400	2	3	9	11	7	7	4	4	1	0	0	0
2	600	2	6	14	23	37	57	41	35	20	6	3	0
3	800	1	5	8	10	9	15	8	7	1	0	0	0
4	1000	1	1	2	5	10	17	11	6	3	3	0	1
5	1000	1	4	5	7	12	9	5	3	1	0	0	0
Irradiated groups													
1	400	0	0	0	3	11	12	11	6	2	2	0	0
2	600	0	4	6	26	29	47	51	39	23	14	5	2
3	800	1	0	4	10	16	10	11	5	3	3	0	0
4	1000	0	1	1	4	7	7	15	14	8	1	2	0
5	1000	1	1	4	3	6	9	9	6	3	2	0	0

Numbers of animals are given in the body of the table.

TABLE 5

Mean error scores for offspring from irradiated and control groups (combined data from all generations and both sexes)

		Control		Irradiated		
Experiment No.	Dose per generation (r)	No. of animals	Mean error score	No. of animals	Mean error score	P (t test)
1	400	48	3.69 ± .28	47	5.43 ± .21	<.001
2	600	244	5.21 ± .12	246	5.72 ± .13	.004
3	800	64	4.17 ± .24	63	4.82 ± .24	.055
4	1000	60	5.25 ± .26	60	5.98 ± .24	.035
5	1000	47	3.98 ± .27	44	5.11 ± .31	.008
Combined		463	4.79 ± .09	460	5.54 ± .09	<.001*

* t=5.78; degrees of freedom=921.

Note: One unit of the normalized score equals 0.5 of a standard deviation and is thus equivalent on a percentile basis to approximately 7.5 points on an I. Q. scale for human intelligence. Thus, the above difference in mean error scores of 0.75 is equivalent to .38 standard deviations and comparable with a difference of 5.35 points on an I. Q. scale.

A similar comparison might be made for animals differing by two or more standard deviations from the mean. Such individuals may be designated “very dull’ and “very bright” respectively. In the irradiated groups there were nine such very dull animals as compared with four in the controls, and eight very bright animals as compared with 26 in the controls. Thus, the irradiation is associated with a twofold increase in very dull and a threefold decrease in very bright animals; the combined effect is statistically significant ($\chi^2 = 8.5$ for one degree of freedom; $P = .0025$) and is larger than that for dull and bright animals.

The most extreme class of animals, the “sitters” which did not attempt to learn the maze at all, were about twice as common in the irradiated groups throughout (Table 8).

Effects on successive generations: A linearly rising effect on learning ability with increasing accumulated exposure over the generations might be expected unless this were offset by reduced fertility in the maze dull animals so that the

TABLE 6

Proportion of “dull” offspring from irradiated and control groups*

		Control		Irradiated			
Experiment No.	Dose per generation (r)	dull (a)	not dull (b)	dull (c)	not dull (d)	Relative incidence irrad./contr. (bc/ad)	χ^2 (d.f.=1)
1	400	5	43	10	37	2.32	
2	600	29	215	44	202	1.61	
3	800	8	56	8	55	1.02	
4	1000	7	53	11	49	1.70	
5	1000	4	43	11	33	3.58	
Weighted mean relative incidence						1.71	8.0†

* i.e., animals with error scores greater than the mean by more than one standard deviation; represented in all by 14.8 percent of the grand total of 923 animals tested.

† P=.0045.

Note: Dull animals, comparable on a percentile basis to humans of I.Q. 85 and below, are approximately 70 percent more common among offspring from the irradiated groups as compared with the controls.

TABLE 7

Proportion of "bright" offspring from irradiated and control groups*

Experiment No.	Dose per generation (r)	Control: bright (a)	Control: not bright (b)	Irradiated: bright (c)	Irradiated: not bright (d)	Relative incidence irrad./contr. (bc/ad)	χ^2 (d.f.=1)
1	400	14	34	0	47	0.00	
2	600	45	199	36	210	0.76	
3	800	14	50	5	58	0.31	
4	1000	9	51	6	54	0.63	
5	1000	10	37	6	38	0.58	
Weighted mean relative incidence						0.64	5.1†

* i.e., animals with error scores less than the mean by more than one standard deviation; represented in all by 15.7 percent of the grand total of 923 animals tested.

† P=.025.

Note: Bright animals, comparable on a percentile basis to humans of I.Q. 115 and above, are approximately 35 percent less common among offspring from the irradiated group as compared with the controls.

TABLE 8

Proportion of "sitters" among offspring from irradiated and control groups (combined data from all generations and both sexes)

Experiment No.	Dose per generation (r)	Control: sitters (a)	Control: not sitters (b)	Irradiated: sitters (c)	Irradiated: not sitters (d)	Relative incidence irrad./contr. (bc/ad)	χ^2 (d.f.=1)
1	400	4	44	8	41	2.18	
2	600	13	231	25	221	2.18	
3	800	3	61	7	56	2.54	
4	1000	1	59	1	59	1.00	
5	1000	3	44	8	36	3.26	
Combined		24	439	49	411	2.12	8.04*

* P=.0045.

error scores approached a new equilibrium. A rise in mean error scores for irradiated groups, between the first and last generation, is in fact observed for each of the five experiments (Table 9), but even the data for the 12 generations of experiment 2 do not adequately distinguish between a linear increase and an approach to a new equilibrium (Figure 2).

Some unexplained effects on learning ability: A number of effects have been observed that are not readily interpretable but are nevertheless too large to be ignored. These relate to differences in the variability of the error scores in irradiated and control groups, and to differences in expression of the radiation effects in male and female offspring.

An increased variability of the error scores might be expected in the irradiated groups but this has not been observed. There is in fact an opposite effect, the variances being in general less for irradiated groups, and consistently less when expressed as fractions of the means (Table 10). The interpretation is by no means

TABLE 9

Mean error scores for first and last generations of offspring from irradiated and control groups (combined data for the two sexes)

Experiment No.	Dose per generation (r)	Control No. of animals	Control Mean error scores	Irradiated No. of animals	Irradiated Mean error scores	P (t test)
First generation						
1	400	16	2.69 ± .46	15	4.40 ± .25	<.01
2	600	16	4.62 ± .55	16	4.25 ± .52	.65
3	800	16	3.75 ± .53	16	3.38 ± .38	.55
4	1000	30	3.83 ± .38	30	4.97 ± .34	.03
5	1000	15	3.00 ± .39	14	3.78 ± .56	.25
Last generation						
1	400	16	3.75 ± .45	16	5.31 ± .48	.03
2	600	16	3.62 ± .51	16	5.31 ± .38	.01
3	800	16	3.06 ± .45	15	4.13 ± .44	.10
4	1000	30	4.20 ± .34	30	4.90 ± .35	.16
5	1000	16	3.50 ± .41	16	5.19 ± .51	.02
Combined, first		93	3.62 ± .066	91	4.29 ± .061	<.001*
Combined, last		94	3.71 ± .041	93	4.97 ± .042	<.001**

* t=7.37; d.f.=182. ** t=21.43; d.f.=185.

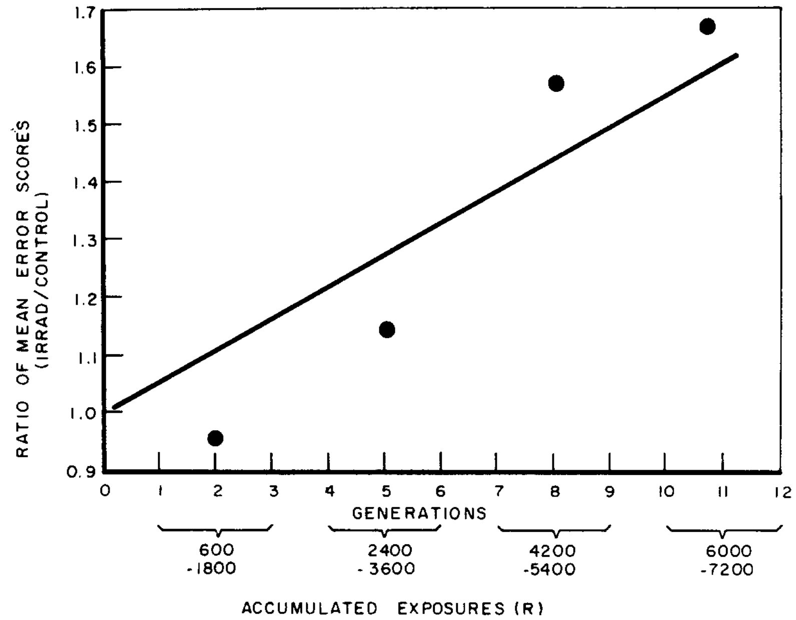

FIGURE 2.—Changes in radiation effects on mean error scores with increasing numbers of generations of exposure. (Based on the 490 animals of experiment number 2.)

obvious. However, the radiation-induced sterility and partial sterility could not have acted through a reduction in the breeding populations to decrease genetic

TABLE 10

Variances of mean error scores for offspring from irradiated and control groups (combined data from all generations and both sexes)

Experiment No.	Dose per generation (r)	Variance		Variance/mean		P (F test for inhomogeneity of variances)
		control	irradiated	control	irradiated	
1	400	3.75	2.16	1.01	.40	<.10
2	600	3.80	3.92	.73	.69	
3	800	3.60	3.56	.86	.74	
4	1000	3.92	3.37	.75	.56	
5	1000	3.40	4.34	.85	.85	
Combined		4.06	3.76	.85	.68	

variability, because the numbers of control matings were always made the same as those in the irradiated groups.

Likewise difficult to explain is an apparently greater radiation-induced reduction in learning ability of male as compared with female offspring (Table 11). This effect was at first thought to be due to expressions of induced recessive changes in the X chromosomes when present in the hemizygous state, but it later seemed too large to be readily accounted for in this way. The interpretation becomes even less probable in view of an evident absence of such male-female differences in expression in data from the one experiment employing irradiations of female as well as male parents (Table 12). The difference between the findings from this experiment and those from all the rest are striking enough to merit comment but no satisfactory theoretical explanation can be advanced.

TABLE 11

Mean error scores for male and female offspring from irradiated and control groups (combined data for all generations)

Experiment No.	Dose per generation (r)	Control		Irradiated		P (t test)
		No. of animals	Mean error scores	No. of animals	Mean error scores	
Male offspring						
1	400	24	3.58 ± .46	23	5.44 ± .28	<.010
2	600	123	5.09 ± .19	124	5.94 ± .18	.001
3	800	32	3.97 ± .34	31	5.10 ± .33	.020
4	1000	30	4.23 ± .37	30	5.03 ± .30	.096
5	1000	24	4.06 ± .37	22	5.09 ± .42	.054
Female offspring						
1	400	24	3.58 ± .37	24	5.50 ± .30	<.001
2	600	121	5.40 ± .18	122	5.62 ± .20	.625
3	800	32	3.50 ± .32	32	3.50 ± .28	. . .
4	1000	30	4.13 ± .31	30	4.87 ± .39	.140
5	1000	23	3.83 ± .28	22	4.95 ± .43	.054
Combined, male		233	4.56 ± .04	230	5.57 ± .03	<.001*
Combined, female		230	4.62 ± .06	230	5.10 ± .04	<.001**

* $t=21.57$; d.f. $=461$. ** $t=6.63$; d.f. $=458$.

TABLE 12

Extent of the difference in response of the two sexes where parents of both sexes were irradiated (combined data from all generations)

Experiment No.	Mean error score control	Mean error score irradiated	Difference	P
Both parents irradiated				
1 (male offspring)	3.58	5.44	1.86	.01*
1 (female offspring)	3.58	5.50	1.92	.001**
Male parent only irradiated				
2–5 (male offspring)	4.68	5.59	0.91	<.001***
2–5 (female offspring)	4.74	5.05	0.31	<.001****

* =3.37; d.f.=45. ** t=4.01; d.f.=46.
*** t=20.52; d.f.=414. **** t=4.08; d.f.=410.

TABLE 13

Mean error scores for offspring of control groups and for irradiated groups mated in the poststerile period

Experiment	Dose per generation (r)	Control No. of animals	Control Mean error score	Irradiated No. of animals	Irradiated Mean error score	P (t test)
Pilot	600	25	4.76 ± .38	24	4.21 ± .37	0.30*

* t=1.04; d.f.=47.

Post-sterility matings and learning ability: One preliminary study of learning ability in offspring from post-sterile matings was carried out. This study was small and failed to show any significant effect (Table 13) but it did indicate that at least an additional four months per generation, using doses of 600r to the gonads of male parents, would be required for studies of this kind.

Interpretation of the radiation effects on learning ability: The observed decrease in maze learning ability in offspring from irradiated groups might be due to one or more of three possible effects. Radiation-induced gene mutations may have had unfavorable effects on mental performance, gross chromosomal rearrangements may have had such effects as a consequence of the resulting aneuploidy, or it is just conceivable that the radiation-induced reductions in litter size may have operated indirectly to produce animals of inferior mental ability. Discrimination between these alternatives is not yet possible, but it is known that weight differences at the time of maze testing, such as might result from the litter size differences, have little if any effect on maze performance. The data are given in the earlier paper.

RESULTS—PHYSICAL WELL-BEING

Some of the observed physical effects are more readily interpretable. For example, increased numbers of dwarf, or runt, animals have been noted among offspring from irradiated ancestors; these are three to four times as common in

TABLE 14

Proportion of dwarfs and infant dead among offspring from irradiated and control groups (a reanalysis of earlier data)

		Control		Irradiated		Relative incidence irrad./contr. (bc/ad)	χ^2 (d.f. $=1$)
Reference*	Litter size	affected (a)	not affected (b)	affected (c)	not affected (d)		
Dwarfs							
(1)	. .	6	1569	14	994	3.68	6.9
Infant dead—disregarding litter size							
(2)	. .	667	1909	140	191	2.10	38.1
Infant dead—broken down by litter size							
(2)	3	6	0	24	18	0.00	
	4	13	19	16	24	0.97	
	5	25	40	40	30	2.13	
	6	26	52	16	38	0.84	
	7	43	132	10	39	0.79	
	8	100	220	14	26	1.18	
	9	99	306	4	14	0.88	
Weighted mean relative incidence						1.12	0.5

* References: (1) McGregor and Newcombe 1961. (Combined results from three irradiated and control groups receiving 400, 600, and 800r respectively per generation; four generations of offspring. Animals weighing 75 percent, or less, of the average for their sex at 3 months were scored as dwarf.) (2) McGregor, James and Newcombe 1960. (Offspring from males exposed to 800r and mated over a period of 24 days immediately following exposure; one generation only.)

irradiated as compared with control groups, the difference being highly significant (Table 14). A single mutant gene affecting pituitary activity appears to be responsible. These animals are definitely handicapped; they tend to die young, have reduced fertility, and are prone to exhibit eye defects.

Risk of infant death before weaning has also been found to be increased, i.e., about doubled, among offspring from fathers who received 800r prior to mating (Table 14). The effect is, in this case, largely but not entirely secondary to the reduction in litter size. The danger is consistently higher for members of small litters independent of whether these arose from irradiated or control fathers. However, with matings 5 to 8 days after irradiation a genetic effect independent of litter size could be demonstrated. There is no evidence from this test that animals from the small litters who managed to survive were at any physical or other disadvantage. Also, since the experiment was restricted to a single generation there is no certainty that the result would have been the same had the radiation exposure been repeated over many successive generations.

DISCUSSION

Possible extrapolation to man: Until the extent of the contribution from a possible adverse effect of small litter size on the maze learning scores can be estimated, there is little assurance that humans would react similarly to radiation exposure of their germ plasm. In both rats and mice, excessive prenatal growth is more common in small litters, and does lead to head injury at birth often followed by infant death; however, there is no evidence that the surviving animals are in any way impaired (SNELL 1933; MCGREGOR, JAMES and NEWCOMBE 1960, and unpublished). It is also a formal possibility that abundance of milk during the postnatal development adversely affects mental development, although this seems unlikely. If extrapolations were to be made from effects on learning ability in rats observed in the present studies to those on intelligence in humans, they would for this reason alone perhaps best be regarded as indicating the unlikely worst that might happen. That the rat irradiations were carried out in a sensitive period of germ cell development provides an additional reason for viewing extrapolations to man in this light.

Other barriers to extrapolation are less serious. The character measured as learning ability in rats may, of course, differ substantially from what is usually measured in humans by means of intelligence tests, but it is certainly much closer to intelligence than, say, bristle number in Drosophila. Induction of chromosomal aneuploidy may be responsible for some part of the decline in learning ability in rats, but this class of genetic change is, in any case, of interest in humans as well. Conversion from the scale for maze learning ability to that for I.Q. scores presents less difficulty than might at first be supposed.

To extrapolate from an observed decline in maze learning ability to the possible magnitude of an effect of similar exposures on human mental ability it must be remembered that 15 points of a human I.Q. scale are approximately equivalent to one standard deviation (PENROSE 1954). Thus an observed decline in learning ability in rats leading to a shift in mean error score by 0.38 standard deviations may be regarded as comparable on a percentile basis to a decline in mean I.Q. for humans of 5.35 points, e.g., from 100 down to 94.65.

Similarly, the maze "dull" and maze "bright" animals each represent about 15 to 16 percent of the total and may be regarded as comparable on a percentile basis to the categories of humans known by the same names, in which are included those with I.Q.'s of 85 and below, and of 115 and above, respectively. On analogy with the rat experiments, a 70 percent increase in the one group and a 30 percent decrease in the other might be inferred.

The statistical treatment could be extended in the same manner to very dull and very bright human groups differing by more than two standard deviations from the mean and having I.Q. scores of 70 and below and of 130 and above. The very dull groups might then be thought of as becoming perhaps twice as common, and the very bright groups as decreasing to a third their present frequency, as a consequence of the radiation exposure.

The very large exposures accumulated over successive generations in the rat experiments vastly exceed the range of greatest practical interest to humans. More appropriate, for example, would be predictions of the consequences of exposures in the vicinity of 5 rads per person per generation, the level suggested by the International Commission on Radiological Protection as an upper limit to be used in "planning for nuclear power programs and other peaceful uses of atomic energy on a large scale."

If the buildup in genetic effects observed in the rat studies over successive generations is assumed to be linear, the effects of smaller accumulated exposures must be taken as strictly proportional. Any correction for a supposed fall-off as the effect approached a new equilibrium in the later generations of the rat experiments would tend to increase the predicted effect for small accumulated doses delivered over just a few generations, but the correction would, in any case, probably not be large.

Taking the mean of the exposures accumulated in the germ plasm of maze-tested rats from the irradiated groups as 2500r (see Table 3) an effect of 5 rads over one generation would be only 1/500th as great. Exposure of both parents to the 5 rads would produce twice this effect if the sexes were equally sensitive, which is of course not necessarily the case. The response per rad where both parents are exposed does, in fact, appear from experiment 1 to be increased, not by twofold but by about tenfold (see Tables 3 and 12), so that if this correction is used the response to 5 rads delivered to both parents over just one generation may be taken as 1/50th of that observed in the experiments.

The shift in mean error score, for example, resulting from this smaller exposure of the two parents (i.e., 5 rads to each in one generation) would then be equivalent to $1/50 \times 0.75 = .015$ units on the normalized scale and to .0075 of a standard deviation. Translated on a percentile basis to a human I.Q. scale this would be comparable to a decline in mean I.Q. by 0.11 points, e.g., from 100 to a new mean of 99.89.

Similarly, the numbers of dull individuals might be expected to be increased by a factor of 1.014 and the numbers of bright individuals to be decreased by a factor of 0.993. For a population of a million individuals, in which these two groups each represented 16 percent of the total, this would be equivalent to a gain of 2,240 dull and a loss of 1,120 bright individuals.

Such an influence operating in a human population should perhaps be regarded as of substantially less importance than other social factors, such as those affecting fertility differences, which may be very much more potent in determining the quality of the genetic determinants of intelligence.

Any such extrapolation to man must be regarded, in the absence of better information on a possible litter size effect or parallel experiments employing poststerile matings, as representing a possible overestimate of the likely effect on the genetic basis of human intelligence. It is quite possible, for example, that rat offspring from poststerile matings will be found to show no detectable effect on learning ability. Such experiments will be just as laborious and considerably more protracted than those which we have carried out, but they are needed if better answers to the practical question are to be had. In the meantime, an estimated maximum probable effect for humans is not without value.

The uses of behavioral studies: Since the studies of learning ability are so laborious and time consuming it may be asked whether similar answers, even as applied to human intelligence, might not be drawn from studies of radiation effects on heritable physical characteristics. However, there are two major uncertainties in such an extrapolation: (a) it is entirely conceivable that the mental and behavioral traits, many of which are acquired late in the evolution of a species, may not possess the same degree of vulnerability to genetic deterioration as do other characteristics of a more obviously physical or biochemical nature; and a plausible case might perhaps be made for their greater sensitivity to erosion with an increase in mutation frequency; (b) for both intelligence and learning ability there is a defensible belief that the optimum lies at the extreme high end of the scale, whereas for most physical characteristics, such as bristle number in flies and birthweight in humans, the optimum is close to the mean; and although elevation of the mutation rate may increase the variability of a physical trait in both directions away from the mean, there are a priori reasons for believing that this is not the case for mental ability of any sort. Both sources of uncertainty are amenable to study in laboratory organisms.

There are, for example, many behavioral traits of an adaptive kind, even in nonmammalian laboratory organisms, that would lend themselves to quantitative studies of losses of function as a result of radiation-induced increases in mutation rate. The web-spinning ability of the spider, for example, although used for pharmacological studies of impairment, does not seem to have been employed in any genetic studies of similar sorts. The social insects such as the ants, termites, wasps, and bees all possess adaptive behavior patterns that could be so studied. Thus, if we cannot now predict the vulnerability of such traits to increased mutation rates the problem is one that could be studied either on a modest scale with lower organisms or, by dint of more labour, in mammals themselves.

A somewhat more vexing problem is whether, for the adaptive behavioral traits, an increase in genetic variability will cause a decline in the degree of adaptation or merely a greater spread in both directions. It has, for example, been argued that a single mutation is sufficient to produce a moron but that many selected mutations are required to make a genius. Nevertheless, despite this plausible line of reasoning, MATHER's (1956) calculation was necessarily ambiguous on the point and he was forced to consider both alternatives: that an increase in mutation rate might increase the variation in intelligence in both directions (as was true for bristle number in flies), or that mutational changes might be predominantly disruptive so that intelligence would be lowered by them but rarely, if ever, raised. Unfortunately, there is a lack both of empirical observations and of theoretical treatments of the problem to help resolve the dilemma.

Even the seeming dichotomy among quantitative traits, into many with optima approximating the means and a few with apparent optima at the high ends of the scales, has not been adequately accounted for on a theoretical basis. It is just possible that high intelligence carries with it a hidden price tag and that its adaptive value is lower than we think, except in special circumstances. Few, however, would press this point of view. It is also conceivable that certain variables which may underly a trait like intelligence do, in fact, have individual optima which closely approximate their means, and that the overall expressions which we measure reach high levels only when the different underlying variables are all, or are predominantly, close to their modal or mean values. If this is true, the hereditary basis of high intelligence must be much more complex than has heretofore been supposed. It also follows that theoretical predictions about the susceptibility of the trait to deterioration through an increase in mutation rate are less certain than has been thought.

The line of argument might be pursued further to show that (a) for high intelligence to be highly heritable the underlying variables must be relatively stable, (b) for this to be the case relatively large numbers of polygene loci must be involved in the determination of each, and (c) the system may for this reason be highly resistant to the influence of newly mutated genes in any but very large numbers. The reasoning is speculative but it emphasizes a fundamental ignorance of the differences between the quantitative traits that have optima that are close to the means and those, like intelligence and learning ability, that have optima at one or other of the extreme ends of the scales.

Until we know why such traits differ in this particular respect it is better not to generalize from one to the other, but to study directly whichever trait is of special interest, even where the study is bound to be difficult.

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SUMMARY

Rats descended from male animals X-irradiated over as many as 12 generations have shown reduced maze-learning ability. The combined results from all experiments, involving totals of 463 animals from irradiated and 461 from control populations, indicate a decline in maze performance which would be comparable on a percentile basis to a decline in mean I.Q. for humans of 5.35 points, e.g. from 100 down to 94.65. There was a 70 percent increase in "dull" and a 30 percent decrease in "bright" animals (groups representing the bottom and top 15 percent of the population, comparable on a percentile basis to humans with I.Q.'s of 85 and below, and of 115 and above, respectively). The accumulated exposures to ancestors of these animals, when averaged over all animals tested from the irradiated groups, amounted to 2587 rads.

There are reasons for believing that this effect may be greater, to an unknown extent, than that of similar accumulated exposures in man. (a) The animals were mated immediately after exposure, a procedure which permitted inheritance of broken and rearranged chromosomes that would not have been transmitted had the matings been substantially delayed. (b) A radiation-induced reduction in litter size may have had adverse effects on offspring from the irradiated groups, an effect which would have no analogy in humans.

Differences in other, nonbehavioral, traits of rats from irradiated and control populations are described.

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