RECEIVED BY TIC JUL 23 1974

Conf-740715--6 WEB 7/8/74

Presented at:

Vth Intern. Cong. Rad. Res.

Seattle, Washington

THE USE OF CHROMOSOME ABERRATIONS FOR PREDICTING
GENETIC HAZARDS TO MAN

J. G. Brewen and R. J. Preston

Biology Division, Oak Ridge National Laboratory,¹ Oak Ridge, Tennessee 37830

NOTICE

This report was prepared as an account of work sponsored by the United States Government. Neither the United States nor the United States Atomic Energy Commission, nor any of their employees, nor any of their contractors, subcontractors, or their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness or usefulness of any information, apparatus, product or process disclosed, or represents that its use would not infringe privately owned rights.

¹

Research sponsored by the U. S. Atomic Energy Commission under contract with Union Carbide Corporation.

MASTER

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

809

Almost twenty-seven years ago, November 1947, to be precise, W. L. Russell began work in Oak Ridge to establish the mouse as the mammalian model for estimating the genetic hazards from ionizing radiations. The ensuing twenty-seven years have resulted in a prodigious amount of research, not only by Russell and colleagues but many other workers,¹ in mammalian radiation genetics and an equally prodigious amount of skepticism, from some workers, about the work; a skepticism that has had the recurring theme, "A mouse is not a man, etc., etc...". This skepticism was, and in part still is, reinforced by the findings that closely related, in addition to diverse, mammalian species exhibited quantitatively different genetic responses to ionizing radiations. Thus it is to the fundamental problem of establishing a "bridge", as it is called, between mouse and man that we address ourselves in this article.

The genetic consequences of exposure to ionizing radiation are diverse and, simultaneously, manifest. Those effects that are demonstrably genetic in nature include gene mutations, reciprocal translocations, chromosomal inversions, dominant lethality expressed as either pre- or post-implantation death of the zygote, and chromosome loss or addition. Of all of these genetic effects, the only one that has not been clearly demonstrated to consist entirely, or predominately, of structural chromosome damage is the effect generally alluded to as specific locus mutations, and data are rapidly being colligated that show that a significant portion of the radiation-induced specific locus mutations are actually minute chromosome deletions. It is obvious, therefore, that structural damage to the chromosomes constitutes the major portion of the genetic damage produced by ionizing radiations.

The advent of the short term tissue culture of human peripheral leukocytes

by Moorhead et al.² enabled cytogeneticists to begin measuring the production of chromosomal aberrations, by ionizing radiations, in a homogeneous population of human cells. The original qualitation and quantitation of aberration production was done by Bender and Gooch^{3,4} and in the subsequent twelve years a copious literature has been amassed on this subject. Two excellent reviews^{5,6} are available on human chromosome aberration production by ionizing radiation, and it suffices to mention that the accumulated data show that the general results found in the classical cytological material, e.g. Vicia faba and Tradescantia, are also found in the human studies. These include (1) the presence of a dose-square component in the kinetics of interchange production by low LET radiations, (2) fractionation effects with low LET radiations, (3) dose rate effects with low LET radiations, (4) linear dose response kinetics with high LET radiations, and (5) a lack of a fractionation, or dose rate, effect with high LET radiations.

Although the data on chromosome aberration production in human cells were very extensive, it was extremely difficult to use them for predicting heritable genetic effects. The reasons for this were (1) the cells used were of somatic origin and the possibility existed of quantitative differences between somatic and germ cells,⁷ and (2) the aberration types analyzed were generally recognized as being cell^{8,9} and organism lethal¹⁰ and thus of no genetic consequences. It was obvious to radiation biologists that if cytogenetic studies could be performed on mouse leukocytes, and the data so derived correlated to genetically recoverable events in the mouse, a reasonable extrapolation from human somatic cell chromosome aberration data to true genetic effects might be made. Although many laboratories endeavored to develop a method for culturing mouse leukocytes, very little progress was made until

Buckton and Nettesheim¹¹ reported success by growing the leukocytes in cell impermeable diffusion chambers placed in the peritoneal cavities of other species.

In the meantime, however, aberration data on other mammalian species were underscoring the fact that diverse species had diverse quantitative, if not qualitative, responses in terms of aberration production by ionizing radiation.¹²⁻¹⁵ These findings made it even more imperative that data be obtained on the mouse if the human data were to be used, with any confidence, in predicting genetic hazards.

The one seemingly consistent pattern that emerged from the studies on different species was that the species with the higher chromosome numbers were the most sensitive to chromosome interchange production. Qualitatively speaking, this observation had been made earlier in plant materials where it was observed that increases in ploidy resulted in increases in sensitivity to interchange production.¹⁶⁻¹⁸ In these instances, however, the DNA content also varied and hence it was not clear whether the increased sensitivity was due to increased chromosome number or DNA content per nucleus. The observation by Griffin et al.¹⁹ that the interchange frequency in amphibians remained constant as DNA content varied but the chromosome number remained the same suggested that sensitivity to interchange production was influenced by chromosome number.

Following these studies Brewen et al.²⁰ reported a comprehensive inter-specific comparison of dicentric and deletion production by acute X rays in six mammalian species. This study was then followed by a comparison of the yields of dicentrics produced in peripheral leukocytes and reciprocal translocations produced in spermatogonial stem cells.²¹ Based on this work, and that of several other investigators, we will attempt to create a working

model for estimating various genetic hazards to man from ionizing radiations. Each of the various aspects of the model and the pertinent data will be discussed in separate sections.

I. Interspecific comparisons of dicentric and deletion production in peripheral leukocytes: The dose response characteristics of dicentric chromosome and deletion production in six mammalian species were studied in a series of experiments.^{12-14,20} The data from these experiments are summarized in Tables 1 and 2. It was observed that both aberration types increased exponentially with dose in all species (Fig. 1). The data also show that the species with the higher number of chromosome arms available for participation in interchange formation are the most sensitive to dicentric production. This correlation between chromosome arm number and sensitivity to exchange induction appears to be linear and consequently, human cells with an "effective arm number" of 81 are twice as sensitive as mouse cells with an "effective arm number" of 40 (Fig. 2). Recent data of Bajerska and Liniecki (personal communication) show that the rabbit and man are equally sensitive to dicentric induction. The rabbit has an "effective arm number" approximately equal to man. There is no obvious karyological effect of this type on the sensitivity to deletion induction, and in fact the human and mouse cells appear equal in sensitivity.

T-1

T-2

F-1

F-2

Since a dicentric is one of the two possible interchange configurations that are formed following irradiation and a reciprocal translocation is the other,²² it seems reasonable to conclude that man is twice as sensitive as the mouse to the induction of reciprocal translocations. It is not clear that dicentrics and reciprocal translocations are induced in equal frequencies per unit dose. Heddle²³ has presented evidence, from studies in Vicia faba, that the two events occur at equal frequencies and Caspersson et al's²⁴ data

on human leukocytes, though not clear as Heddle's, suggest the two events occur with approximately equal frequencies. Recently, however, several authors,^{25,26} utilizing the new band staining techniques, have presented data showing that dicentrics occur more frequently than reciprocal translocations. Not all reciprocal translocations are expected to be seen, even with the new staining techniques,²⁷ and consequently an excess of dicentrics should not be considered proof that the two events do not occur at equal frequencies. However, even if the two exchange types do not occur with equal frequency the dicentric data can be used to (1) demonstrate inequalities in sensitivity to interchange induction between species, and (2) as a common index of mouse and man for comparing events in somatic cells to events in germ cells.

II. The comparison of dicentric yields in leukocytes to reciprocal translocation yields in spermatogonia. The production of reciprocal translocations in spermatogonial stem cells by X rays was studied in young adult male mice and Chinese hamsters by irradiating the animals with various doses of 250 Kv X rays, waiting an appropriate time, and analyzing diplotene-metaphase I primary spermatocytes for multivalent configurations.^{21,28} The frequencies of reciprocal translocations were then compared to the frequencies of dicentrics observed in leukocytes over the same range of doses.^{21,29}

Figure 3 summarizes the data. The mouse and hamster have been demonstrated to be equally sensitive to dicentric induction and Figure 3 shows that they are also equally sensitive to reciprocal translocation induction. It is also seen in Figure 3 that the ratio of dicentrics to reciprocal translocations is approximately 3-4:1, and the slopes of the two curves are the same, i.e. about 1.5 indicating the presence of a two-track process in exchange formation. This latter observation is in contrast to other published data in that other workers have consistently reported linear dose kinetics for reciprocal

translocation induction.³⁰⁻³³ The dose rate effects and fractionation effects that have been demonstrated argue for the presence of a two-track component,^{31,34-37} however, and the present result is therefore not surprising.

In order to determine if the interspecific variations in radiosensitivity to interchange induction demonstrated in the peripheral leukocyte system extended to the germ cells, several male marmosets* and guinea pigs were testicularly irradiated with various doses of X rays. The results to date are presented in Table 3 and Figure 4. The data clearly show that both the marmoset and guinea pig are more sensitive than the mouse and Chinese hamster to the production of reciprocal translocations at the lower (25-200 R) doses. There is an indication that both species demonstrate the unusual "humped" dose response curve and the peak yield occurs at a lower dose than in the mouse.

T-3

F-4

We have some data on the induction of reciprocal translocations in testicularly irradiated men. The data come from three dose points, namely 78, 200, and 600 R. The yields of translocations observed are $4.0 \pm 1.0\%$, $7.0 \pm 1.3\%$, and 6.1 ± 1.8 respectively. The number of cells analyzed, however, is small (371, 300, and 180) and the data carry a large standard error. The data indicate, however, that, as in the case of the marmoset, man is more sensitive than the mouse to translocation induction at lower doses.

* In collaboration with N. Gengozian, Oak Ridge Associated Universities, Oak Ridge, Tn.

Recovery of spermatogonia induced translocations in the sons of irradiated males. Ford *et al.*³⁹ have reported that following a dose of 1,200 R separated into two equal fractions of 600 R administered eight weeks apart to male mice the yields of reciprocal translocation bearing primary spermatocytes were 41.2% and 32.6%. Subsequent testing of sons of identically irradiated males for semi-sterility and translocations revealed five translocation heterozygotes in 150 F₁ males. Using the distribution of translocations scored cytologically in the primary spermatocytes Ford *et al.*³⁹ calculated an expected recovery of translocations twice that observed. Ford *et al.*³⁹ concluded that a selection process may be in operation that affects the haploid spermatids or sperm. This observation in itself would permit geneticists to conclude that the risk of recovering a radiation-induced translocation in the F₁ is only one-half of the expectation of 1/4 or 1/8 of the observed yield in primary spermatocytes. Using the previously presented data on the ratio of reciprocal translocations in primary spermatocytes to dicentrics in peripheral leukocytes of the mouse, i.e. 1/4, we conclude that the yield of dicentrics in human leukocytes after radiation exposure can be corrected by approximately 1/32 (i.e. 1/4 x 1/8) to arrive at an estimate of recovered translocations in the offspring of irradiated men.

There are two lines of evidence, however, that must be considered. First, in surveys of families known to carry a balanced translocation the ratio of normal plus balanced heterozygote births to abortions exceeds the expected 1:1 ratio in that there are far too few abortions.^{40,41} It can be argued that most of the abortions occur before implantation and subsequently

the mother is not aware of her pregnancy. This question must be investigated more thoroughly. Second, and perhaps more significant, are the findings of Generoso,⁴² and Brewen et al.⁴³ Generoso studied the incidence of semisterility and sterility in F_1 males of spermatogonial stem cell irradiated fathers. The doses and frequencies of semi-sterile and semi-sterile plus sterile sons are presented in Table 4. All of the semi-sterile sons were confirmed cytologically, by Brewen and Preston, to be translocation heterozygotes. The cytological constitution of the steriles has been studied by Cacheiro and Russell (personal communication) and four of the males were shown to be translocation heterozygotes. The data can be used to estimate the frequency of translocation recovery. If these frequencies are compared to the frequencies of cytologically scored translocations in primary spermatocytes at the same doses it is seen that the probability of recovery varies with the dose (Table 4). In fact, at the lowest dose (150 R) approximately 25%, or the 'expected' number, are recovered. These observations are preliminary in nature and are in the process of being expanded. If the variation in recovery rate as a function of dose is confirmed, we will have to reassess our estimates of hazard from translocations.

T-4

Cytologically and genetically detected deletions. Data were presented (Table 2) that indicated that mouse and human leukocytes were equally sensitive to the induction of microscopically visible deletions by X rays. The deletions scored in those experiments represent size variations from loss of entire chromosome arms down to minute intercalary deletions, and there is no a priori reason to believe that this apparent equivalence in

sensitivity to deletion induction cannot be extended to include deletions that are submicroscopic in size. If we accept this premise, we can postulate that human and mouse cells are equally sensitive to the production of chromosome deletions of the order of one map unit and less. Russell⁴⁴ has shown that 13.5% of the specific locus mutations produced at the d-se loci in spermatogonia are in fact minute deletions. The proportion of the mutations known to be associated with deletions ranges from 13.5% to 42.3%, the variations being determined by the male germ cell stage irradiated and the LET of the radiation. More recent studies by Russell (personal communication) indicate that a significant number of mutants at the c locus are deficiencies in that they are homozygous lethals. Erickson et al.⁴⁵ have also recently reported the existence of deletions for the structural gene MOD-2 in existing mutant stocks at the c locus. These mutants were induced by X rays. Based on the cytological data derived from the leukocyte studies we conclude that mouse and man are equally sensitive to the production of those gene mutations that result from small deletions.

In addition, there are some data on X ray induced autosomal recessive lethals in mouse spermatogonia.⁴⁶ It is generally assumed that these result from small deficiencies and the mean overall rate of production is about 2×10^{-4} /gamete/rad. Again, if the results from the leukocytes are indicative of an equality in the sensitivities of mouse and human cells to deletion induction, these data can be used to make an estimate of expected autosomal recessive frequencies in man. Finally, it has been assumed that the preponderance of dominant lethality produced in post meiotic germ cell stages results from large deficiencies.^{47,48} It is not known what proportion

is contributed by simple deletions and what proportion is the result of unbalanced segregants of interchanges, but the existing data allow us to estimate that man might be anywhere from equally to twice as sensitive as the mouse.

None of these assumptions take into consideration the possibility of varying degrees of selection operating against the aberration bearing cells in different species. There is evidence that such selection occurs in the mouse⁴⁹ and the possibility of lesser, or greater, selection in man introduces an uncertainty in the extrapolations.

Current gaps in our knowledge and problems of future interest. The great majority of data on the cytological effects of ionizing radiation on germ cells has been accumulated from studies on males and very little information is available on the effects on female germ cells. New techniques⁵⁰⁻⁵² for analyzing oocyte meiosis will enable researchers to collect data on translocation and deletion induction in both mature and embryonic females.

Although there is a plethora of data on the induction of translocations by chronic exposures in the male mouse, no comparable data exist for other mammalian species. Although the mouse data show that the translocation frequency is lower at reduced dose rates at the lower (< 400 R) doses,^{53,54} the possibility exists that the well documented loss of translocation bearing cells following acute exposures might be greater in other species. This could conceivably result in spuriously low yields with acute exposures and a higher recovery rate with chronic exposures due to the complexities introduced by the interaction of cell killing and translocation induction.

Just recently two articles appeared that report a failure to induce translocations in embryonic male mice.^{55,56} We have data that is contrary to these reports in that we observed no significant differences in the translocation yields observed in irradiated 13-1/2 day fetuses, newborns, and young adults. More information is needed here.

Comprehensive cytogenetic studies on the effects of low dose and chronic dose rate exposures are possible because of the relative ease of analyzing thousands of cells. Such studies on the mouse, coupled with more interspecific comparisons, should enable us to make highly meaningful predictions of man's hazards. It appears that the first "bridge" between mouse and man has been made and the next few years should result in the filling of many of the gaps in our knowledge.

REFERENCES

1. United Nations Scientific Committee on the Effects of Atomic Radiation, General Assembly Document, 17th Session, Suppl. No. 16 (A/5216). United Nations, N. Y. (1962).
2. Moorehead, P. S., P. C. Nowell, W. J. Mellman, D. M. Battips and D. A. Hungerford, Exptl. Cell Res. 20 (1960) 613-616.
3. Bender, M. A, and P. C. Gooch, Proc. Natl. Acad. Sci. U.S. 48 (1962) 522-532.
4. Gooch, P. C., M. A Bender, and M. L. Randolph, In "Biological Effects of Neutron and Proton Irradiation." Vol. I, pp 325-342. I.A.E.A., Vienna (1964).
5. United Nations Scientific Committee on the Effects of Atomic Radiation, General Assembly Document, 24th Session, Suppl. No. 13 (A/7613). United Nations, N. Y. (1969).
6. Bender, M. A, In L. G. Augenstein, R. Mason, and M. Zelle (Eds.) "Advances in Radiation Biology," Vol. 3, Academic Press, New York, pp 215-275 (1969).
7. Brooks, A. L. and F. W. Lengemann, Radiation Res. 32 (1967) 587-595.
8. Conger, A. D., Radiation Botany 5 (1965) 81-96.
9. Grote, S. J. and S. H. Revell, In "IVth Intern. Congr. Radiation Res., Evian, France" (1970) Abstract 332.
10. Muller, H. J., In A. Hollaender (Ed.) "Radiation Biology," Vol. I, McGraw-Hill, New York, pp 351-626 (1954).
11. Buckton, K. E. and P. Nettesheim, Proc. Soc. Exptl. Biol. Med. 128 (1968) 1106-1110.

12. Brewen, J. G. and R. D. Brock, Mutation Res. 6 (1968) 245-255.
13. Brewen, J. G. and N. Gengozian, Mutation Res. 13 (1971) 383-391.
14. Preston, R. J., J. G. Brewen and K. P. Jones, Intern. J. Radiation Biol. 21 (1972) 397-400.
15. Clemenger, J. F. P. and D. Scott, Intern. J. Radiation Biol. 24 (1973) 487-496.
16. Conger, A. D. and A. H. Johnston, Nature 178 (1956) 271.
17. Swaminathan, M. S. and A. T. Natarajan, Nature 179 (1957) 479-480.
18. Evans, H. J., Genetics 46 (1961) 257-275.
19. Griffin, C. S., D. Scott, and D. G. Papworth, Chromosoma 30 (1970) 228-249.
20. Brewen, J. G., R. J. Preston, K. P. Jones, and D. G. Gosslee, Mutation Res. 17 (1973) 245-254.
21. Brewen, J. G. and R. J. Preston, Nature New Biology 244 (1973) 111-113.
22. Sax, K., Genetics 25 (1940) 41-68.
23. Heddle, J. A., Genetics 52 (1965) 1329-1334.
24. Caspersson, T., U. Haglund, B. Lindell, and L. Zech, Exp. Cell Res. 75 (1972) 541-543.
25. Seabright, M., Chromosoma 40 (1973) 333-346.
26. San Roman, C. and M. Bobrow, Mutation Res. 18 (1973) 325-331.
27. Chandley, A. C., S. Christie, J. Fletcher, A. Frackiewicz, and P. A. Jacobs, Cytogenetics 11 (1972) 516-533.
28. Preston, R. J. and J. G. Brewen, Mutation Res. 19 (1973) 215-223.
29. Brewen, J. G. and R. J. Preston, Mutation Res., in press.
30. Léonard, A. and Gh. Deknudt, Radiation Res. 40 (1969) 276-284.

31. Lyon, M. F. and T. Morris, Mutation Res. 8 (1969) 191-198.
32. Evans, E. P., C. E. Ford, A. G. Searle and B. J. West, Mutation Res. 9 (1970) 501-506.
33. Muramatsu, S., W. Nakamura, and H. Eto, Japan. J. Genet. 46 (1971) 281-283.
34. Léonard, A. and Gh. Deknuddt, Radiation Res. 45 (1971) 72-79.
35. Lyon, M. F., T. Morris, P. Glenister, and S. E. O'Grady, Mutation Res. 9 (1970) 219-223.
36. Morris, T. and S. E. O'Grady, Mutation Res. 9 (1970) 411-415.
37. Searle, A. G., C. V. Beechey, E. P. Evans, and C. E. Ford, Mutation Res. 15 (1972) 169-174.
38. Lyon, M. F., and B. D. Smith, Mutation Res. 11 (1971) 45-58.
39. Ford, C. E., A. G. Searle, E. P. Evans, and B. J. West, Cytogenetics 8 (1969) 447-470.
40. Ford, C. E. and H. M. Clegg, Brit. Med. Bull. 25 (1969) 110-114.
41. Lejeune, J., B. Dutrillaux, and J. de Crouchy, In P. A. Jacobs, W. H. Price and P. Law (Eds.) "Human Population Cytogenetics," Williams and Wilkins, Baltimore, pp 82-87 (1970).
42. Generoso, W. M., Biology Division Annual Progress Report, ORNL, in preparation.
43. Brewen, J. G., R. J. Preston and W. M. Generoso, ibid.
44. Russell, L. B., Mutation Res. 11 (1971) 107-123.
45. Erickson, R. P., G. M. Eicher and S. Gluecksohn-Waelsch, Nature 248 (1974) 416-418.
46. Luning, K. G. and A. G. Searle, Mutation Res. 12 (1971) 291-304.

47. Lifschytz, E. and R. Falk, Mutation Res. 6 (1968) 235-244.
48. United Nations Scientific Committee on the Effects of Atomic Radiation, General Assembly Document, 21st Session, Suppl. No. 14, (A/6314), United Nations, N. Y. (1966).
49. Gerber, G. B. and A. Léonard, Mutation Res. 12 (1971) 175-182.
50. Donahue, R. P., In "4th International Congress of Human Genetics, Paris, 1971," Excerpta Medica (1971) 233.
51. Hansmann, I., Mutation Res. 20 (1973) 353-367.
52. Hoppe, P. C. and S. Pitts, Biology of Reproduction 8 (1973) 420-426.
53. Searle, A. G., E. P. Evans, C. E. Ford, B. J. West and D. G. Papworth, Mutation Res. 6 (1968) 427-436.
54. Searle, A. G., C. V. Beechey, M. J. Corp and D. G. Papworth, Mutation Res. 15 (1972) 89-91.
55. Ivanov, B., A. Léonard, and Gh. Deknudt, Mutation Res. 18 (1973) 89-92.
56. Tsuchida, W. S. and I. A. Uchida, Mutation Res. 22 (1974) 277-280.

Table 1. Frequencies of dicentric chromosomes per 100 cells observed in the peripheral leukocytes of different species following irradiation with various doses of X rays.

Dose (R)	<u>W. bicolor</u> 19 [†]	<u>C. griseus</u> 38	<u>M. musculus</u> 40	<u>S. scrofa</u> 64	<u>H. sapiens</u> 81	<u>S. fuscicollis</u> 83
0	0	0	0.3 ± 0.3	0	0	0
50	0.3 ± 0.3	1.6 ± 0.6	2.3 ± 0.9	1.3 ± 0.7	4.3 ± 0.8	6.5 ± 1.8
100	1.0 ± 0.6	6.0 ± 1.5	6.7 ± 1.5	10.0 ± 1.8	13.2 ± 1.5	12.7 ± 2.0
150	5.4 ± 0.9	-	-	19.7 ± 2.6	20.8 ± 1.9	34.3 ± 3.4
200	9.5 ± 1.5	12.6 ± 1.6	14.3 ± 2.2	27.0 ± 3.0	33.7 ± 2.4	50.3 ± 4.1
300	23.0 ± 2.8	30.3 ± 2.8	31.3 ± 3.2	61.0 ± 4.5	67.5 ± 3.4	80.0 ± 5.2
400	51.3 ± 4.1	51.4 ± 3.8	55.0 ± 3.7	92.7 ± 5.6	120.5 ± 4.5	-

†

The numbers below the species' names indicate the "effective arm number."

Table 2. Frequencies of deletions per 100 cells observed in the peripheral leukocytes of different species following irradiation with various doses of X rays.

Dose (R)	<u>W. bicolor</u> 19†	<u>C. griseus</u> 38	<u>M. musculus</u> 40	<u>S. scrofa</u> 64	<u>H. sapiens</u> 81	<u>S. fuscicollis</u> 83
0	2.6 ± 0.6	0.5 ± 0.4	0	0	0.3 ± 0.2	0
50	5.3 ± 1.1	2.4 ± 0.7	2.0 ± 0.8	4.7 ± 1.2	4.2 ± 0.8	5.0 ± 1.6
100	6.7 ± 1.5	8.3 ± 1.4	3.0 ± 1.0	7.7 ± 1.6	6.0 ± 1.0	11.0 ± 1.9
150	15.1 ± 1.5	-	-	22.0 ± 2.7	8.8 ± 1.2	24.3 ± 2.8
200	23.8 ± 2.4	15.8 ± 1.8	16.7 ± 2.4	32.3 ± 3.3	15.8 ± 1.6	32.0 ± 3.3
300	50.0 ± 4.1	38.8 ± 3.1	29.3 ± 3.1	69.3 ± 4.8	33.8 ± 2.4	53.7 ± 3.3
400	114.7 ± 6.2	61.4 ± 4.2	52.8 ± 3.5	105.0 ± 5.9	61.8 ± 3.2	-

† The numbers below the species' names indicate the "effective arm number."

**Table 3. Frequencies of Reciprocal Translocations in Primary Spermatocytes After
Spermatogonia Irradiation of Several Mammals**

Dose (R)	Mouse	Ch. hamster	Guinea Pig	Guinea pig [†]	Rabbit [†]	Marmoset
0	0	0	0	0	0.15 ± 0.2	0
25	-	-	-	-	-	2.8 ± 0.7
50	0.7 ± 0.3	1.0 ± 0.6	1.4 ± 0.6	-	-	3.4 ± 0.8
100	1.5 ± 0.5	2.0 ± 0.8	2.7 ± 0.9	0.85 ± 0.6	-	7.5 ± 1.1
200	4.3 ± 0.8	4.3 ± 1.2	6.1 ± 1.1	4.62 ± 0.9	-	7.3 ± 2.2
250	-	-	-	-	1.17 ± 0.4	-
300	7.8 ± 1.1	-	8.0 ± 2.0	-	5.79 ± 0.9	6.7 ± 1.5
400	13.5 ± 1.3	-	-	0.31 ± 0.2	-	-
500	17.0 ± 1.5	-	-	-	0.23 ± 0.2	-
600	19.5 ± 1.6	-	-	-	0	-

³⁸
† Data of Lyon and Smith.

Table 4. Frequencies of cytologically scored and genetically recovered reciprocal translocations following irradiation of spermatogonial stem cells

Dose (R)	% Translocations scored*	No. F ₁ males tested	% Translocations Heterozygotes Minimum**	Ratio recovered/scored
0	0.0	2,633	0.0	-
150	2.5 (2.5)	1,122	0.62	.25
300	7.8 (5.7)	1,053	0.95	.12
600	17.2 (16.2)	1,062	1.90	.11
1,200	8.6 (8.6)	1,038	0.58	.07

* Numbers in brackets are percentages of cell with a single translocation.

** Minimum frequency of translocation heterozygotes are the cytologically confirmed semi-steriles.

FIGURE LEGENDS

- Fig. 1. Best-estimate regression curves for dicentric production in six mammalian species.¹³
- Fig. 2. Best-estimate regression curves for dicentric yields vs. chromosome arm number in six mammalian species. Observed yields are plotted with standard errors at each of the four doses considered.¹³
- Fig. 3. Log-log plot of chromosome exchange yield and X-ray dose for the pooled Chinese hamster and mouse leukocyte data and the mouse spermatogonial stem cell data. ○—○, Mouse leukocytes; △—△, hamster leukocytes; ●—●, mouse spermatogonia; ▲—▲, hamster spermatogonia.
- Fig. 4. Log-log plot of reciprocal translocations, induced in spermatogonia and observed in primary spermatocytes, and X-ray dose for the mouse (solid line), guinea pig (▲) and marmoset (○). The shaded areas represent the range of expected yields for guinea pig (▨) and marmoset or man (▩).

26602

Fig 1

26603

Fig. 2

Fig. 4