MUTATIONS OF THE GENE IN DIFFERENT DIRECTIONS

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INTRODUCTION

BATESON's "presence-absence" hypothesis is the most persistent basis for the views upon the nature of the gene and of gene mutations. The modern critique of this hypothesis is chiefly based on more or less indirect counter evidence, shown by the phenomenon of multiple allelomorphism and by the whole, general picture of the mutability of Drosophila (MORGAN, BRIDGES, STURTEVANT 1925, MORGAN, STURTEVANT, MULLER and BRIDGES 1923, STERN 1930b). This criticism has led to some modernized alterations of the original extreme "presence-absence" hypothesis, for instance, to the view that gene mutations are merely quantitative changes of the gene (GOLDSCHMIDT 1928).

But the acceptance of each modification of the "presence-absence" hypothesis leads us to the conclusion that the gene mutability is merely a process of degradation and even of loss of the previously present genic material. If so, then we must take the next step and admit that gene mutations have no positive significance at all in the process of evolution and that the mutability of the species as studied by geneticists is a purely "pathological" phenomenon which is permanently controlled and suppressed by natural selection.

The possibility of proving the "presence-absence" hypothesis in a more or less direct experimental way would thus be of great interest. I think that the study of reverse gene mutations and the quantitative study of the mutability of single individual genes can give us a conclusive experimental basis for our views upon the general nature of the gene changes.

The study of spontaneous mutations in *Drosophila melanogaster* and in some other species has already shown that different mutational steps are probably occurring with different frequencies, and that reversions of previously mutated genes may occur in some cases (MORGAN 1926, MORGAN, BRIDGES, STURTEVANT 1925, MULLER 1920, MOHR 1922, KEELER 1931, STERN 1930a, TIMOFÉEFF-RESSOVSKY 1925, 1928, ZELENY 1921). The most convictive cases of reversions, excluding contamination, are those in which reversions occurred in somatic tissue (TIMOFÉEFF-RESSOVSKY 1928) and the "frequently mutating genes" in *Drosophila virilis* and in some plants (DEMEREC 1928, 1929a, 1929b, 1931, BAUR 1926, CORRENS 1919, EMERSON 1917, EYSTER 1924, IKENO 1923, IMAI 1925, PLOUGH 1928).

An exact quantitative study of reversions and of the mutability of single

individual genes is in the spontaneous process of mutability possible only in the cases of "frequently mutating genes." And these latter could be interpreted as a special group of mutations. But with the help of X-rays we can hope to get statistically significant data also upon the mutability of different "normal" genes.

In this paper an attempt will be made to give a review of our X-ray experiments upon reversions and mutational potencies of some individual genes in *Drosophila melanogaster* and to draw some conclusions relating to the nature of the gene changes.

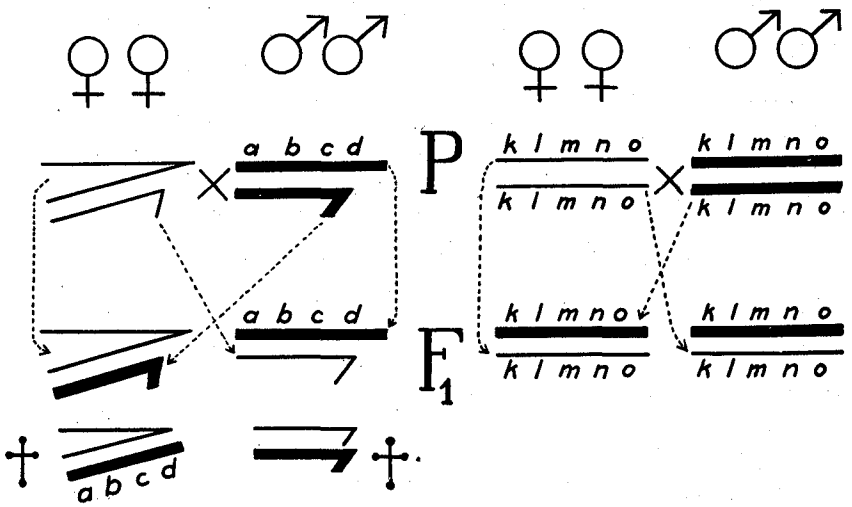

FIGURE 1.—Scheme of crossings in the X-ray experiments upon reverse gene mutations in *Drosophila melanogaster.*

At the left: X-rayed males, containing sex-linked recessive mutations are mated to "attached X" females; all reversions induced in the X chromosome of the fathers will manifest themselves in their sons. At the right: males homozygous for several recessive genes in the III chromosome are X-rayed and crossed with homozygous females from the same stock; the induced reversions will manifest themselves in F_1. The X-rayed chromosomes are represented by solid lines.

REVERSE GENE MUTATIONS INDUCED BY X-RAYS IN DROSOPHILA

The first question to be solved was whether reversions of previously mutated genes could be produced at all by means of X-ray treatment.

F. B. HANSON has shown that reversions from Bar to full-eye can be produced by X-rays in Drosophila (HANSON 1928). But these reversions can be interpreted as gene deficiencies because Bar is probably a quite new gene and the normal flies seem to have no allelomorph of Bar (STURTEVANT 1925). In the early X-ray work of MULLER and of myself some re-

versions of recessive mutations were observed in Drosophila (MULLER 1928b, 1930a, 1930b, TIMOFÉEFF-RESSOVSKY 1929a, b and d).

In order to prove exactly the occurrence and the "generality" of the phenomenon of reversions induced by X-rays, special experiments were ar-

TABLE 1

Reversions of recessive gene mutations in the X and III chromosomes of Drosophila melanogaster, produced by X-rays (dosages approximately 3600 r and 4800 r).

THE X-RAYED ALLELOMORPHS AND THEIR LOCI IN THE CHROMOSOMES			NUMBER OF ANALYZED X-RAYED CHROMOSOMES, CONTAINING THE LOCI	TYPE AND NUMBER OF REVERSIONS
I Chromosome,	0	y	11781	..
I Chromosome,	0+	s_c	17676	$3\, s_c \rightarrow S_c$
I Chromosome,	2	w	29233	$1\, w \rightarrow w^a$
I Chromosome,	2	w	29233	$1\, w \rightarrow w^b$
I Chromosome,	2	w^a	23472	$1\, w^a \rightarrow w^b$
I Chromosome,	2	w^a	23472	$1\, w^a \rightarrow W$
I Chromosome,	7	e_c	17676	..
I Chromosome,	16	c_v	6354	$1\, c_v \rightarrow C_v$
I Chromosome,	25	c_t	12914	..
I Chromosome,	40	v	19268	$1\, v \rightarrow V$?
I Chromosome,	51	g	12914	..
I Chromosome,	62	f	24695	$5f \rightarrow F$
III Chromosome,	0	r_u	16936	..
III Chromosome,	26	h	16936	$1\, h \rightarrow H$
III Chromosome,	42	t_h	5681	..
III Chromosome,	44	s_t	16936	..
III Chromosome,	48	p	11255	$2\, p \rightarrow P$
III Chromosome,	50	c_u	5681	..
III Chromosome,	58	s_e	11255	..
III Chromosome,	62	s_r	5681	..
III Chromosome,	71	e^s	16936	$1\, e^s \rightarrow E$?
III Chromosome,	101	c_a	5681	..
Total number of X-rayed chromosomes, containing the above loci and number of reversions			288961	18
Controls			139234	..

ranged on a large scale (TIMOFÉEFF-RESSOVSKY 1930a and b). Twenty different recessive mutant allelomorphs of *Drosophila melanogaster,* 10 in the X chromosome (yellow, scute, white, eosin, echinus, crossveinless, cut, vermilion, garnet and forked) and 10 in the III chromosome (roughoid, hairy, thread, scarlet, pink, curled, spineless, stripe, sooty and claret) were X-rayed. In order to raise the chance of obtaining reversions among a limited

number of flies, males from poly-recessive cultures (such as X-pl, III-pl and "rucuca"), containing simultaneously several recessive mutations, were X-rayed. The X-rayed males were then mated either with females of the same genetic composition or (if sex-linked genes were studied) with "attached-X" females. These methods of crossing are shown in figure 1.

All cases of reversions obtained in these experiments are summarized in table 1. Reversions to the normal allelomorphs were obtained from scute, eosin, crossveinless, vermilion and forked in the X chromosome and from hairy, pink and sooty in the III chromosome. Besides this the following reversions towards normal were obtained: from white to eosin, from white to blood and from eosin to blood. Purely phenotypical, occasional non-manifestation or a suppression of the characters in question by specific suppressors (BRIDGES 1932, MORGAN 1929, PLOUGH 1928) can imitate a reverse gene mutation. Therefore all flies showing reversions were tested by further crossings, and in table 1 only those cases are mentioned which proved to be true reverse gene mutations. Contamination, as another possible source of errors, is practically excluded in these experiments, since multiple stocks were used; only one of the genes reverted in each case and several other genes, contained in each culture, served as markers.

In total, 18 reversions were observed among 289,000 treated mutant allelomorphs. One hundred thirty-nine thousand controls gave no reversions. This difference is statistically quite significant, so that the production of reversions must be ascribed to X-rays. At the loci of scute, white, forked and pink, reversions occurred more than once.

Some of the cultures, containing normal allelomorphs which arose as reversions under X-ray treatment, were further X-rayed and in some cases gave secondary mutations back to or toward the original mutant allelomorphs. In figure 2 are summarized all such cases in which mutations in both directions were induced by X-rays directly one from another. These cases together with similar cases obtained by PATTERSON and MULLER (1930) are of special interest. They show that the action of X-rays upon the genes is in general by no means of a purely destructive but rather of a reconstructive kind, because, as MULLER has figuratively expressed it, it is highly improbable that "if with one blow we punch the gene out, with the next we would punch it in again." Thus also the gene changes (gene mutations) can not be losses of the specifically differentiated gene material, but, in some cases at least, must consist of some kind of intra-genic rearrangements of a reversible nature.

MUTATIONS IN OPPOSITE DIRECTIONS AT THE LOCUS OF FORKED IN DROSOPHILA, INDUCED BY X-RAYS

The above mentioned extensive first sets of experiments had to establish the fact of occurrence of reverse gene mutations in general and to prove whether their origin could be ascribed to X-rays. These experiments gave positive results and then the next step was to try to get statistically significant data upon the mutability of some definite individual loci.

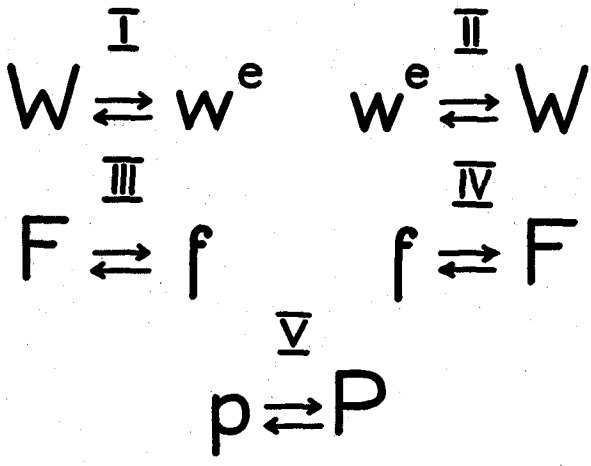

FIGURE 2.—Allelomorphic pairs of *Drosophila melanogaster,* in which mutations were produced directly one from another by means of X-rays. I. From a normal allelomorph of the white series eosin was induced, and this latter produced under further treatment a reversion back to normal. II. A spontaneously arisen eosin gave under treatment a reversion to normal, and this normal mutated under further treatment back to eosin. III-IV. Mutations produced by X-rays: from normal to forked and from this forked back to normal, and from forked to normal and from this normal back to forked. V. Mutations from pink to normal and from this normal back to pink.

The most practicable loci for such intensive experiments seemed to be scute, white, forked and pink, since in these loci mutations in both directions were repeatedly induced by X-rays. Scute mutations have been intensively studied by DUBININ and SEREBROVSKY (DUBININ 1929, SEREBROVSKY and DUBININ 1930); therefore, I have concentrated my work upon white and forked.

In the meantime the excellent work of PATTERSON and MULLER was published, in which the authors describe their X-ray experiments dealing with the same problem and based chiefly upon induced forked mutations (PATTERSON and MULLER 1930).

In table 2 are summarized the forked mutations induced by X-rays in

the experiments of PATTERSON and MULLER and of myself. The mean dosage of X-rays was about 3500 r in the experiment of PATTERSON and MULLER and about 4800 r in my experiments. The results are summarized on the basis of 4800 r. The calculations are based on the admission of a direct proportionality between the dosages and the induced mutation rates.

Both independent sets of experiments gave substantially the same results. The frequencies of "direct" and "reverse" gene mutations at the locus of forked seem to be of the same quantitative order, reversions being even somewhat more frequent ($F \rightarrow f = 11 : 43000$, $f \rightarrow F = 15 : 44000$).

As was already mentioned above (figure 2), direct and reverse gene mutations at the forked locus were produced directly one from another by X-

TABLE 2

"Direct" and "reverse" mutations of the forked gene in Drosophila melanogaster, produced by X-ray treatment.

AUTHORS	"DIRECT" MUTATIONS FROM *F* TO OR TOWARD FORKED		"REVERSE" MUTATIONS FROM FORKED TO OR TOWARD *F*	
	NUMBER OF X-RAYED CHROMOSOMES	NUMBER OF MUTATIONS	NUMBER OF X-RAYED CHROMOSOMES	NUMBER OF MUTATIONS
PATTERSON and MULLER (Dosage approximately 3500 r)	32000	6	20000	8
TIMOFÉEFF-RESSOVSKY (Dosage approximately 4800 r)	19000	5	29000	7
Total, on the basis of 4800 r	43000	11	44000	15

rays. In the experiments of PATTERSON and MULLER also 4 of the forked mutations ($F \rightarrow f$) were induced by X-rays from a normal allelomorph, which itself derived from forked as an X-ray induced reversion (PATTERSON and MULLER 1930).

Experiments with forked have shown that at this locus mutations in both directions can be produced with practically the same frequency. The preliminary results of some X-ray experiments with the bobbed locus of *Drosophila melanogaster* (these experiments are not yet accomplished) are showing that at this locus reversions from an extreme mutant allelomorph bobbed-lethal (kindly given me by C. STERN) to or toward normal are probably much more frequent than "direct" mutations from normal to or toward bobbed. This extreme bobbed allelomorph (bobbed-lethal) behaves like an ordinary sex-linked recessive lethal, the only difference being that it does not kill the males, since they always contain the normal allelomorph of

bobbed in their Y chromosome (STERN 1930b). If the above mentioned results are confirmed by further experiments, they will show that even such "pathological" mutations as the lethals can be reversible and therefore are not always destructions or losses of the "normal" genes (gene deficiencies, PATTERSON 1932).

MUTABILITY IN DIFFERENT DIRECTIONS WITHIN THE WHITE-EYE SERIES OF DROSOPHILA, PRODUCED BY X-RAY TREATMENT

The most intensive study was done upon the mutability in the white-eye series of *Drosophila melanogaster*. This locus was chosen for the following reasons:

1. Spontaneously and under X-ray treatment it proved to be one of the most mutable loci.

2. At this locus many allelomorphs are known, so that one could hope to produce many different mutations from and to different allelomorphs.

3. Phenotypically this series of allelomorphs shows a quantitative scale of eye colors, so that one could easily assume that the gene changes leading to the different allelomorphs are in this series also of a purely quantitative kind.

A uniform method was used in all X-ray experiments with the white-eye series. Males from different cultures, containing the white allelomorphs and also some other sex-linked genes as markers (in order to avoid contamination), were X-rayed with the same, rather heavy dosage of about 4800 r and mated with "attached X" females (figure 1). All mutations of the *W* gene could be detected in the F_1 males. In order to eliminate those cases in which specific modifiers arising at other loci or some other eye-color mutations are imitating mutations of the white locus, all newly arisen eye-color mutations were tested by further crossings.

The following allelomorphs of the white-eye series were X-rayed: Normal (*W*), coral (w^{co}), blood (w^{b}), cherry (w^{ch}), apricot (w^{a}), eosin (w^{e}), buff (w^{bf}) and white (*w*). The newly arisen mutations were classified by careful comparison with the known ones. Most of them proved to be recurrences of previously known allelomorphs, but some of them showed slight differences and were classified as new ones.

Altogether about 185,000 F_1 males from X-rayed parents were examined and 68 mutations of the white locus were found among them. The mean mutation rate was thus about 1 : 2700.

First we will consider the mutability of the white locus only qualitatively. In figure 3 it is shown that white was induced as a mutation from all those

allelomorphs which were X-rayed. Figure 4 shows that the allelomorphs blood, eosin and buff were induced as "direct" mutations from normal ($W \rightarrow w^b$, $W \rightarrow w^e$ and $W \rightarrow w^{bf}$) and also as "reversions" from white ($w \rightarrow w^b$, $w \rightarrow w^e$ and $w \rightarrow w^{bf}$). In figure 5 are shown the different mutations to and from eosin which were induced by X-rays. Mutations to eosin were induced from normal ($W \rightarrow w^e$), from blood ($w^b \rightarrow w^e$), from apricot

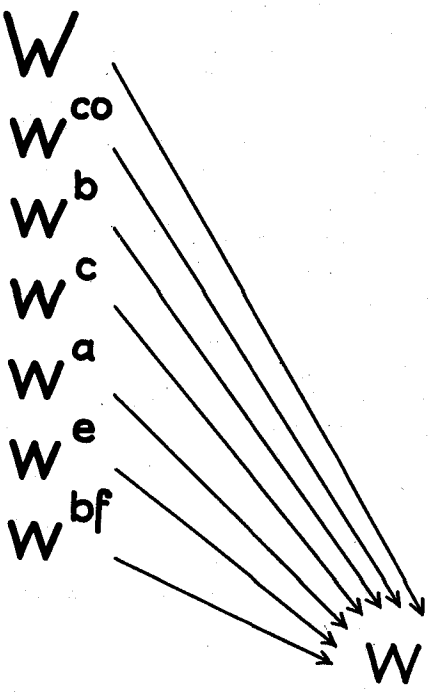

FIGURE 3.—Mutations from different W allelomorphs to white, produced by X-rays in *Drosophila melanogaster.*

($w^a \rightarrow w^e$) and from white ($w \rightarrow w^e$). From eosin mutations were induced to normal ($w^e \rightarrow W$), to blood ($w^e \rightarrow w^b$) and to white ($w^e \rightarrow w$).

Mutations from eosin to normal and from this normal back to eosin ($w^e \rightleftarrows W$) and mutations from normal to eosin and from this eosin back to normal ($W \rightleftarrows w^e$) were directly induced one from another by X-rays (figure 2). The eosin allelomorph, which arose as an X-ray induced reversion from white, has under further treatment given two independent mutations back to white ($w \rightleftarrows w^e$).

All the above facts show that at the white locus quite different mutational steps and mutations in different directions can be induced by X-rays. At least some of the mutational processes within this locus are reversi-

ble. In this respect the results are in principle the same as those obtained at the forked locus. On the other hand we can already note some differences. At the forked locus the extreme mutations in both directions ($F \rightarrow f$ and $f \rightarrow F$) were produced. At the white locus the extreme reversion from

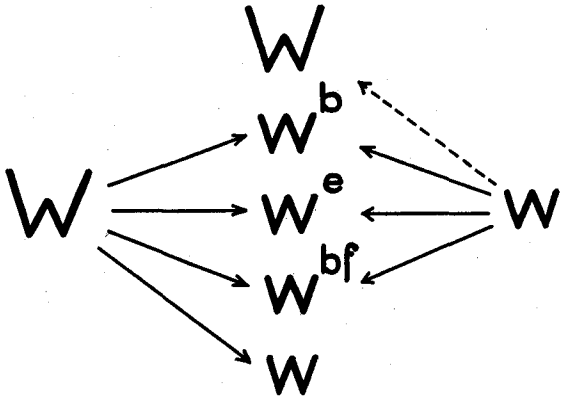

FIGURE 4.—The same intermediate allelomorphs of the white series in *Drosophila melanogaster* (blood, eosin and buff), produced by X-rays from the extreme allelomorphs W (normal) and w (white). The extreme reversion $w \rightarrow W$ was never observed.

white direct to normal ($w \rightarrow W$) was never observed. But this reversion can be produced in two steps: from white to eosin and from eosin to normal ($w \rightarrow w^e \rightarrow W$).

If we now consider quantitatively the single mutation rates at the white locus, then the "unordered" general picture of the mutability will change

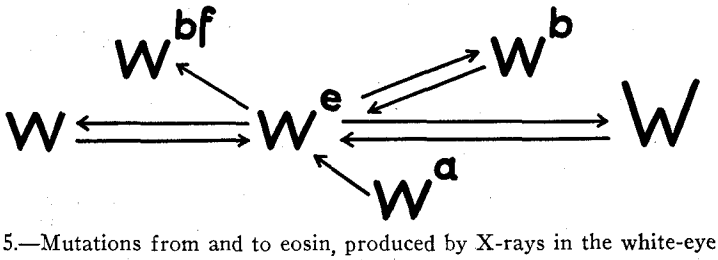

FIGURE 5.—Mutations from and to eosin, produced by X-rays in the white-eye series of *Drosophila melanogaster*.

its face and further differences from the mutability of the locus of forked can be noted.

In table 3 are summarized all mutations induced at the white locus and the corresponding numbers of treated gametes (F_1 males) among which they were found. It is quite evident that different mutations are not produced

with equal frequencies. The normal allelomorph (W) mutated 37 times in a total of 48,500 tested gametes, while the allelomorph white (w) mutated only 3 times in a total of 54,000 tested gametes. Among 37 mutations from normal (W) are 25 white mutations ($W \rightarrow w$) and only 12 mutations to at least six different other allelomorphs. Eosin (w^e) seems also to mutate much more frequently to white than to all other allelomorphs, but the total mutability of eosin is lower than that of normal.

TABLE 3

Summary of all mutations in different directions within the white-eye series of Drosophila melanogaster, produced by X-ray treatment (dosage approximately 4800 r).

"DIRECT" GENE MUTATIONS IN THE W LOCUS				"REVERSE" GENE MUTATIONS IN THE W LOCUS			
MUTATIONS	NUMBER OF MUTATIONS	NUMBER OF FLIES	RATE OF MUTATION IN 0/00	MUTATIONS	NUMBER OF MUTATIONS	NUMBER OF FLIES	RATE OF MUTATION IN 0/00
$W \rightarrow w$	25	48500	0.763	$w \ldots\ldots W$	0	54000	0
$W \rightarrow w^{bf}$	1	48500		$w \rightarrow w^{bf}$	1	54000	0.055
$W \rightarrow w^e$	3	48500		$w \rightarrow w^e$	1	54000	
$W \rightarrow w^a$	1	48500		$w \rightarrow w^b$	1	54000	
$W \rightarrow w^b$	2	48500					
$W \rightarrow w^x$	5	48500		$w^{bf} \ldots\ldots ?$	0	7500	0
$w^{co} \rightarrow w$	1	6000	..	$w^e \rightarrow w^b$	1	39000	0.077
$w^b \rightarrow w$	3	12000	0.333	$w^e \rightarrow W$	2	39000	
$w^b \rightarrow w^e$	1	12000					
$w^c \rightarrow w$	1	5000	..	$w^a \ldots\ldots ?$	0	11000	0
$w^a \rightarrow w$	2	11000	0.272	$w^c \ldots\ldots ?$	0	5000	0
$w^a \rightarrow w^e$	1	11000		$w^b \ldots\ldots ?$	0	12000	0
$w^e \rightarrow w$	13	39000	0.385	$w^{co} \ldots\ldots ?$	0	6000	0
$w^e \rightarrow w^x$	2	39000		$W \ldots\ldots ?$	0	48500	0
$w^{bf} \rightarrow w$	1	7500	..				

In table 4 the different mutations of the white locus are classified and their mutation rates are compared. In a total of 129,000 tested gametes 62 "direct" mutations (from darker allelomorphs to lighter ones) were induced. On the other hand only 6 "reverse" mutations (from lighter allelomorphs to darker ones) were induced in a total of 134,500 tested gametes. The difference between these mutation rates is statistically quite significant. Statistically significant also are the differences between the rates of mutations from eosin to lighter allelomorphs (15 : 39,000) and from eosin to darker allelomorphs (3 : 39,000), and the rates of mutations from normal and from white to different other allelomorphs ($W \rightarrow w^x = 37 : 48{,}500$ and $w \rightarrow w^x = 3 : 54{,}000$). We can group all the tested allelomorphs into three classes: (1) normal, (2) intermediate allelomorphs (coral, blood, cherry, apricot and

eosin) and (3) light allelomorphs (buff and white). Then the highest mutability is shown by normal, the intermediate allelomorphs have a mutability which is half as high as that of normal, and the lowest mutability is shown by the lightest allelomorphs.

The quantitative study of mutation rates thus shows that the mutability within the white-eye series is not unordered and not merely a matter of chance, but rather has some characters of "determinate variation" (VOGT 1929). The "directing principle" is manifested by the following facts: (1) different mutational steps and mutations from different allelomorphs are

TABLE 4

Comparison of different mutation rates within the white-eye series of Drosophila melanogaster, produced by X-ray treatment (dosage approximately 4800 r).

MUTATIONS	NUMBER OF MUTATIONS	NUMBER OF FLIES	RATE OF MUTATION IN 0/00 ± m	DIFFERENCE OF RATES ± $m_{dif.}$
All "direct"	62	129000	0.481±0.061	0.436±0.063
All "reverse"	6	134500	0.045±0.018	
$w^e \rightarrow w^{-e}$	15	39000	0.385±0.111	0.308±0.119
$w^e \rightarrow w^{+e}$	3	39000	0.077±0.044	
$W \rightarrow w^x$	37	48500	0.763±0.125	0.708±0.128
$w \rightarrow w^x$	3	54000	0.055±0.032	
$W \rightarrow w^x$	37	48500	0.763±0.125	0.393±0.143
$w^{e-co} \rightarrow w^x$	27	73000	0.370±0.071	0.305±0.078
$w^{-bf} \rightarrow w^x$	4	61500	0.065±0.032	
$W \rightarrow w$	25	48500	0.515±0.102	0.254±0.116
$w^x \rightarrow w$	21	80500	0.261±0.056	

produced with quite different frequencies; (2) "direct" mutations are much more frequent than "reversions"; (3) some of the theoretically conceivable mutational steps are probably not realizable (for instance, $w \rightarrow W$); (4) mutational end-results which are not realizable at once can be attained in two definite steps ($w \rightarrow w^e \rightarrow W$).

COMPARISON OF IDENTICAL ALLELOMORPHS OF DIFFERENT ORIGIN AND THE EXISTENCE OF DIFFERENT "NORMAL" ALLELOMORPHS OF THE WHITE-EYE SERIES OF DROSOPHILA

The last series of experiments deals with the question of whether W allelomorphs of different origin, classified as identical according to their eye-color effects, are really identical. An exact classification of eye colors is dif-

ficult and *a priori* it could be possible to admit that practically each mutation is leading to a somewhat different new allelomorph, that the eye colors are really forming a continuous series and that our classification of allelomorphs is artificial. A confirmation of this assumption would be a strong support for the hypothesis of purely quantitative mutational changes at this locus.

The first evidence against the assumption of a continuous quantitative series of eye-color allelomorphs is the fact that some of the white allelomorphs are showing specific peculiarities in their eye-color effects: eosin has, for instance, a pronounced sex dimorphism, and blood shows a high degree of fluctuation in its eye color.

Another way to solve this question would be by the study of manifold effects of certain allelomorphs of different origin. We can test whether mutations classified as identical according to their eye colors are also identical in respect to other effects of the gene.

Within the white-eye series of *Drosophila melanogaster* the normal, blood, eosin and white allelomorphs can be most easily and exactly identified on the basis of their eye-color effects. Different mutations to these allelomorphs were thus chosen for the study of the manifold effects of identical allelomorphs.

The following cultures were used: (1) Four white mutations of different origin (a "spontaneous" white obtained from H. J. MULLER in 1922 and designated as w — *1;* two different $W \rightarrow w$ mutations, induced by X-rays and designated as w — *4* and w — *7*; one $w^e \rightarrow w$ X-ray induced mutation, designated as w — *11*); (2) Four eosins of different origin (the original "spontaneous" w^e — *1;* w^e — *3* and w^e — *6,* induced as W — w^e mutations; w^e — *4,* an X-ray induced $w \rightarrow w^e$ reversion); (3) Four different blood-cultures (a "spontaneous" w^b — *1; two independent X-ray induced* $W \rightarrow w^b$ mutations designated as w^b — *2* and w^b — *3* and a $w^e \rightarrow w^b$ reversion designated as w^b — *5*); (4) Four normal allelomorphs of different origin (W^A from American cultures, W^R from a Russian culture; W^{X1} and W^{X2} — two X-ray induced reversions from eosin to normal).

Besides the eye colors, which served as a basis for the classification of the above mutations, the following effects of the four allelomorphs were tested: color of the testicle tunic (DOBZHANSKY 1927), viability of the males (measured by the deviation of the mutant type from the 1:1 ratio in the male progeny of heterozygous females) and fertility of the females (measured by the mean number of eggs laid by 1 female in the first 10 days of the egg-laying period). Before the tests of these effects were made, all the white, eosin and blood cultures were backcrossed through more than 20 generations

TABLE 5

Manifold effects of w, w^e, w^b and W allelomorphs of different origin; the allelomorphs were identified and classified by comparison of their eye-color effects. The viability rates are given in percentage of the viability of W^A (=100 percent) and are based on the deviations from the 1:1 ratio in the male progeny of heterozygous females. The fecundity rates are given in the mean number of eggs per female, laid during the first 10 days of the egg-laying period.

ALLELOMORPHS	COLOR OF THE TUNIC OF THE TESTICLES	VIABILITY IN PERCENTAGE, AS COMPARED WITH *W*	FECUNDITY IN MEAN NUMBER OF EGGS PER FEMALE IN THE FIRST 10 DAYS	REMARKS
w — 1	pellucid	79±1.0	550± 9.5	Viability rates based on
w — 4	pellucid	67±1.0	503±13.5	deviations from 1:1 ratio
w — 7	pellucid	82±2.0	543±18.0	in the male progenies of
w —11	pellucid	69±1.5	481±16.5	heterozygous W^A/w (and
Total *w*	pellucid	72±1	533±17	W^A/w^e or W^A/w^b) females
w^e— *1*	pellucid	88±1.0	402±17.0	where the viability of
w^e— *3*	pellucid	90±1.5	391±19.5	W^A is taken as equal to
w^e— *4*	pellucid	89±1.0	398±22.0	100 percent
w^e— *6*	pellucid	92±1.5	411±18.5	
Total w^e	pellucid	90±1	395±23	
w^b— *1*	pellucid	83±1.5	418±20.0	
w^b— *2*	pellucid	76±1.5	441±23.0	
w^b— *3*	pellucid	80±1.0	422±17.0	
w^b— *5*	pellucid	84±1.5	436±19.0	
Total w^b	pellucid	81±1	438±14	
W^A	yellow	100	653±18.0	Viability rates based on
W^R	yellow	108±1.0	691±29.5	male progenies of hetero-
W^{X_1}	yellow	96±1.0	622±15.5	zygous *w—1/W* females.
W^{X_2}	yellow	103±1.5	672±20.5	
Total *W*	yellow	102±1	664±19	

with a definite pure-bred normal culture. This was done in order to eliminate eventual influences of other genes upon the differences in the above mentioned effects, to be found between allelomorphs of different origin.

In table 5 are summarized the results of these tests. White, eosin, blood and normal show very pronounced differences in viability and fertility. But it is evident, that all four eosins of different origin are quite identical in respect to all four tested effects. The same is true for blood. The four whites show greater differences in viability and fertility. This latter fact can be

ascribed to chance or could be perhaps explained by the assumption that there are different white allelomorphs which are indistinguishable in their eye color. But the results on eosins and bloods of different origin clearly show that definite mutational steps and recurrences of exactly the same allelomorphs really exist.

A second important fact shown by the results of the tests summarized in table 5 is that the quantitative gradation of the allelomorphs of the white-eye series will be different if based on different effects of this gene. The sequence of the four tested allelomorphs (W, w^b, w^e and w) in the direction from "normal" toward the "abnormal condition" is, if based on their eye-color effects: normal (W)>blood (w^b)>eosin (w^e)>white (w). If based on viability rates, the sequence is $W>w^e>w^b>w$. And if based on fertility rates, the sequence is $W>w>w^b>w^e$. From the above tests it is evident: (1) that definite, recurrent mutational steps exist within the white-eye series and (2) that the different allelomorphs can not be ordered in a simple quantitative series if manifold effects of the gene are taken into consideration. (When these experiments were already accomplished and the paper was written, a paper by G. FRISEN came to my attention [FRISEN 1931]. In this paper the author examines the fertility of several W allelomorphs, their compounds and heterozygotes with wild-type and proposes, as explanation of the results obtained, a hypothesis of "chain-mutations." Without being able to give here a full discussion of the matter, I can only briefly mention that my results, showing the identity of similar recurrent mutations, seem to disprove the hypothesis of "chain-mutations.")

The last question to be mentioned here is: are all allelomorphs which we designate as "normal" and can not distinguish one from another really identical or not? This question arose in connection with the following facts. In our X-ray work two "normal" cultures of *Drosophila melanogaster* were used, one derived from a Russian wild population and the other from America. In summarizing the germinal and somatic white mutations obtained in the first sets of X-ray experiments, it was found that the "American" flies gave about twice as many mutations at the white locus as the "Russian" flies (under the same experimental conditions). The data showing this peculiar race difference were not statistically significant. But nevertheless this question was pursued in all further X-ray experiments in order to test this phenomenon on a large scale.

Such race differences in the mutation rate of a definite gene can be caused either by the general differences in the two genotypes (in some way controlling the mutability of the single gene) or by the structural difference of

this gene itself. In order to solve this question, four cultures were produced by crossings (with the help of "markers" in different chromosomes): (1) a purely "American" culture, (2) a culture containing the "American" left end of the X chromosome in a "Russian" set of chromosomes (the American W^A allelomorph in Russian "genotypical environment"), (3) a purely

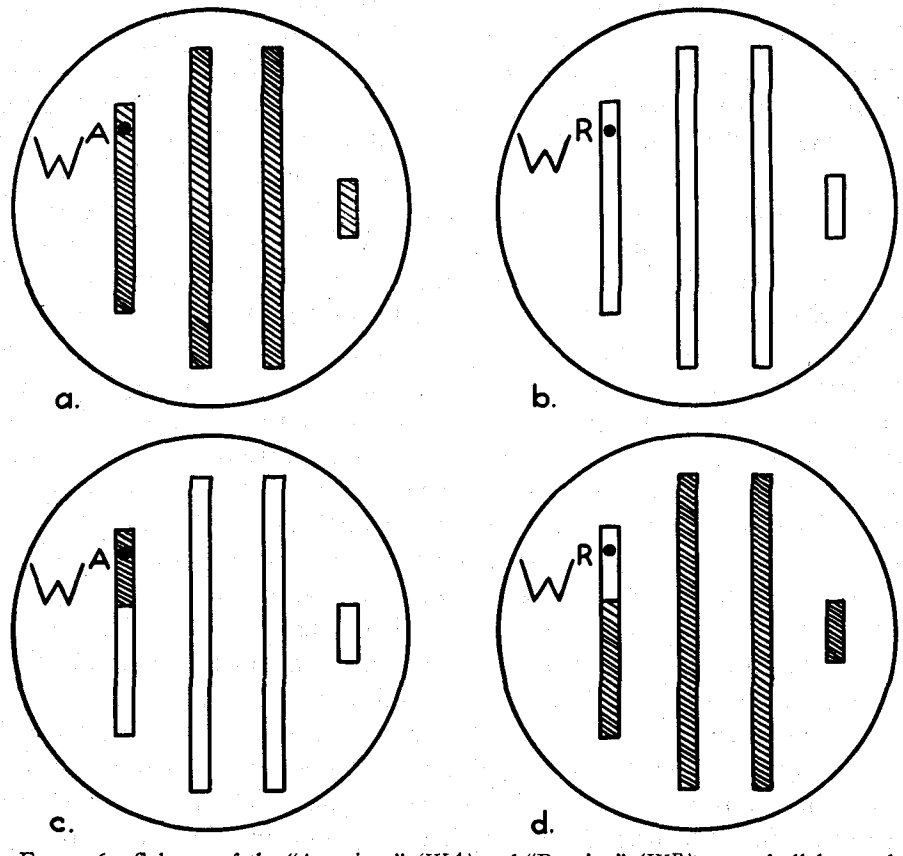

FIGURE 6.—Scheme of the "American" *(W^A)* and "Russian" *(W^R)* normal allelomorphs of the white-eye series of *Drosophila melanogaster* in "Russian" and in "American" genotypical environment. a. W^A in its own, American genotype. b. W^R in its own, Russian genotype. c. W^A in Russian genotype. d. W^R in American genotype.

"Russian" culture and (4) a culture containing the "Russian" left end of the X chromosome in an "American" set of chromosomes (the Russian W^R allelomorph in American "genotypical environment"). Schematical drawings of these four genotypes are shown in figure 6.

Males from these four cultures were then used in all further X-ray ex-

periments. All induced mutations at the locus of white were registered according to the above four genotypes of the X-rayed males and were classified into two groups: 1, white ($W \rightarrow w$) and 2, all other colored allelomorphs ($W \rightarrow w^x$).

Table 6 shows the results of all X-ray experiments in which the four above cultures were used. The original observation was confirmed by these

TABLE 6

Mutability, produced by X-ray treatment, of the American (W^A) and Russian (W^R) normal allelomorphs of the white-eye series of Drosophila melanogaster. The W gene mutations produced are classified into two groups: 1, white ($W \rightarrow w$) and 2, all other, intermediate eye-colors ($W \rightarrow w^x$). X-ray dosage= approximately 4800 r.

CULTURES	NUMBER OF X-RAYED W GENES	NUMBER OF PRODUCED W MUTATIONS			PERCENTAGES		
		$W \rightarrow w$	$W \rightarrow w^x$	TOTAL	OF ALL W GENE MUTATIONS	OF $W \rightarrow w$ AMONG ALL W GENE MUTATIONS	OF $W \rightarrow w^x$ AMONG ALL GENE MUTATIONS
W^A in American "genotypic environment"	31000	22	5	27	0.087	81	19
W^A in Russian "genotypic environment"	28200	19	9	28	0.100	68	32
W^A total	59200	41	14	55	0.093 ±0.012	75±5	25±5
W^R in Russian "genotypic environment"	49200	13	13	26	0.053	50	50
W^R in American "genotypic environment"	26100	6	8	14	0.054	43	57
W^R total	75300	19	21	40	0.053 ±0.008	47±7	53±7

The difference between the mutabilities of W^A and $W^R = 0.040 \pm 0.013$ percent.

The difference between the relative percentages of w and w^x gene mutations from W^A and $W^R = 28 \pm 8.5$ percent.

results: the American W^A allelomorph has given nearly twice as many mutations as the Russian W^R allelomorph (55 : 59200=0.093 percent and 40 : 75300=0.053 percent respectively). A second difference between the two normal allelomorphs is that the more frequently mutating American W^A gives many more mutations direct to white than to all other allelomorphs (41 $W^A \rightarrow w$: 14 $W^A \rightarrow w^x$), and the more stable Russian W^R pro-

duced white and colored allelomorphs in approximately equal numbers (19 $W^R \rightarrow w$: 21 $W^R \rightarrow w^r$). Both differences are statistically significant. The summarized results of all experiments also show that the above mentioned differences in the mutability of W^A and W^R are not due to different "genotypical environment." The American W^A mutates in the same way in its own American and in the Russian genotypes. And the mutability of the Russian W^R remains substantially the same in Russian and in American "genotypical environment."

We thus had two "normal" allelomorphs differing in their mutabilities but otherwise indistinguishable.

CONCLUSIONS

From the results obtained in all above reviewed experiments, some conclusions can be drawn upon three intimately connected questions: (1) the nature of the action of X-rays on the genes, (2) the general nature of mutational gene changes and (3) the general nature of the gene structure.

The following statements concerning the nature of the genetic X-ray action can be made:

1. The action of X-rays upon the genes is by no means purely destructive. A direct proof of this statement is given by those cases in which mutations in both opposite directions were produced by X-ray treatment directly one from another (figure 2). Each mutational change can *a priori* be ascribed to total or partial gene destruction, but mutations in opposite directions, as, for instance, $F \rightarrow f$ and $f \rightarrow F$, cannot possibly both be destructions: if one of them is so, then the other must be a gene construction. This point has already been emphasized in the excellent work of PATTERSON and MULLER and in some of my own previous papers.

2. X-rays can, even in a definite single locus, produce quite different mutational changes. The best example illustrating this statement is given by the different mutations from and to eosin shown in figure 5. This property of X-rays is to be expected if we recall the nature of physical action of X-ray quanta upon the matter. Even monochromatic X-rays can produce in the X-rayed matter electrons of very different speeds; this depends upon the amounts of energy which happen to be given up by the X-ray quanta to the accidentally hit and ejected electrons. These ejected electrons of different speed build a large scale of different energetic quanta which now can be delivered to other molecules and produce quite different effects. Since the kind of reactions which the struck molecules will undergo is also dependent upon the kind of atoms and molecules present at the moment in

their surroundings, it is clear that quite different end-effects can be produced by X-ray treatment. Some of the reactions can, of course, as MULLER has already pointed out (PATTERSON and MULLER 1930), lead to the "breakdown" or to a "simplification" of the previous physico-chemical structure, but at least some of the others must be of the nature of syntheses.

3. The specific nature and the relative frequencies of different mutations are primarily dependent upon the specific structures of the treated genes and not upon the specific action of X-rays. This becomes evident from the general parallelism shown by the "spontaneous" and the X-ray induced mutations in Drosophila. And this is particularly proved by the general differences in the mutabilities at two different loci (for instance, those of white and forked in Drosophila) induced by the same X-ray dosage.

Concerning the nature of mutational gene changes the following can be stated:

1. In general gene mutations are not losses of the specific and probably highly differentiated genic material. This is proved by the fact that at least some of the mutational processes are reversible. But even those cases in which reversions can not be produced are by no means proving the loss hypothesis. The reversion from white to normal ($w \rightarrow W$) is probably not realizable, but the occurrence (although only in very rare cases) of reversions from white to eosin proves that white is not "nothing," is not a loss of the gene. True "gene deficiencies" probably occur in certain cases (PATTERSON 1932), but they are surely not the typical kind of gene mutations.

2. In general the gene mutations are not merely quantitative alterations of the previous genic material. The quantitative theories of gene mutations are primarily based on some phenotypical phenomena, chiefly upon the fact that some series of multiple allelomorphs can be ordered in a quantitative scale according to their phenotypic effects. But against this view some objections can be made. An important logical objection is that we have no reasons to transfer a quantitative scale of phenotypical effects into the gene structure. Still more important is the fact that even the phenotypes of multiple allelomorphic series can not always be arranged in simple quantitative scales. In some cases different allelomorphs manifest qualitatively different characters (DUBININ 1929, STERN 1930b). In still other cases the same multiple allelomorphs must be arranged in different sequence on a quantitative scale if different effects of the gene are taken into consideration. This was shown by the results of the analysis of the manifold effects of the white-eye allelomorphs of *Drosophila melanogaster*. Finally, against a purely quantitative theory of gene mutations the same objections

can be made as against the extreme "presence-absence" hypothesis: the loss of the whole gene or of a half or a quarter of the gene is equally improbable in all those cases of mutations which are reversible. Thus mutations must in general consist of some kind of intra-genic rearrangements altering the physico-chemical structure of the gene, and purely quantitative gene mutations are (like the "gene deficiencies") conceivable only as a special group of mutational changes.

3. The specific structures of the genes determine the relative frequencies and the direction of mutational changes. At some loci (for instance, at that of forked) the mutability seems to be, within certain limits, quantitatively unordered: even both extreme allelomorphs (normal and the "spontaneous" forked used in our experiments) show the same degree of mutability. In other cases, as in that of the white-eye series, the mutability is a clearly determinate or directed one: not all theoretically conceivable mutational steps are realizable, and those which are possible show different, specific frequencies. V. JOLLOS, applying GOLDSCHMIDT's method of induction of mutations (treatment of Drosophila larvae with high temperature), has shown that an almost absolutely directed series of mutational steps can be induced at the white locus of *Drosophila melanogaster* (GOLDSCHMIDT 1929, JOLLOS 1930, 1931a, 1931b). In our X-ray experiments the mutability at the white locus was not by far as absolutely directed as in the experiments of JOLLOS. But this difference is not at all surprising if we consider the high power and the heterogeneity of X-ray action. Thus the results of X-ray and temperature experiments with the white locus of Drosophila and especially the finding of differently mutating "normal" allelomorphs of white show that the gene structures can determine the direction of mutability and the relative frequencies of different mutations of a species and even of a race.

Some conclusions upon the nature of the gene structure spontaneously result from the above statements.

Are the genes fixed quantities of specialized matter, consisting of a definite number of identical physico-chemical units (for instance, molecules)? Or is the gene itself a physico-chemical unit of some kind (a large molecule, a micella or a colloid particle of specific structure)?

The first hypothesis is, I think, unacceptable as a general scheme. It seems to be very improbable that X-rays would simultaneously change in the same way all the identical physico-chemical units constituting the gene. We would be thus forced to accept the quantitative theory of gene mutation, which, as we have seen above, encounters many serious objections.

The most plausible general scheme of gene structures is thus the ac-

ceptance of the second hypothesis: genes are probably physico-chemical units which can undergo definite reactions, and some of these mutations-reactions are of reversible nature. I think that further details concerning a general scheme of gene structure are now of little importance and might do more harm than good for the progress of experimental work. The mutabilities of the scute (DUBININ 1929), white and forked (PATTERSON and MULLER 1930) loci in *Drosophila melanogaster* and of the "frequently mutating" genes in *Drosophila virilis,* the only well analyzed cases, are in some respects so different that we must admit that different genes differ profoundly one from another in their structures.

I am at the end of my paper. We geneticists are in a very happy condition: our science is young, its "developmental curve" is rising rapidly and the future will bring us the most interesting facts and views concerning the gene problem.

We must and can be optimists. And the chief purpose of my paper is to show (besides those theoretical aspects which were mentioned above) that with the help of the X-ray method the mutability of individual genes and the study of their evolutionary potencies can be attacked experimentally. In connection with phenogenetical work the study of mutability can show us the intimate nature of gene mutations. And a quantitative comparative study of the mutability in related species can elucidate some of the profound problems of evolution. But surely it will furnish us exact empirical materials on which our views upon the method of evolution and the nature of the genes can be based.

SUMMARY

1. The following reverse gene mutations were induced by X-rays in *Drosophila melanogaster:* from scute, eosin, crossveinless, vermilion and forked to their normal allelomorphs, from white to eosin and to blood and from eosin to blood in the X chromosome and from hairy, pink and sooty to their normal allelomorphs in the III chromosome (figure 2 and table 1).

2. At the locus of forked (in the X chromosome of *Drosophila melanogaster*) 11 direct mutations from normal to or toward forked ($F \rightarrow f$) and 15 reverse mutations from forked to or toward normal ($f \rightarrow F$) were induced by X-rays in a total of 43,000 normal and 44,000 forked treated gametes (in experiments of PATTERSON and MULLER and of the present author). This result proves that at this locus mutations in both opposite directions are arising with approximately equal frequencies (table 2).

3. Within the white-eye series of Drosophila mutations in almost all conceivable directions were induced by X-ray treatment (figures 3, 4 and 5,

table 3). But the frequencies of different mutations are quite different, reversions being much less frequent than direct mutations and the mutability of normal being higher than that of intermediate and especially than that of the lightest allelomorphs (table 4).

4. A study of viability and fertility rates and of the testicle-tunic color of white, eosin, blood and normal allelomorphs of different origin has shown that: (a) allelomorphs of different origin, classified as identical according to their eye-color effects, are really identical, showing no differences in their manifold effects; (b) normal, blood, eosin and white must be arranged in different orders on a quantitative scale if different effects of the gene (eye-color, viability, fertility) are taken as the basis of classification (table 5).

5. Two distinct "normal" allelomorphs of the white-eye series, showing different stability (mutating with different frequencies) but otherwise indistinguishable, could be detected in the X-rayed material (figure 6 and table 6).

6. Some conclusions upon the general nature of X-ray action and the gene structure were drawn from the experimental results (see Conclusions).

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