January 20, 1950.

Dr. James Watson,
Dept. Bacteriology,
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Bloomington, Indiana.

Dear Jim:

Your question about the possibility of isolating balanced lethal diploids after irradiation is certainly a very pertinent one, and I wish I could give a positive answer. If balanced lethal diploids occur at all among the survivors of UV (either at the 10^{-1} or 10^{-6} level) they are not common, for I haven't been able to find any as yet. Nor have there been partial eliminations as one might expect from terminal breaks, which are described as the predominant effect of UV in higher organisms. The unit of inactivation seems to be the chromosome or nucleus - not the cell, because irradiated diploid cells appear to be converted to effectively haploid cells-, nor the recessive lethal gene- for no balanced lethal diploids that would be evidence for the occurrence of recessive mutations have been picked up. It would be incredible if no mutations occurred which, to the bacterium, made the "complete" medium the equivalent of "minimal" medium, on which the nutritional requirements act precisely like recessive lethals, but it would appear that a second mechanism is quantitatively predominant, and obscures recessive mutations. I have in mind a type of effect which would prevent a chromosome from proliferating, even in the company of unhit neighbours. This might be related to the division-inhibiting effects of UV in other organisms, and would imply that for bacteria, at least, the genic effects are less significant. On the other hand, such effects might be the result of actual hits on chromosome parts, such as the centromere, which are essential for its reduplication. The situation is a bit confused, but the only conclusion I have been able to draw even tentatively is that killing may not be due predominantly to lethal mutations. Atwood, with slightly different material and models, reaches about the same conclusion, although he has been able to find evidence that recessive lethal mutations at least do occur after UV. The next thing is, of course, to try X-rays, with which I will be very surprised to find the same picture.

Sincerely,

Joshua Lederberg

P.S. I've been looking at Werner Braun's unstable "segregating" B/r, but am convinced that this is merely mutation. JL