tic clarity and abounds in happy and stimulating allusions. It can not fail to suggest to every serious reader numerous subjects for further observational and theoretical investigation. In future editions the value of the book would be enhanced for the reviewer, and possibly also for other observational astronomers of slender mathematical attainments, by the interpolation of a chapter between III and IV giving a brief and as nearly as possible self-contained mathematical development of the whole theory. Reference could then be made forward from this chapter to the subsequent chapters, which would retain much their present form, for a detailed discussion of the various assumptions, for the quadrature of the differential equations, for the discussion of the opacity law and so on. I do not believe that such an interpolation would seriously interfere with the logical treatment of the theory, and it is conceivable that it might eliminate some of the many cross references, forwards and backwards, which are essential with the present arrangement.

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ARTIFICIAL TRANSMUTATION OF THE GENE

MOST modern geneticists will agree that gene mutations form the chief basis of organic evolution, and therefore of most of the complexities of living things. Unfortunately for the geneticists, however, the study of these mutations, and, through them, of the genes themselves, has heretofore been very seriously hampered by the extreme infrequency of their occurrence under ordinary conditions, and by the general unsuccessfulness of attempts to modify decidedly, and in a sure and detectable way, this sluggish "natural" mutation rate. Modification of the innate nature of organisms, for more directly utilitarian purposes, has of course been subject to these same restrictions, and the practical breeder has hence been compelled to remain content with the mere making of recombinations of the material already at hand, providentially supplemented, on rare and isolated occasions, by an unexpected mutational windfall. To these circumstances are due the wide-spread desire on the part of biologists to gain some measure of control over the hereditary changes within the genes.

It has been repeatedly reported that germinal changes, presumably mutational, could be induced by X or radium rays, but, as in the case of the similar published claims involving other agents (alcohol, lead, antibodies, etc.), the work has been done in such a way that the meaning of the data, as analyzed from a modern genetic standpoint, has been highly disputatious at best; moreover, what were apparently the clearest cases have given negative or contrary results on repetition. Nevertheless, on theoretical grounds, it has appeared to the present writer that radiations of short wave length should be especially promising for the production of mutational changes, and for this and other reasons a series of experiments concerned with this problem has been undertaken during the past year on the fruit fly, *Drosophila melanogaster*, in an attempt to provide critical data. The well-known favorableness of this species for genetic study, and the special methods evolved during the writer's eight years' intensive work on its mutation rate (including the work on temperature, to be referred to later), have finally made possible the finding of some decisive effects, consequent upon the application of X-rays. The effects here referred to are truly mutational, and not to be confused with the well-known effects of X-rays upon the distribution of the chromatin, expressed by non-disjunction, non-inherited crossover modifications, etc. In the present condensed digest of the work, only the broad facts and conclusions therefrom, and some of the problems raised, can be presented, without any details of the genetic methods employed, or of the individual results obtained.

It has been found quite conclusively that treatment of the sperm with relatively heavy doses of X-rays induces the occurrence of true "gene mutations" in a high proportion of the treated germ cells. Several hundred mutants have been obtained in this way in a short time and considerably more than a hundred of the mutant genes have been followed through three, four or more generations. They are (nearly all of them, at any rate) stable in their inheritance, and most of them behave in the manner typical of the Mendelian chromosomal mutant genes found in organisms generally. The nature of the crosses was such as to be much more favorable for the detection of mutations in the X-chromosomes than in the other chromosomes, so that most of the mutant genes dealt with were sex-linked; there was, however, ample proof that mutations were occurring similarly throughout the chromatin. When the heaviest treatment was given to the sperm, about a seventh of the offspring that hatched from them and bred contained individually detectable mutations in their treated X-chromosome. Since the X forms about one fourth of the haploid chromatin, then, if we assume an equal rate of mutation in all the chromosomes (per unit of their length), it follows that almost "every other one" of the sperm cells capable of producing a fertile adult contained an "individually detectable" mutation in some chromosome or other. Thousands of untreated parent flies were bred as controls in the same way as the treated

ones. Comparison of the mutation rates under the two sets of conditions showed that the heavy treatment had caused a rise of about fifteen thousand per cent. in the mutation rate over that in the untreated germ cells.

Regarding the types of mutations produced, it was found that, as was to have been expected both on theoretical grounds and on the basis of the previous mutation studies of Altenburg and the writer, the lethals (recessive for the lethal effect, though some were dominant for visible effects) greatly outnumbered the non-lethals producing a visible morphological abnormality. There were some "semi-lethals" also (defining these as mutants having a viability ordinarily between about 0.5 per cent. and 10 per cent. of the normal), but, fortunately for the use of lethals as an index of mutation rate, these were not nearly so numerous as the lethals. The elusive class of "invisible" mutations that caused an even lesser reduction of viability, not readily confusable with lethals, appeared larger than that of the semi-lethals, but they were not subjected to study. In addition, it was also possible to obtain evidence in these experiments for the first time, of the occurrence of dominant lethal genetic changes, both in the X and in the other chromosomes. Since the zygotes receiving these never developed to maturity, such lethals could not be detected individually, but their number was so great that through egg counts and effects on the sex ratio evidence could be obtained of them *en masse*. It was found that their numbers are of the same order of magnitude as those of the recessive lethals. The "partial sterility" of treated males is, to an appreciable extent at least, caused by these dominant lethals. Another abundant class of mutations not previously recognized was found to be those which, when heterozygons, cause sterility but produce no detectable change in appearance; these too occur in numbers rather similar to those of the recessive lethals, and they may hereafter afford one of the readiest indices of the general mutation rate, when this is high. The sterility thus caused, occurring as it does in the offspring of the treated individuals, is of course a separate phenomenon from the "partial sterility" of the treated individuals themselves, caused by the dominant lethals.

In the statement that the proportion of "individually detectable mutations" was about one seventh for the X, and therefore nearly one half for all the chromatin, only the recessive lethals and semi-lethals and the "visible" mutants were referred to. If the dominant lethals, the dominant and recessive sterility genes and the "invisible" genes that merely reduce (or otherwise affect) viability or fertility had been taken into account, the percentage of mutants given would have been far higher, and it is accordingly evident that in reality the great majority of the treated sperm cells contained mutations of some kind or other. It appears that the rate of gene mutation after X-ray treatment is high enough, in proportion to the total number of genes, so that it will be practicable to study it even in the case of individual loci, in an attack on problems of allelomorphism, etc.

Returning to a consideration of the induced mutations that produced visible effects, it is to be noted that the conditions of the present experiment allowed the detection of many which approached or overlapped the normal type to such an extent that ordinarily they would have escaped observation, and definite evidence was thus obtained of the relatively high frequency of such changes here, as compared with the more conspicuous ones. The belief has several times been expressed in the *Drosophila* literature that this holds true in the case of "natural" mutations in this organism, but it has been founded only on "general impressions"; Baur, however, has demonstrated the truth of it in *Antirrhinum*. On the whole, the visible mutations caused by raying were found to be similar, in their general characteristics, to those previously detected in non-rayed material in the extensive observations on visible mutations in *Drosophila* carried out by Bridges and others. A considerable proportion of the induced visible mutations were, it is true, in loci in which mutation apparently had never been observed before, and some of these involved morphological effects of a sort not exactly like any seen previously (*e.g.*, "splotched wing," "sex-combless," etc.), but, on the other hand, there were also numerous repetitions of mutations previously known. In fact, the majority of the well-known mutations in the X-chromosome of *Drosophila melanogaster*, such as "white eye," "miniature wing," "forked bristles," etc., were reobtained, some of them several times. Among the visible mutations found, the great majority were recessive, yet there was a considerable "sprinkling" of dominants, just as in other work. All in all, then, there can be no doubt that many, at least, of the changes produced by X-rays are of just the same kind as the "gene mutations" which are obtained, with so much greater rarity, without such treatment, and which we believe furnish the building blocks of evolution.

In addition to the gene mutations, it was found that there is also caused by X-ray treatment a high proportion of rearrangements in the linear order of the genes. This was evidenced in general by the frequent inherited disturbances in crossover frequency (at least 3 per cent. were detected in the X-chromosome alone, many accompanied but some unaccompanied by lethal effects), and evidenced specifically by various cases that were proved in other ways to involve inversions,

"deficiencies," fragmentations, translocations, etc., of portions of a chromosome. These cases are making possible attacks on a number of genetic problems otherwise difficult of approach.

The transmuting action of X-rays on the genes is not confined to the sperm cells, for treatment of the unfertilized females causes mutations about as readily as treatment of the males. The effect is produced both on oöcytes and early oögonia. It should be noted especially that, as in mammals, X-rays (in the doses used) cause a period of extreme infertility, which commences soon after treatment and later is partially recovered from. It can be stated positively that the return of fertility does not mean that the new crop of eggs is unaffected, for these, like those mature eggs that managed to survive, were found in the present experiments to contain a high proportion of mutant genes (chiefly lethals, as usual). The practice, common in current X-ray therapy, of giving treatments that do not certainly result in permanent sterilization, has been defended chiefly on the ground of a purely theoretical conception that eggs produced after the return of fertility must necessarily represent "uninjured" tissue. As this presumption is hereby demonstrated to be faulty it would seem incumbent for medical practice to be modified accordingly, at least until genetically sound experimentation upon mammals can be shown to yield results of a decisively negative character. Such work upon mammals would involve a highly elaborate undertaking, as compared with the above experiments on flies.

From the standpoint of biological theory, the chief interest of the present experiments lies in their bearing on the problems of the composition and behavior of chromosomes and genes. Through special genetic methods it has been possible to obtain some information concerning the manner of distribution of the transmuted genes amongst the cells of the first and later zygote generations following treatment. It is found that the mutation does not usually involve a permanent alteration of all of the gene substance present at a given chromosome locus at the time of treatment, but either affects in this way only a portion of that substance, or else occurs subsequently, as an after-effect, in only one of two or more descendant genes derived from the treated gene. An extensive series of experiments, now in project, will be necessary for deciding conclusively between these two possibilities, but such evidence as is already at hand speaks rather in favor of the former. This would imply a somewhat compound structure for the gene (or chromosome as a whole) in the sperm cell. On the other hand, the mutated tissue is distributed in a manner that seems inconsistent with a general applicability of the theory of "gene elements" first suggested by Anderson in connection with variegated pericarp in maize, then taken up by Eyster, and recently reenforced by Demerec in *Drosophila virilis*.

A precociously doubled (or further multiplied) condition of the chromosomes (in "preparation" for later mitoses) is all that is necessary to account for the above-mentioned *fractional effect* of X-rays on a given locus; but the theory of a divided condition of each gene, into a number of (originally identical) "elements" that can become separated somewhat indeterminately at mitosis, would lead to expectations different from the results that have been obtained in the present work. It should, on that theory, often have been found here, as in the variegated corn and the eversporting races of *D. virilis*, that mutated tissue gives rise to normal by frequent "reverse mutation"; moreover, treated tissues not at first showing a mutation might frequently give rise to one, through a "sorting out" of diverse elements, several generations after treatment. Neither of these effects was found. As has been mentioned, the mutants were found to be stable through several generations, in the great majority of cases at least. Hundreds of non-mutated descendants of treated germ cells, also, were carried through several generations, without evidence appearing of the production of mutations in generations subsequent to the first. Larger numbers will be desirable here, however, and further experiments of a different type have also been planned in the attack on this problem of gene structure, which probably can be answered definitely.

Certain of the above points which have already been determined, especially that of the fractional effect of X-rays, taken in conjunction with that of the production of dominant lethals, seem to give a clue to the especially destructive action of X-rays on tissues in which, as in cancer, embryonic and epidermal tissues, the cells undergo repeated divisions (though the operation of additional factors, *e.g.*, abnormal mitoses, tending towards the same result, is not thereby precluded); moreover, the converse effect of X-rays, in occasionally producing cancer, may also be associated with their action in producing mutations. It would be premature, however, at this time to consider in detail the various X-ray effects previously considered as "physiological," which may now receive a possible interpretation in terms of the gene-transmuting property of X-rays; we may more appropriately confine ourselves here to matters which can more strictly be demonstrated to be genetic.

Further facts concerning the nature of the gene may emerge from a study of the comparative effects of varied dosages of X-rays, and of X-rays administered at different points in the life cycle and under varied conditions. In the experiments herein re-

ported, several different dosages were made use of, and while the figures are not yet quite conclusive they make it probable that, within the limits used, the number of recessive lethals does not vary directly with the X-ray energy absorbed, but more nearly with the square root of the latter. Should this lack of exact proportionality be confirmed, then, as Dr. Irving Langmuir has pointed out to me, we should have to conclude that these mutations are not caused directly by single quanta of X-ray energy that happen to be absorbed at some critical spot. If the transmuting effect were thus relatively indirect there would be a greater likelihood of its being influenceable by other physico-chemical agencies as well, but our problems would tend to become more complicated. There is, however, some danger in using the total of lethal mutations produced by X-rays as an index of gene mutations occurring in single loci, for some lethals, involving changes in crossover frequency, are probably associated with rearrangements of chromosome regions, and such changes would be much less likely than "point mutations" to depend on single quanta. A reexamination of the effect of different dosages must therefore be carried out, in which the different types of mutations are clearly distinguished from one another. When this question is settled, for a wide range of dosages and developmental stages, we shall also be in a position to decide whether or not the minute amounts of gamma radiation present in nature cause the ordinary mutations which occur in wild and in cultivated organisms in the absence of artificially administered X-ray treatment.

As a beginning in the study of the effect of varying other conditions, upon the frequency of the mutations produced by X-rays, a comparison has been made between the mutation frequencies following the raying of sperm in the male and in the female receptacles, and from germ cells that were in different portions of the male genital system at the time of raying. No decisive differences have been observed. It is found, in addition, that aging the sperm after treatment, before fertilization, causes no noticeable alteration in the frequency of detectable mutations. Therefore the death rate of the mutant sperm is no higher than that of the unaffected ones; moreover, the mutations can not be regarded as secondary effects of any semi-lethal physiological changes which might be supposed to have occurred more intensely in some ("more highly susceptible") spermatozoa than in others.

Despite the "negative results" just mentioned, however, it is already certain that differences in X-ray influences, by themselves, are not sufficient to account for all variations in mutation frequency, for the present X-ray work comes on the heels of the determination of mutation rate being dependent upon temperature (work as yet unpublished). This relation had first been made probable by work of Altenburg and the writer in 1918, but was not finally established until the completion of some experiments in 1926. These gave the first definite evidence that gene mutation may be to any extent controllable, but the magnitude of the heat effect, being similar to that found for chemical reactions in general, is too small, in connection with the almost imperceptible "natural" mutation rate, for it, by itself, to provide a powerful tool in the mutation study. The result, however, is enough to indicate that various factors besides X-rays probably do affect the composition of the gene, and that the measurement of their effects, at least when in combination with X-rays, will be practicable. Thus we may hope that problems of the composition and behavior of the gene can shortly be approached from various new angles, and new handles found for their investigation, so that it will be legitimate to speak of the subject of "gene physiology," at least, if not of gene physics and chemistry.

In conclusion, the attention of those working along classical genetic lines may be drawn to the opportunity, afforded them by the use of X-rays, of creating in their chosen organisms a series of artificial races for use in the study of genetic and "phaenogenetic" phenomena. If, as seems likely on general considerations, the effect is common to most organisms, it should be possible to produce, "to order," enough mutations to furnish respectable genetic maps, in their selected species, and, by the use of the mapped genes, to analyze the aberrant chromosome phenomena simultaneously obtained. Similarly, for the practical breeder, it is hoped that the method will ultimately prove useful. The time is not ripe to discuss here such possibilities with reference to the human species.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

AN INSTRUMENT FOR REPEATED DETERMINATIONS OF BLOOD VISCOSITY IN AN ANIMAL[1]

IN experiments where it is desirable to make repeated determinations of the viscosity of the blood of an animal, the withdrawal of the amount of blood

[1] From the Physiological Laboratories of the University of Chicago and the University of Western Ontario, London, Canada.