SYMPOSIUM NO. 3: RADIATION GENETICS

Introduction by the Chairman

FUTURE RESEARCH IN MOUSE RADIATION GENETICS

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IN contrast to the other speakers on this symposium, who will be talking about new findings, I should like to devote my few introductory remarks as chairman to some of the things we have not yet discovered.

Suggestions for future research in radiation genetics have been made, from time to time, by various committees, for example, the United Nations Scientific Committee on the Effects of Atomic Radiation (1972). My suggestions do not attempt to be as broad as these. I am limiting myself to items in my own sphere of experience, namely, mouse genetics, and, within this field, to gene mutations and small deficiencies. Major chromosomal aberrations are not included. Consideration is given primarily to those problems which are the next logical extensions from the discoveries we have already made, and emphasis is placed on information that is still needed for an adequate estimation of genetic hazards of radiation.

For those who are not familiar with our work in the branch of mouse radiation genetics delineated above, the findings can be summarized by saying that we have concentrated on exploring, with the specific-locus method, the effect of various biological and physical factors on radiation-induced mutation frequency at a sample of seven gene loci. The biological factors included sex, cell stage, and interval between irradiation and fertilization. The physical factors were radiation dose, dose rate, dose fractionation, and radiation quality. The results uncovered a series of basic radiation genetic principles not suspected even from the extensive earlier work on Drosophila (W. L. Russell 1963, 1967, 1972, in press).

What remains to be discovered? The suggestions offered here fall into three main groups.

The first category consists simply of extensions of the studies on the effects of the various biological and physical factors on mutation frequency. These might be called clean-up operations.

One of these is the collection of more data on mutation frequency induced in mouse spermatogonia at very low radiation dose rates. The existing data show a marked effect of dose rate in the range from approximately 100 R/min, to 1 R/min, but no significant further reduction in mutation frequency as dose rate is reduced approximately 1000-fold to the very low rate of 0.001 R/min. These data are consistent with the view that a low plateau has been reached below which...

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mutation frequency will not be depressed by further reductions in radiation dose rate (Russell 1963).

However, a recent paper by Lyon, Papworth and Phillips (1972), while not rejecting the plateau concept, suggests two additional mathematical models. Our data had shown a somewhat higher mutation frequency at the lowest dose rate of 0.001 R/min than at the next higher dose rate of 0.009 R/min (Russell 1963). The difference is not statistically significant and, therefore, not at variance with a plateau concept. However, Lyon, Papworth and Phillips focus on this difference and propose two new mathematical relationships based on the strange concept that mutation frequency steadily increases as radiation dose rate is lowered below a point in the neighborhood of 0.01 R/min. As radiation dose rate becomes infinitely low, these models have mutation frequency per R becoming infinitely high.

An entirely different suggestion of what may be happening at low levels of radiation is provided by Newcombe (1973) and McGregor and Newcombe (1972). From their studies on embryo mortality following irradiation of trout sperm, they report a “beneficial” effect of low doses of radiation. The mortality was less than in the controls. The authors suggest that the low levels of radiation may have stimulated the repair processes into repairing part of the naturally occurring damage.

A detailed analysis of their data might reveal the presence of enough extra-binomial variation to throw some doubt on the degree of statistical significance of the “beneficial” effect claimed. However, taking the direction of the effect at face value, it is clear that the Newcombe and McGregor result on the one hand, and the Lyon, Papworth and Phillips suggestions on the other, deviate in opposite directions from the concept of a plateau mutation frequency per R at low levels of radiation.

The clean-up operation proposed, therefore, is the collection of more data to give greater precision to our estimates of mutation frequency at low radiation dose rates in mouse spermatogonia.

More precision is also desirable in our estimates of mutation frequency at low radiation dose rates in late dictyate oocytes. This oocyte stage is not easily killed by radiation, and, in this respect at least, is comparable to human oocytes.

Another mouse oocyte stage that is resistant to killing by radiation is that found at and shortly before birth. Selby (1971) has collected preliminary data on induced mutation frequency at high radiation dose rate in this stage, but more information should be obtained at both high and low dose rates.

The second category of suggestions for future research has to do with investigations on the actual nature and effect of the individual mutations induced by radiation. Some useful knowledge has already been obtained, for example, the viability of homozygotes of large samples of mutations obtained at the seven specific loci. In addition, painstaking work has provided information on the relative frequency of deficiencies and apparent gene mutations, as well as on the size of deficiencies induced, under various radiation conditions, in various germ-cell stages, in the dilute–shortear region (Russell 1971). This work has
recently been extended to include the region of the albino locus (Russell and DeHamer 1973). However, much more of this kind of information is needed. These studies have also been valuable in identifying a number of new functional units in small chromosomal segments surrounding the specific loci.

A vitally important requirement in the estimation of genetic hazards of radiation is knowledge on the effects of mutations in heterozygous condition. Some mutations, for example most of those induced at the s locus in the mouse, produce obvious and marked deleterious effects as heterozygotes. At some other loci, heterozygous damage, if any, is not obvious. Extensive tests, carefully designed to pick up small effects, will have to be made over a wide range of mutations before any general conclusions can be reached.

We are now attempting the induction of mutations at the hemoglobin loci (Russell, Vaughan and Jacobson 1972). If an adequate frequency is obtained, the hemoglobin variants, which can be characterized in minute detail, should provide valuable insight into the nature of induced mutations in the mouse.

The third category of what has not been found out yet represents probably the most serious lack in information necessary for the adequate estimation of genetic hazards of radiation in man. This is the nature, extent, and persistence of the actual anatomical and physiological damage expressed in the descendants of irradiated populations.

Some effects on the overall health and well-being of descendants of irradiated populations have been observed, but the bulk of the laboratory investigations, like the studies on human populations, have yielded somewhat equivocal results (Symposium 1964). They did not clearly establish whether the damage was really small or whether a sizable damage might have been obscured by the "background noise".

Some of our own explorations gave indeterminate results and were not pursued further. However, one investigation in our laboratory by Ehlisch (1966) seemed to give clear-cut and sizable effects. This was a study on skeletal damage in the offspring of irradiated male mice. More work is now being done along this line.

It is to be hoped that some other broad characteristics of the phenotype, in addition to the skeleton, will prove useful in filling in this serious gap in our knowledge. Mutation rates by themselves, whether they are measured by irradiation of germ cells in the living animal or, at the other extreme, in somatic cell cultures, will never provide adequate information on the phenotypic damage to be expected from the total mutational events in the population. Only by empirical investigations can such information be gained. Since the studies on irradiated human populations have not yet proved conclusive, some definitive results in the mouse would obviously be of value.

LITERATURE CITED


