A CRITIQUE OF THE USE OF MOUSE GENETIC DATA IN ESTIMATION OF THE HAZARD OF RADIATION TO HUMANS, BOTH SOMATIC AND GENETIC

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Chairman Chet Holifield, of the Joint Committee on Atomic Energy, recently produced the following incorrect statement, misusing the extensive mouse genetics researches of Drs. William and Liane Russell (3 — 22). Let us quote Chairman Holifield during his exchange of recorded conversation with Rep. Jonathan Bingham of New York (1).

Chairman Holifield:

> "It is true that the standards of, let us say, 170 milliroentgens a year exposure to the population is set by the Federal Radiation Council and the International Commission on Radiological Protection as being abundantly safe by a factor it so happens — well, originally thought to be 10, but in testimony several weeks ago before the committee by Dr. Russell, it was said if we had known at the time what we know today about the effect of radiation on mammals, we could have just as well set it at one roentgen; in other words, six times as high, 1000 millir oentgens in the place of 170 milliroentgens.
>
> "But he said we had not experimented to the point where we were sufficiently confident so we arbitrarily put a very high standard there based upon the judgment of the scientific people who understand about radiation.
>
> "He said we could have gone six times as high. We could have set the permissible dose at a roentgen which is 1000 milliroentgens. "

Undoubtedly Dr. William Russell must be more than a little surprised to read the misstatement and misinterpretation of his own testimony, to which we shall return later.

First, there exists no evidence anywhere in the world to support the cavalier statement by Chairman Holifield that the 170 milliroentgen per year exposure limit is abundantly safe by any factor like six_or ten. Indeed, it is not safe, period! "Chairman Holifield has apparently missed all the evidence concerning the cancer-leukemia risk from radiation, and he has distorted the implications of Dr. Russell's testimony concerning genetic hazard to man.

From our own estimate of an additional 32, 000 cancers and leukemias per year for 170 millirad average exposure per year. Chairman Holifield's "abundantly safe" means 192,000 to 320,000 additional cancers per year (23).

From Pauling's estimate (24) of an additional 96, 000 cancers per year for 170 millirad average exposure per year; Chairman Holifield'.s "abundantly safe" means 576, 000 to 960, 000 extra cancer deaths per year.

From Dr. R. H. Mole's (United Kingdom Atomic Energy Authority) estimate (25), which would lead to 10, 000 — 20, 000 additional cancers plus leukemia deaths per year. Chairman Holifield's "abundantly safe" means 60, 000 to 120, 000 extra cancer deaths per year.

Even, finally, from AEC's Dr. Victor C. Bond's "conservative" estimate of 3200 extra cancer deaths per year for 170 millirads (26), Chairman Holifield's "abundantly safe" would mean 19, 200 to 32, 000 additional cancer plus leukemia deaths per year.

So Chairman Holifield of JCAE, boldly misquoting Dr. Russell, indicates that between 19, 200 and 960, 000 extra cancer deaths per year is abundantly safe, to say nothing of the additional massive genetic death toll that would result.

What did Dr. Russell really say in his testimony and how defensible are his statements?

Under the title "Genetic Risk One-Sixth the Former Estimate" the following exchange occurred in those same JCAE Hearings.

> Dr. Russell: "Putting these and other pieces of information together, we conclude that our present best estimate of the average genetic risk from exposure of both sexes at low dose rates or low doses is one-sixth of what it was estimated to be when the currently used figure for maximum permissible dose was chosen. "
>
> Chairman Holifield: "Now let us analyze that. What you are really saying there is, that your conclusion is 'our present best estimate of the average genetic risk from exposure of both sexes at low dose rates or low doses is only about one-sixth.of what it was estimated to be when the currently used figure for maximum permissible dose was chosen. '[1]'
>
> Dr. Russell: "What this argues is that the 170 milliroentgens would cause about one-sixth of the damage that was originally estimated. "
>
> Chairman Holifield: "That is how it should be stated. I agree. I am not suggesting that it be lowered, but I am trying to accent the prudence of the level of 170 milliroentgens. In fact it is more conservative today, according to your experiments than it was at the time it was set with the data we had at that time. "

From this exchange, in which Russell says absolutely nothing about the cancer-leukemia risk, Chairman Holifield derives the utterly erroneous and absurd conclusion that the Federal radiation standards are "abundantly safe"----- could even be raised 6-fold, according to Holifield.

Similar nonsensical statements concerning "new evidence" which indicates the radiation standards were too conservative abound from Tompkins, Executive Director of the Federal Radiation Council (27) and Taylor of the National Committee on Radiation Protection (28).

Since the Holifield, Tompkins, and Taylor statements all have their origins from the mouse genetics data of Russell and Russell, we must examine these data closely. As they are examined, there are certain questions we must ask ourselves:

(1) Was the estimate of genetic hazard made when the standards were set at all reasonable?

(2) Do the Russell data really indicate that the hazard is 1/6 of these estimates?

(3) Even if the Russell data are optimistically interpreted, would we consider the genetic hazard of the radiation standards to be reasonable now?

Gofman and Tamplin (23, 29) have estimated that exposure of the U. S. public at an average of 170 millirads per year would lead to a 5% to 50% increase in mutation rate. This estimate is based upon a 30-year accumulation of 5 rads (30 X 0. 17), 30 years being taken as average reproductive age, and a doubling dose between 10—100 rads from UNSCEAR estimates'(30).

Since the evidence is now convincing that most of the serious diseases causing premature deaths have a multi-gene component of etiology (31), the conservative approach is to consider 100% of causes of death as having a genetic origin. One could quibble about removal of accidental deaths, but in any event at least 50% of all deaths are already firmly in the category of being due to diseases with a multigene component, for example atherosclerosis and coronary heart disease. The conservative approach means that a 5% to 50% increase in mutation rate will, in some as yet undetermined number of generations, lead to a 5% to 50% increase in annual death rate from genetically-determined diseases.

For ZOO million people, this means 100,000—1,000,000 extra deaths/year

For 300 million people, this means 150,000— 1,500,000 extra deaths/year.

Lederberg, independently, has also assessed the impact of the multigene origin of common diseases (32). His .calculation indicates that currently allowable radiation exposures of 170 millirads per year will lead to a 10% increase in mutation rate. (Compare with 5 — 50%, of Gofman and Tamplin.) Lederberg does not calculate extra annual genetic deaths. Instead he estimates the medical and health care burdea cost for such radiation exposure. His estimate is 10 billion dollars annually in additional medical and health costs (range 1 billion—100 billion dollars). Lederberg indicates that in all likelihood at least 50% of disease is genetic in origin.

When the present "permissible" radiation doses were set, genetie considerations by the "standard setters" must obviously have overlooked essentially all of the important genetically-determined multigene diseases. One cannot fault the "standard-setters" for not knowing these diseases had a genetic component, for the knowledge was not available then. One can fault them for not realizing that knowledge is always incomplete at any point in time. If by any chance the "standard-setter s " did know about the multigene diseases at that time, and still set the standards as they did, this could only mean gross irresponsibility in a public health sense.

Let us now examine the Russells' researches and the bearing such researches might have on the Gofman-Tamplin or Lederberg estimates of genetic hazard.

The Russell studies are called specific locus studies, based upon observations of seven visible traits in the mouse. Russell states that the relevant cell stages, in assessing genetic hazard of radiation, are the spermatogonia of the male and the oocytes of the female. This argument of Russell is very reasonable.

The Russell factor of 1/6 comes about as follows. Studies of the seven visible traits in the male mouse show that for extremely high total doses, 300 r or more, acute x-ray exposure (90 r/min) produces approximately three times as many mutations as does chronic radiation

(y-rays at dose rates 0.8 r/min, 0.009 r/min, and 0.001 r/min). The experimental data support this three-fold difference for male spermatogonia for 300 r or more. As we shall see later, there is no reason to believe any appreciable difference between acute and chronic radiation would be observed for total doses of 50 r or less, the truly relevant exposure region for man (34).

This then is the source of the factor of 3 that is incorporated into the Russell "optimism" factor of 6. The other part derives from the study of oocytes in the female mouse. Russell claims to have discovered a threshold dose rate in the female oocyte response to chronic radiation. And therefore Russell eliminates mutations in the female from consideration altogether, thus changing the three-fold "optimism" factor to six-fold. As we shall show below, this so-called threshold dose rate has by no means been proven within the Russell experimental data. Further, this optimistic assessment of the female mouse data neglects, with no justification at all, a large body of Russell's own data on the female mouse which indicates the female to be as sensitive as or more sensitive than the male mouse.

Do any of the Russell findings on protracted radiation alter the exceedingly high hazard estimates of "permissible" radiation exposures, as calculated either by Gofman-Tamplin or by Lederberg? We submit they certainly do not, and we shall show this by analyses of the Russell data both for the male and female mouse, in turn.

The Data for the Male Mouse

If the most optimistic interpretation of the Russell male mouse genetics data is chosen, will it alter the 10 tq 100 rad estimate of doubling dose used by Gofman-Tamplin? Since the Lederberg estimate uses 50 rads as doubling dose, we need only consider the 10—100 rad estimate. For if the disheartening genetic death projections from Gofman-Tamplin or Lederberg are to be materially altered, this can only occur if the Russell mouse genetic data lead to a very much higher doubling dose than 100 rads. This they do not do.

How can we arrive at a doubling dose for genetic mutation in the male mouse from the Russell data? To do this for any particular genetic locus requires the spontaneous mutation rate for that locus and the radiation-induced mutation rate.

Russell points out (20):

> " (1) Radiation-induced mutation frequency varies markedly with gene locus. In spermatogonia, where the data are most extensive, the difference between loci with the lowest and highest mutation rates, for the seven loci tested, is more than thirty-fold.
>
> " (2) Information on the distribution of spontaneous mutation rates among the loci is not yet extensive. As far as it goes, it shows some differences from that for induced rates in spermatogonia, but the general pattern appears to be similar. [11]

From these statements that the spontaneous mutation rates for individual loci are not known, we realize Russell is in no position to

determine doubling doses for specific gene-loci. He cannot therefore know how the seven loci compare with each other in radiation-sensitivity. And lastly, Russell cannot possibly know how the mouse data should be extrapolated to man.

Least embarrassing to Russell's statement that the standards may have been too conservative with respect to genetic hazard estimate would be for no genetic locus to be inordinately sensitive to radiation mutation, that is for no genetic locus to show an inordinately low doubling dose for mutation, when contrasted with other sites. If all the loci are to have equivalent doubling doses, one requirement is that the spontaneous mutations must have the same relative frequency spectrum as do the radiation-induced mutations. We shall use this assumption first, since it is least embarrassing to the Russell statement. Thereafter, we can consider other assumptions which would operate to make the genetic hazard much more perilous.

Russell's overall data (12) for the seven loci as a group are reproduced in Table I (for spermatogonia in the male mouse).

TABLE I

Effect of Radiation Dose Rate on Mutation Frequency in Mice

Reproductive cells irradiated	Radiation source	Approximate dose rate (r/min)	Dose (r)	Number of offspring	Number of mutations at 7 loci	Mean no. of mutations per locus per gamete X 10^5
Spermatogonia	Y-rays (Cs-137)	—	0	531,500	28	0.8
		0.001	86	59,800	6	1.4
		0.001	300	49,569	15	4.3
		0.001	600	31,652	13	5.9
		0.009	300	58,457	10	2.4
		0.009	516	26,325	5	2.7
v	v	0.009	861	24,281	12	7.1

■ Fig. 1, using the best linear fit (as per Russell)

0.001 r /min and 0.009 r/min. Russell has

pointed out that between 0.8 r/min and 0.001 r/min, there is no significant reduction in mutation rate per roentgen. Thus the plot of Fig. 1 represents the most optimistic (low) genetic hazard of mutations in the spermatogonial cells of the male mouse achievable through dose rate protraction.

From Fig. 1, it is estimated

For 600 r (from Russell's best linear fit) . 4.8 (mutations per locus per gamete) X 10^{-5}

For Or (spontaneous rate) 0.

Difference 4.0

$$\text{Doubling doses} = \frac{\text{radiation induced excess}}{\text{spontaneous}} = \frac{4.0}{0.8} = 5.0$$

Therefore 600 r represent 5 doubling doses, or $\frac{600}{5}$ = 120 r

for one doubling dose. Converting r units to rads (factor = 0. 83)

120 X 0. 83 = 100 rads as the doubling dose, for the average of the seven visible traits in spermatogonia.

Thus with the most favorable interpretation of the Russell male mouse data, crediting all the available protection due to low dose rate, we end up with a doubling dose of 100 rads, which is precisely one of the limits used by Gofman and Tamplin. If the Russell estimate for male mouse is extrapolated directly to man, this would correspond to the 100, 000 extra genetic deaths per year for a population of 200 million people. It is hard to see how Russell could interpret his male mouse data as suggesting the standards may have overestimated the seriousness of radiation-induced genetic hazard for man. It can be stated, however, that since Lederberg used 50 rads as doubling dose, the Russell data would lead to a 5 billion dollar burden annually for health and medical care at "permissible" standards instead of 10 billion dollars per year. Thus, the most favorable interpretation of Russell's data on the male mouse genetics is anything but comforting with respect to safety of standards for human exposure, standards unfortunately still codified in Federal Regulations.

We must now consider several possibilities that make the Russell findings even more disquieting. Russell states (9):

> "From additional confirmatory experiments in the mouse and the collection of data from a closely parallel experiment with irradiation of Drosophila spermatogonia, the best estimate of the magnitude of the difference is that the induced mutation rate per gene locus in the mouse is fifteen times the Drosophila rate. On the. assumption that the response in man may resemble that of the mouse more closely than that of Drosophila, estimation of human mutation rates, and consequent genetic hazards, are now considered to be greater than had been calculated before on the basis of the Drosophila results. ″

We are certain, with such a drastic increase in sensitivity between Drosophila and mouse, that Dr. Russell has seriously contemplated the eminently reasonable possibility that man might be appreciably more sensitive than the mouse. UNSCEAR indicates chromosomes of monkey to be more sensitive to radiation'than of mouse (30). It would not be unreasonable to consider man may be at least as sensitive as the monkey. Since the most favorable interpretation of the low dose rate data of Russell leads to 100 rads as doubling dose and 100, 000 extra genetic deaths annually, such a mouse to man change in sensitivity would lower the 100 rad doubling dose and raise the 100,000 extra deaths per year'from genetic diseases. If man is more sensitive than mouse, even Russell's most favorable data on low dose rate could lead him even to more pessimistic estimates of hazard than either Gofman- Tamplin or Lederberg.

Thus far we have addressed only the most optimistic interpretation of the Russell results, namely where the doubling dose for genetic mutations is identical for all loci. As shown above, Russell concedes he doesn't know the spectrum of mutation frequencies for the spontaneous mutations among

the seven loci. If the spontaneous mutation rates do not show the same relative frequencies as do the radiation-induced mutations, then some of the loci will necessarily show doubling doses below 100 rads, others, above 100 rads. How much below 100 rads? No one knows. How the critical loci in humans related to such a multi-gene disorder as coronary artery atherosclerosis will compare in radiation sensitivity with the possibly highly sensitive mouse loci, no one knows.

Viewing all the Russell mouse genetic data for the male mouse in the most optimistic fashion, we are finally left with nothing but chilling prospects with respect to the human genetic hazard from radiation at the "permissible" standards. We believe Dr. Russell would agree with this concern.

We must finally return to the 3-fold factor of Russell, claimed to develop from the male mouse data. If, indeed, the "standard-setters[11] did use acute, high dose rate data to estimate the genetic hazard, the doubling dose they would have been led to is $\frac{100}{3}$, or 33 rads. Thus instead of 100, 000 extra genetic deaths per year resulting from Russell's male mouse data, one would, estimate 300, 000 extra genetic deaths per year. A more appropriate statement by Dr. Russell would have been that the current "permissible"standards would lead to a massive calamity in public health before his discoveries, and just to a major calamity (1/3 as high as massive) as a result of the most favorable interpretation of his excellent data on the male mouse.

The Data for the Female Mouse

The two major optimistic conclusions from the Russell female mouse data are the following:

(1) There is a threshold dose rate below which mutations are not induced in oocytes of the .female mouse.

(2) The oocytes are grossly less sensitive to mutation by low-dose rate radiation than are spermatogonia.

Neither of these conclusions can be supported by the Russell data for the female mouse, as we shall show by analysis of those data.

The oocyte is the cell stage considered relevant for genetic hazard evaluation in the female mouse, according to Russell. There is no reason to disagree with this premise of Russell. For high total doses (400 r), Russell has unquestionably demonstrated that mutation frequency in oocytes is greater at high dose rate (90 r/min) than at low dose rate (0. 009 r/min). We shall, therefore, focus upon the most favorable data on the female mouse, namely, the data for low dose rate since this should lead to the least serious hazard estimate for the female mouse.

The Russell data for the female mouse oocytes are sparse, compared to the data for the male spermatogonia. Russell presents data, in various of his publications, for female mice at two ages (when irradiated):

2 — 4-month-old female mice (Reference 33)

6 — 9-month-old female mice (Reference 33).

It is of the greatest interest to note that Russell's data indicate that the 6 —9-month-old female mice are as sensitive to radiation mutation induction in oocytes, or more sensitive, than male mice spermatonia! The 2 — 4-month-old mice show an oocyte sensitivity much lower than spermatogonial sensitivity. The comparisons for the two groups of female mice are presented in Table.II, reproduced from the Russell data of Reference 33.

TABLE II (From Reference 33)

Effect of Age and Parity on Mutations Induced in Oocytes of Mice Exposed to 400 r

Approx. dose rate r/min	All litters of young females and first litters of older females ("young" females are 2 — 4 months of age at irradiation)			Second (plus later) litters of older females ("older" females are 6 — 9 months of age' at irradiation)		
	No. of offspring	No. of mutations at 7 loci	Mean no. of mutations per locus per gamete X 10^5	No. of offspring	No. of mutations at 7 loci	Mean no. of mutations per locus per gamete X 10^5
0. 009	44,811	2	0. 64	7321	2	3. 90
0. 8	61,771	18	4. 16	9094	12	18. 85
90	11,124	15	19. 26	No data presented by Russell		

^Russell states that first litters of older females show mutation rates like those of younger females.

The striking observations to be noted in the data for Table II are the following:

(1) Both at 0. 009 r/min and 0. 8 r/min (the low dose rate regimes) the older females show oocyte mutation rates in the neighborhood of

five to six times as high as the radiation-induced mutation rates in the younger females.

(2) At 0. 8 r/min ("chronic low dose rate") the older females are showing oocyte mutation rates as large as younger females at 90 r/min (acute radiation).

(3) The older females show a higher mutation rate (or at least comparable) in oocytes than is noted for male spermatogonia (Table I) at the same total dose and dose rate, 400 r total and 0. 009 r/min.

From Table II, for older females, 3. 90 (mutations) X 10^{5}

(Fig. 1) From Table 1, for males, ~3. 0 (mutations) X 10^{5}

(The observed female mutation rate is higher than the male rate. While this difference cannot be proved significant, it certainly indicates the mutation rates for males and "older" females is, at least, comparable in magnitude.)

After examining these findings, one must simply disagree with Russell's recent conclusions, indicating that mutations in the female mouse can be neglected in assessing human hazard. The data Russell presents indicate, depending upon age and parity, female oocytes may be more sensitive or less sensitive than male spermatogonia. Nowhere in any of his publications does Russell justify choosing the 2 — 4-month female mouse for his evaluation of human genetic hazards. Female mice at 6 — 9 months

of age would be at a point approximately 1/4 of the mouse life span. What conceivable reason could Russell have for rejecting these data, and using only the younger female mouse data? He presents no justification.

Until and unless Russell presents an acceptable justification for this exclusion, there is no reason to consider his suggestion that the female oocytes should be considered less sensitive to radiation-induced mutations than are male spermatogonia. With the large uncertainties of extrapolation from the female mouse to human females, it is impossible to say which of the mouse data, for young or old females, is relevant for humans. We reject the Russell suggestion of a two-fold lowering of genetic hazard of radiation in women based upon the mouse data.

The Purported "Threshold Dose Rate" in the Female Mouse Oocyte

The Russell claim of a threshold dose rate for mutation in the female mouse oocyte is even less supportable than his selection of the oocyte data only for young female mice. Let us turn to the actual data which underlie this "threshold dose rate. " We shall find that the data do not support Russell's conclusion.

As for the male mouse analysis, the first step in considering doubling dose'for female oocyte mutations requires the spontaneous mutation rate as well as the radiation-induced mutation rates. Russell points out in numerous publications that he does not have a reliable estimate for the

spontaneous mutation rate in the female mouse oocyte, although it is, he states, lower than for the male spermatogonial cell. If Russell has no satisfactory estimate of the spontaneous rate of oocyte mutation, it is not possible to draw any conclusions at all concerning existence of a threshold dose rate for mutations in the female mouse.

Worse yet, examination of all the Russell publications reveals that the case for his "threshold dose rate" (already without support because of the absence of a spontaneous rate) rests upon one experiment with 1 observed mutation and another with 2 observed mutations. The standard errors are, of course, enormous. The best that can be said, reviewing this Russell evidence, is that no experiments of consequence have even been performed that permit of any statements concerning a threshold dose rate in the female.

Let us say that the low mutation rates (spontaneous or radiation-induced) in the 2 — 4-month female mouse do make the studies difficult, and do require more animals than for the male. It is obvious from the Russell data that 500, 000 mice would serve very well to study the question concerning oocyte mutation rate in the female mouse. Such studies would be required if a serious investigation of possible threshold dose rates were of interest.

If Russell truly believes that 0. 009 r/min represents a possible "threshold dose rate, [11] he himself has showed how the question could be studied, namely through the study of the 6 — 9-month female mice, as

reported in Table II. There the mutation rate for 0. 009 r/min appears to be as high as for the male spermatogonia or possibly higher. The data of Table II are too sparse to settle the issue, although they argue against any threshold dose rate. It is obvious that with 50, 000 mice committed to this study, the issue could readily be resolved with high statistical significance. Again we urge that an adequate study be performed.

In 1959 Russell did report some data concerning the spontaneous rate of mutations in mouse oocytes (22). There were 47, 612 gametes tested, with no mutants being found. The spontaneous mutation rate may therefore be as low as zero. The data (no mutations observed) are highly compatible with a mutation rate in the region of 0. 1 — 0. 2 (mutations per locus per gamete) $\times 10^{-5}$. Russell's sparse observations at 258 r and 400 r led him to a mean mutation rate of ~ 0. 65 (mutations per locus per gamete) $\times 10^{-5}$ for a mean dose of ~ 375 r. The standard error of this value is also large. What can assuredly be stated is that these data are entirely compatible (at high probability) with a doubling dose of 100 rads for female oocytes. Indeed, the doubling dose could be 10 rads and still be highly compatible with the observational data. So, not only do the Russell data suggest nothing concerning a threshold dose rale, they arc quite consistent with a radiation sensitivity, expressed in doubling dose, much higher for female oocytes than for male spermatogonia.

In summary, we reject completely all the Russell claims concerning genetic hazard of radiation in the female mouse. Not only do we reject the claim of a lesser radiation sensitivity for oocytes than for spermatogonia, but we find the sensitivity could'even be higher, since age of the female is proved by Russell to be important.

In 1970, Russell has repeated the profound claim of a threshold dose rate for mutation in the female mouse oocyte. He has, in Congressional testimony, further stated that this justifies consideration of a two-fold reduction in genetic risk for human radiation, presuming a threshold dose rate for females. This wholly unsupported claim is very dangerous, unless one understands that it is purely a speculation, based upon no acceptable evidence.

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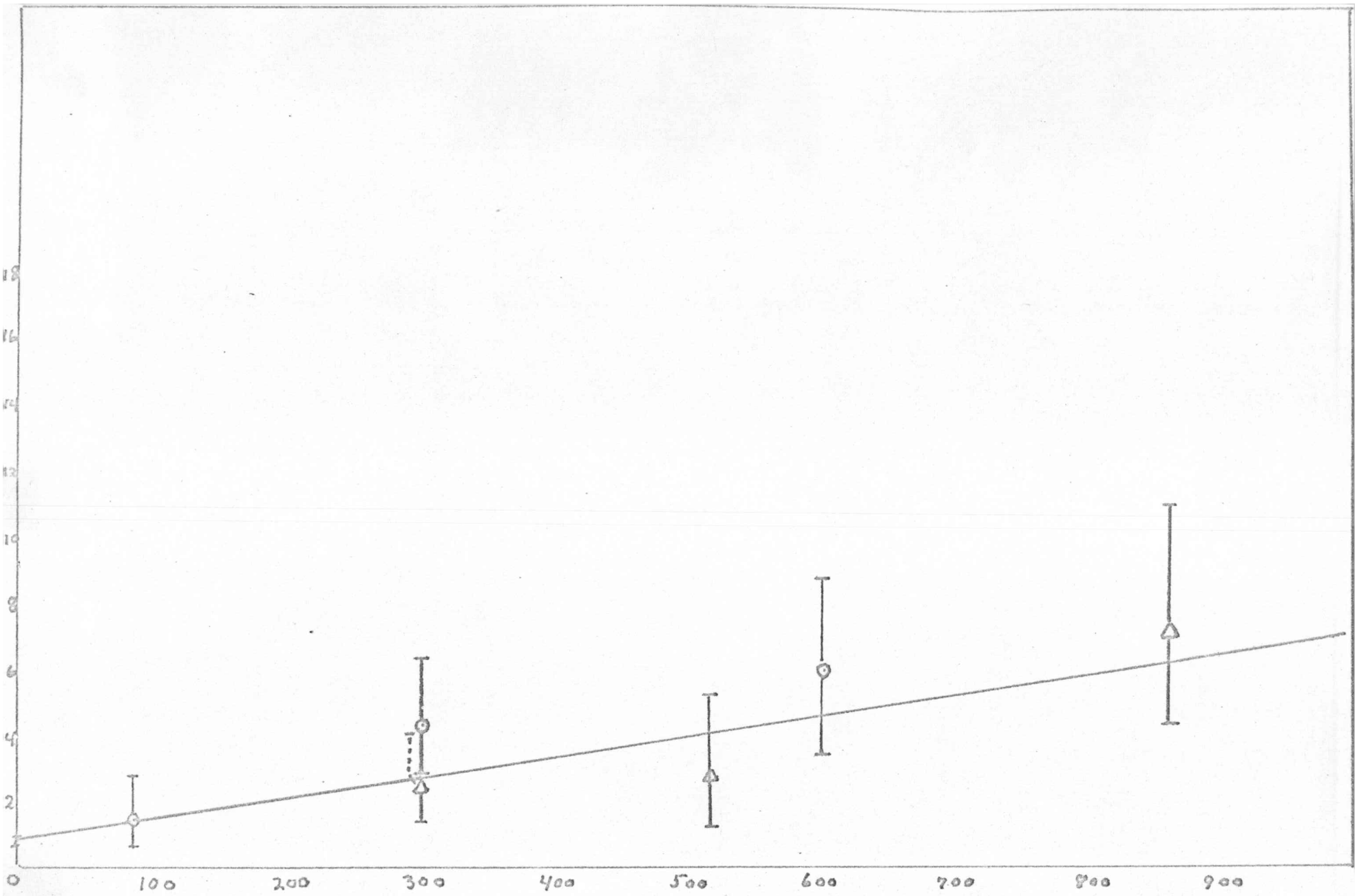

• Spontaneous
⊙ 0.001 r/min.
Δ 0.009 r/min.

Figure I
Specific Locus Mutation Rates
In Spermatogonia