

THE MECHANISM OF MOSAIC FORMATION IN DROSOPHILA

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INTRODUCTION

The effects of X-radiation on the chromosomes make it possible to produce several different kinds of mosaics in *Drosophila melanogaster*. In general, these mosaics fall into two classes: (1) those that result from induced point mutations, and (2) those that result from breaks in the chromosomes. It is the object of this paper to describe the mechanism underlying the formation of mosaic flies that have resulted from breaks in the X chromosome.

The method for obtaining such mosaics has been described elsewhere (PATTERSON 1931). In brief, it consists in X-raying the wild-type fly and then crossing the treated individual to one carrying an X chromosome that contains several mutant genes scattered along its length. In case the X chromosome has not been affected by the treatment the heterozygous F₁ females will, of course, appear phenotypically normal. If, however, the irradiation has caused the loss, through breakage and elimination, of a piece of the treated X, the fact can be detected by the appearance of mosaic areas that show recessive characters in the F₁ fly. The particular recessive characters revealed will indicate the section of the treated X that has been eliminated, because the loss of a section containing the normal or dominant genes will allow such mutant genes as lie within the corresponding section of the untreated X to be phenotypically expressed.

Not all of the variant flies arising from zygotes that have received one broken and one unbroken X chromosome will exhibit mosaicism. The appearance of mosaic tissue depends upon the condition of the chromosome at the time the break was produced. If the chromosome is broken while it is in the single strand stage, the resulting fly will not exhibit mosaic areas, but will show the deficiency in all of its tissues, constituting what we have termed an aberrant fly. Such a variant may be either a male or a female, depending upon the region of the X chromosome that has been lost. The elimination of a piece from one of the strands of the two-strand stage of this chromosome is the condition necessary for the production of mosaic tissue, for in this event only a part (usually a half) of the zygote will inherit the broken or deficient chromosome. The resultant variant will be either a sex-mosaic (gynandromorph) or a mosaic female, again depending upon the particular region eliminated.

In previous experiments dealing with this subject it was found that owing to certain difficulties inherent in the stocks ordinarily used the data obtained could not be subjected to exact statistical treatment. The chief difficulty to which I allude lies in the fact that a zygote receiving an unbroken X and another X, from which a piece had been broken off of the left end by X-rays, usually did not survive. It was found that the few aberrant females which did appear in the F₁ cultures had lost but a very small piece from the extreme left end of their treated X chromosome. No female was obtained which had lost a piece by a break occurring as far to the right as the locus of prune. Since the X-radiation must break the chromosome at different levels, we should expect to find females containing chromosomes broken to the right of that locus. A study of this problem led to the discovery that the left end of the X chromosome contained a vital region, or a "gene for viability," which lies near the locus of broad. A female zygote will not develop unless this region is represented in duplicate (PATTERSON 1932a).

Attempts were made to obviate this difficulty by using as the treated parent a special stock called *Theta*. The X chromosome of the *Theta* fly carries a duplication in the form of a fragment attached to its right or fiber-bearing end. The fragment has the viability gene and the normal genes for yellow, scute, and broad, and consequently pieces of considerable length may be broken off of the left end of the *Theta* X without at the same time causing the death of a female zygote inheriting the broken element. While the *Theta* X has this great advantage over the wild-type X, yet it has one serious drawback. Aberrant females produced by breaks occurring at the left end, and falling within the range covered by the *Theta* fragment, cannot be detected in the F₁ cultures, because of the dominant effect of the wild-type genes contained in this fragment.

Since the simplest and presumably the most common type of break to be expected would be one causing the elimination of the left end of the chromosome, it is especially desirable to obtain as many as possible of the variant flies that could thus be produced. The problem was then to find an X chromosome in which the viability gene lay far removed from the left end. One might expect to find such a condition in a chromosome having an inverted section. Two X chromosomes known to have inversions were tested, but in each instance the viability region was found not to be included in the inverted section. At this point Doctor S. G. LEVIT called my attention to a stock, known as scute-8 apricot, which has in its X chromosome a long inversion. This inversion extends from a point lying just to the right of the locus of scute to some point lying between the locus of bobbed and the right end of the chromosome. The genes in the inverted section occur in reverse order, and hence the locus of bobbed lies near the left end

of the reconstituted chromosome, while that of the viability gene is situated well toward the right end.

In all of the experiments given in the following section of this paper, scute-8 apricot flies were treated and crossed to untreated yellow white crossveinless miniature forked-3 flies. The diagrams for these two chromosomes are shown in figure 1. It will be clear from the diagrams that if

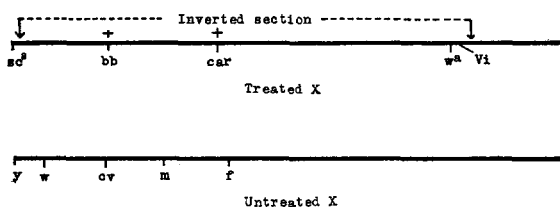


FIGURE 1.—The figure gives the diagrams of the treated and untreated X chromosomes used in the experiments. The upper diagram gives the composition of the scute-8 apricot chromosome, which contains a long inverted section. Note that the loci of white (w_a) and the viability gene are located toward the right or fiber-bearing end. The lower diagram shows the mutant genes carried by the untreated chromosome. These diagrams are based on the cytological map of the X chromosome as determined by the studies of MULLER and PAINTER (1932).

the left end of the scute-8 apricot chromosome is broken off and eliminated, the female zygote inheriting the untreated X and the broken X will show yellow body color, that is, the locus of yellow will be "deficient." Such a fly will be viable because the gene for viability will not have been eliminated by the break. She will also have heterozygous apricot eyes. A similar break occurring in one of the strands of the split chromosome will produce a mosaic female that will be half yellow and half gray.

EXPERIMENTS

Treated females

In the first experiment, young females, homozygous for scute-8 and apricot, were treated with a dosage of 1325 r units and immediately mated to males belonging to the recessive stock. For the first four days the flies were transferred to fresh bottles at the end of each twenty-four hour period, and after that they were changed at the end of each forty-eight hours, until the end of the tenth day. In this, as in all of the succeeding experiments, the cultures were kept in a room in which the temperature varied from 25 to 27.5 degrees Centigrade, with an average of 26 degrees. The flies for any lot began coming out on the eighth day and all had emerged by the end of the ninth day. The F_1 flies were examined for variants of all kinds, and a record kept of all individuals that had arisen from treated eggs fertilized by untreated X-bearing sperms.

The data from this experiment are given in table 1. They include for all, except the first daily period, the first five thousand flies counted for each

TABLE 1

Scute-8 apricot females, aged 0-12 hours, treated at 1325 r units, and crossed to yellow white cross-veinless miniature forked-3 males.

| DAYS | APRICOT FEMALES | ABERRANT FLIES | | SEX-MOSAICS | | LETHAL MUTATIONS | | | | | TOTALS |
|--------|--------------------|------------------------|--|-------------|------|------------------|------------------------|----------------------|----------|----------|--------|
| | | <i>y w^a</i> | <i>w c_v m f₃</i> | PARTIAL | HALF | <i>w</i> | <i>w-f_a</i> | <i>f_a</i> | <i>m</i> | <i>f</i> | |
| | | FEMALES | MALES | | | | | | | | |
| 1 | 109 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 109 |
| 2 | 4,983 | 8 | 2 | 1 | 3 | 2 | 0 | 0 | 1 | 0 | 5,000 |
| 3 | 4,988 | 5 | 0 | 3 | 0 | 2 | 0 | 0 | 2 | 0 | 5,000 |
| 4 | 4,994 | 3 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 5,000 |
| 5+6 | 4,997 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 5,000 |
| 7+8 | 4,999 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 9+10 | 4,997 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| Totals | 30,067 | 18 | 2 | 7 | 4 | 6 | 0 | 1 | 4 | 0 | 30,109 |

period. It was not practicable to attempt to obtain this number for the first period because of the fact that young females lay very few eggs within the first twenty-four hours. The variant flies, other than those due to point mutations, are listed under the general headings of aberrants, sex-mosaics, and lethal mutations. The point mutation cases are included with the non-variant apricot females. This method of recording reveals at once the frequency of occurrence of the different types of variants produced by deficiencies, for the total number of flies listed corresponds to the number of treated X chromosomes. Furthermore, the periodic transfer method shows the time in the germ-cell cycle at which the irradiation is most effective in breaking the chromosome.

Eighteen aberrant yellow apricot females were produced in a total of 30,109 treated X chromosomes, or about one in every 1672 chromosomes. It will be noted that the greatest number occurred on the second day (practically from the first eggs laid) and that they appeared in decreasing numbers for the succeeding days. Only two aberrant males were found, and both of these appeared on the second day. Among the eleven sex-mosaics, seven belonged to the partial type, that is, the fly was practically all female, with a small amount of male tissue present, such as a sex-comb, or male genitalia, or a small area of male coloration. Such flies usually do not result from X-raying, for they occur with about equal frequency among the controls. Most of them are due to the spontaneous elimination of one of the X chromosomes at one of the late somatic divisions. Four half-and-half gynandromorphs were found, three appearing on the second day, and one on the fourth day. The male parts of the first three had lost the maternal or treated X from one daughter cell at the first somatic division, while those of the fourth case had lost the paternal X. The three that had lost the treated X were probably caused by the X-raying. The flies were examined

for variations at the marked loci for white, facet (notched flies), miniature and forked, and all cases that showed, from breeding tests, the mutation to be lethal for the male (and therefore deficient) have been included in the table. Most of these came from eggs that had been laid during the first few days.

If we consider all of the variants to which the effect of X-radiation may be assigned, their frequency for the several periods of laying are as follows: one in 312 for the second day; one in 555 for the third day; one in 1000 for the fourth day; one in 1666 for the fifth period; one in 5000 for the sixth period; and none in 5000 for the last period. From this one may conclude that the nearer the female germ cell is to maturity at the time of treatment, the greater will be the effect of the irradiation in producing breaks and other disturbances in the chromosome.

The control flies for this experiment are given in table 2. The parent flies for the control series were taken from the same lots as those for the

TABLE 2
Scute-8 apricot females, aged 0-12 hours, and crossed to yellow white cross-veinless miniature forked-3 males.

| DAYS | APRICOT FEMALES | ABERRANT FLIES | | SEX-MOSAICS | | LETHAL MUTATIONS | | | | | TOTALS |
|--------|--------------------|------------------------|--|-------------|------|------------------|------------------------|----------------------|----------|----------|--------|
| | | <i>y w^a</i> | <i>w c_v m f₃</i> | PARTIAL | HALF | <i>w</i> | <i>w-f_a</i> | <i>f_a</i> | <i>m</i> | <i>f</i> | |
| | | FEMALES | MALES | | | | | | | | |
| 1 | 502 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 502 |
| 2 | 4,997 | 0 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 3 | 4,998 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 4 | 4,997 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 5+6 | 4,999 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 7+8 | 4,999 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 9+10 | 4,999 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| Totals | 30,491 | 1 | 0 | 9 | 1 | 0 | 0 | 0 | 0 | 0 | 30,502 |

experimental series, and were handled in exactly the same manner, except that the X-ray treatment was omitted. The only variant flies found were nine partial sex-mosaics, one half and half gynandromorph in which the male parts had lost the maternal X, and a single aberrant female.

The second experiment was similar to the first. In this, however, the females were "aged" for seven days before giving the treatment and mating to the recessive males. The counted F₁ flies are listed in table 3. The total number of flies obtained for the seven periods was 30,506 which is an increase of almost 400 over that secured in the first experiment. The increase is confined, of course, to the first day. The older females lay many eggs on this day, although the vast majority of them fail to develop. Under these conditions the cultures tend to become sour. In a measure, this difficulty can be overcome by "seeding" the food bottles with eggs laid for a

TABLE 3

Scute-8 apricot females, aged seven days, treated at 1325 r units, and crossed to yellow white cross-veinless miniature forked-3 males.

| DAYS | APRICOT FEMALES | ABERRANT FLIES | | SEX-MOSAICS | | LETHAL MUTATIONS | | | | | TOTALS |
|--------|--------------------|------------------------|--|-------------|------|------------------|------------------------|----------------------|----------|----------|--------|
| | | <i>y w^a</i> | <i>w c_o m f₃</i> | PARTIAL | HALF | <i>w</i> | <i>w-f_a</i> | <i>f_a</i> | <i>m</i> | <i>f</i> | |
| | | FEMALES | MALES | | | | | | | | |
| 1 | 504 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 506 |
| 2 | 4,980 | 14 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 5,000 |
| 3 | 4,981 | 13 | 2 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 5,000 |
| 4 | 4,987 | 12 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 5+6 | 4,994 | 1 | 0 | 2 | 1 | 1 | 0 | 1 | 0 | 0 | 5,000 |
| 7+8 | 4,996 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 9+10 | 4,999 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| Totals | 30,441 | 42 | 3 | 8 | 4 | 3 | 2 | 2 | 1 | 0 | 30,506 |

few hours by foreign flies, whose offspring can be easily recognized (for example, wild-type), before introducing the treated flies. The foreign larvae work the culture so that more individuals of the desired kind succeed in developing.

Among the F_1 flies of this series were found fifty-seven variants that could be attributed to the effects of X-rays. The frequency of their occurrence is one in every 250, 263, 294, 461, 1250, 2500, respectively, for the first six periods of laying, and one for the seventh or last period. The effect of aging virgin females, before treatment and mating, on the production of variants is clearly seen. As we have shown elsewhere, this is due to the fact that virgin females aged for several days retain most of their fully developed eggs in the ovaries, and, consequently, they have more eggs that are susceptible to the effects of radiation than is the case of younger or unaged females (PATTERSON, BREWSTER, and WINCHESTER 1932).

The control flies for the second experiment are given in table 4. Eleven

TABLE 4

Scute-8 apricot females, aged seven days, and crossed to yellow white crossveinless miniature forked-3 males.

| DAYS | APRICOT FEMALES | ABERRANT FLIES | | SEX-MOSAICS | | LETHAL MUTATIONS | | | | | TOTALS |
|--------|--------------------|------------------------|--|-------------|------|------------------|------------------------|----------------------|----------|----------|--------|
| | | <i>y w^a</i> | <i>w c_o m f₃</i> | PARTIAL | HALF | <i>w</i> | <i>w-f_a</i> | <i>f_a</i> | <i>m</i> | <i>f</i> | |
| | | FEMALES | MALES | | | | | | | | |
| 1 | 2,113 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2,115 |
| 2 | 4,999 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 3 | 4,998 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 4 | 5,000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 5+6 | 4,999 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 7+8 | 4,997 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| 9+10 | 4,997 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 5,000 |
| Totals | 32,103 | 0 | 0 | 11 | 1 | 0 | 0 | 0 | 0 | 0 | 32,115 |

partial sex-mosaics, and one half-and-half gynandromorph were found. The male parts of the latter had lost the maternal X chromosome.

The interesting point brought out by these two experiments is the fact that no mosaic flies, other than the sex-mosaics, were produced by X-raying the female germ cells. The significance of this will be discussed in a later section.

Treated males

For the treatment of the male germ cells, two groups of unmated scute-8 apricot males were at first used. In one group the males were not over eighteen hours old, while in the other group they were five days old. By the time half of the projected experiments had been completed, it was seen that there was no fundamental difference in the results that had been obtained from the two groups. This was true both for the rate and for the character of the F_1 variant flies. It was then decided to combine the results under a single experiment. The tests were continued with males of various ages, but in no test were the males used more than five days old.

The males were given a dosage of 3975 r units, or exactly three times as strong as that administered to the females, and then mated to females of the recessive stock. This stock was balanced to the well-known CIB X chromosome. Both the homozygous females and the heterozygous bar females were mated to the males, but the F_1 bar females were of no use and were not counted or recorded.

Half of the males from any lot were treated, and half were not treated, the latter serving as controls. The periodic transfer method was employed, and for each culture twenty males and from thirty to forty females were placed in a food vial. At the end of each transfer period, the flies were etherized and the males and females separated. For the next period the males were again mated to virgin females, while the fertilized females were placed in a bottle containing food rich in yeast. At the end of six or seven days these females were removed from the bottle, and later their offspring in the bottle and its corresponding mating vial were examined and classified as in the previous experiments. It is possible roughly to tell, by this method, the age of the sperm (at the time of treatment) that fertilized a particular set of eggs, for all of the offspring of any given period came from eggs that were inseminated by sperm received by the females over a definite period of time.

In table 5 are given the data that were obtained in this series of experiments. The total number of flies that had come from eggs fertilized by treated X-bearing sperm was 20,303. In the last column are also given the number of flies obtained for each of the seven periods. The numbers vary from 244 for the sixth period to 6051 for the third period. This varia-

TABLE 5

Scute-8 apricot males, treated at 3975 r units, and crossed to y w c_v m f-3/C 1 B females.

| DAYS | APRICOT FEMALES | ABERRANT FLIES | | MOSAIC FLIES | | | | LETHAL MUTATIONS | | | | | TOTALS |
|--------|--------------------|------------------------|--|--------------|--------|-------------|------|--------------------------|----------------------|----------|----------|---|--------|
| | | <i>y w^a</i> | <i>w c_v m f_s</i> | MOSAIC | GRAY- | SEX-MOSAICS | | <i>w w-f_a</i> | <i>f_a</i> | <i>m</i> | <i>f</i> | | |
| | | FEMALES | MALES | MALES | YELLOW | PARTIAL | HALF | FEMALES | | | | | |
| 1 | 4,690 | 33 | 6 | 6 | 7 | 2 | 2 | 8 | 1 | 2 | 13 | 0 | 4,770 |
| 2 | 5,655 | 14 | 14 | 2 | 5 | 1 | 2 | 8 | 2 | 2 | 6 | 2 | 5,713 |
| 3 | 5,976 | 20 | 11 | 4 | 4 | 6 | 6 | 9 | 5 | 2 | 5 | 3 | 6,051 |
| 4 | 2,620 | 11 | 5 | 0 | 1 | 0 | 2 | 4 | 2 | 0 | 2 | 1 | 2,648 |
| 5+6 | 425 | 5 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 1 | 1 | 435 |
| 7+8 | 239 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 244 |
| 9+10 | 441 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 442 |
| Totals | 20,046 | 86 | 38 | 12 | 17 | 9 | 12 | 31 | 10 | 8 | 27 | 7 | 20,303 |

tion is due in part to the fact that the same number of cultures were not examined for each of the several periods, and in part to the fact that irradiation reduces the fertility, especially when applied to certain stages of the germ-cell cycle. There were forty-nine cultures carried through the entire seven periods, and a variable number for the first four periods. The best way in which to show the effects of irradiation on fertility is to calculate the average number of F₁ flies per culture. These calculations give the following results for the seven periods: first (114), 41.8; second (97) 58.8; third (105), 57.6; fourth (97), 27.3; fifth (49), 8.8; sixth (49), 4.9; seventh (49), 9.0. The figures in parentheses indicate the number of cultures examined.

In general, X-rayed males produce distinctly fewer offspring than untreated males. This is evidenced by the much larger number of offspring obtained from the corresponding control cultures. The average numbers of flies per control cultures for the seven periods were 285, 286, 251, 244, 271, 221, 208, respectively. In addition to this general reduction in fertility, there was also noted a differential effect for certain stages of the germ cells. The detection of the selective effect of X-rays was made possible by the periodic remating of the treated males to virgin females. As the figures given in the last paragraph show, the flies were less fertile on the first day than on either of the two succeeding days. This must be due to the effect of irradiation on the sperm cells that were the oldest at the time of treatment. On the fourth day there is a decided drop in fertility. In fact, the number of offspring produced is less than half of that for either the second or the third day. The three remaining periods show a still greater decrease, with the lowest average on the sixth period. The increase in the average for the seventh or last period above that for the sixth indicates, possibly, a slight recovery in fertility.

The extreme reduction in fertility, extending from the fourth day through the tenth day, must be due to the destructive effect of the irradiation on immature germ cells. The periodic remating of the treated males to a surplus of virgin females results in the rapid using up of the germ cells that were nearest to maturity at the time of treatment. The destruction by irradiation of the immature cells is certain to bring on a period of great infertility, or even that of sterility. This is in accord with the facts developed in the field of radiotherapy where it has long been known that immature cells are much more radiosensitive than are old cells (DESJARDINS 1932).

We may now consider the variant flies that were secured from the series of treated males, as shown in table 5. There were 246 variants (omitting the partial sex-mosaics, and correcting for controls) that could be attributed to the effects of X-rays. These occurred among 20,303 F₁ flies that had been derived from eggs fertilized by treated X-bearing sperms. This gives an average of one variant in every eighty-two flies. That is to say, one out of every eighty-two X chromosomes, treated with a dose of 3975 r units, resulted in producing some type of chromosome irregularity detectable among the F₁ offspring.

Of the eighty-six yellow apricot aberrant females, at least eighty-four (two were found among the controls, table 6) must have been the result of the irradiation breaking off the left end of the treated scute-8 apricot chromosome. This gives a rate of about one in every 240 flies. The rate of their appearance varies for the different days, being one in 144, 408, 302, 240, 87, 122, and 442 flies respectively, for the seven periods included in the table.

TABLE 6
Scute-8 apricot males, untreated, crossed to y w c_v m f-3/C 1 B females.

| DAYS | APRICOT FEMALES | ABERRANT FLIES | | MOSAIC FLIES | | | LETHAL MUTATIONS | TOTALS |
|--------|--------------------|------------------------|--|----------------------------|-------------|------|---------------------|--------|
| | | <i>y w^a</i> | <i>w c_v m f₃</i> | GRAY- YELLOW FEMALES | SEX-MOSAICS | | | |
| | | FEMALES | MALES | | PARTIAL | HALF | | |
| 1 | 5,132 | 1 | 0 | 0 | 0 | 0 | 0 | 5,133 |
| 2 | 6,007 | 0 | 0 | 0 | 1 | 0 | 0 | 6,008 |
| 3 | 6,049 | 0 | 0 | 0 | 1 | 0 | 0 | 6,050 |
| 4 | 3,170 | 0 | 0 | 0 | 1 | 0 | 0 | 3,171 |
| 5+6 | 1,497 | 1 | 0 | 0 | 2 | 0 | 0 | 1,500 |
| 7+8 | 1,500 | 0 | 0 | 0 | 0 | 0 | 0 | 1,500 |
| 9+10 | 1,499 | 0 | 0 | 0 | 1 | 0 | 0 | 1,500 |
| Totals | 24,854 | 2 | 0 | 0 | 6 | 0 | 0 | 24,862 |

There were exactly fifty aberrant males produced, at the rate of one in about every 406 flies. The aberrant male carries the untreated X and a treated X chromosome that has been deleted, that is, the middle section has been eliminated. It usually has gray body color, but shows the four

remaining recessive characters—white, crossveinless, miniature, and forked-3. However, twelve of these fifty males were mosaic for gray and yellow. The significance and a possible explanation of their mosaic condition will be discussed in the next section.

The next group of variants represents one of the classes with which this study is primarily concerned, namely, gray-yellow mosaic females. There were seventeen such females obtained, seven appearing on the first day, five on the second, four on the third, and one on the fourth. This class did not appear among the offspring from treated females (tables 1 and 3). These flies are characterized by having approximately one-half of the body gray and the other half yellow.

Twenty-one sex-mosaics were found, and of these nine were of the partial type, and the other twelve were typical half-and-half gynandromorphs. In each of these twelve flies the male parts had lost the treated X chromosome, or part thereof, at the first somatic division.

The last group of variants includes the so-called lethal mutation class. These represent deficiencies at one or more of the several marked loci indicated in the table. There were eighty-three such cases, of which thirty-one occurred at the locus of white, ten involving the loci of both white and facet (Notch), eight at facet, twenty-seven at miniature, and seven at forked. The writer has elsewhere discussed this type of variant fly (PATTERSON 1932c), but the point of interest here is that nine of these cases were "fractionals," that is, only a part of the fly showed the deficiency. For example, the fly would have one miniature wing and one normal wing. The number of these mosaics, occurring at the different loci, was as follows: four at white, one at facet, three at miniature, and one at forked.

The control flies for this experiment are given in table 6. The six partial sex-mosaics require no further consideration. The only other variant flies were two aberrant yellow-apricot females. Both of these had resulted from spontaneous breaks that had eliminated the left end of the scute-8 apricot chromosome. There were no lethal mutations found at any of the marked loci.

TYPES OF MOSAICS

Sex-mosaics or gynandromorphs

The experimental results presented above have brought out the fact that several different kinds of mosaic flies are produced, including the sex-mosaics. Seventy-two sex-mosaics were detected, and fifty of these belonged to what we have termed partial sex-mosaics. This type of fly is almost entirely female, but has a limited area of male tissue, such as a sex-comb, male genitalia, or male coloration on a part of the tip of the abdomen. In this series these mosaics occurred with equal frequency among the

control and experimental series. Among 80,918 flies of the experimental series, twenty-four partials were found. This gives a rate of one in every 3371 flies. Among 87,479 flies of the control series, twenty-six partials occurred, and this gives a rate of one in every 3364 flies. As stated above, these mosaics are usually not produced by X-rays, but are the result of spontaneous elimination of one of the X chromosomes in a relatively late somatic division. Occasionally, the elimination may occur at one of the early cleavage divisions, and if this should take place at the first division, there would be produced a half-and-half gynandromorph indistinguishable from one caused by irradiation.

In the treated female series, eight typical half-and-half gynandromorphs were found. The male parts of seven of these had lost the maternal or treated X chromosome, while those of one had lost the untreated or paternal X. One might infer that the latter case had occurred spontaneously, since the untreated X was missing, but, as I have elsewhere shown, there is an indirect effect of irradiation on the cytoplasm of treated eggs which not infrequently causes the elimination of the X chromosome introduced by the sperm (PATTERSON 1931). However, since two half-and-half gynandromorphs were found among the control flies, it is very probable that one or two of the cases found in the experimental series were also the result of spontaneous elimination.

In the treated male series twelve half-and-half gynandromorphs appeared, but none was found among the control series. The male parts of each of these flies had lost all or a part of the paternal or treated X chromosome. In five of the cases an extensive deletion had resulted in the elimination of the middle region of the X, so that the male parts were gray, but with the exception of yellow, they showed the other recessive markers of the untreated X. The male half of such gynandromorphs is the counterpart of the aberrant male, which is produced by a similar deletion that affects the single-strand stage of the chromosome. In the case of the gynandromorph, the deletion takes place in the two-strand stage, and affects only one of the two strands. Consequently, the initial somatic division gives the first opportunity for the deleted and non-deleted elements to separate into separate cells.

On this basis, one can readily understand why treating the female germ cell does not result in the formation of a gynandromorph that carries in its male tissue a broken or deleted X chromosome, because at the time of treatment the two-strand stage of the gametic chromosome has not been reached. X-raying the eggs, therefore, usually results in the production of aberrant males and females, although a gynandromorph is occasionally formed as a result of the elimination of one of the daughter X chromosomes at the first cleavage division. Gynandromorphs derived from X-rayed

mothers should not possess male parts carrying a broken or deleted X chromosome. I have, however, reported three such cases and attributed the breaks to the effects of X-radiation (PATTERSON 1931a). Two of these cases were due to the elimination of the X chromosome to which the *Theta* fragment was attached, but, since this phenomenon may occur spontaneously, these two cases do not constitute proof that the effect was due to X-rays. The third case represented one in which the X chromosome was broken at a point lying to the left of forked. It now seems probable that this case resulted from a spontaneous break which occurred after the beginning of maturation and before the first cleavage took place. This would give time enough for a break to take place after the split in the gametic element had occurred. This interpretation is strengthened by the recent discovery of a gynandromorph among untreated flies that had male parts with a broken maternal X chromosome.

At rare intervals gynandromorphs appear that cannot be explained on the simple elimination hypothesis, but can be accounted for on the basis of binucleated eggs. Such cases were first reported by MORGAN and BRIDGES (1919), and have since been discussed by L. V. MORGAN (1929). STERN and SEKIGUTI (1931) have described a mosaic male derived from a binucleated egg, but they were not able to determine whether the two nuclei were the partial products of the maturation divisions of an originally single egg nucleus, or whether the oocyte was binucleated from the first.

Mosaic females

Several different types of mosaic females are produced by breaks induced in one of the strands of the two-strand stage of the X chromosome of the sperm. One type is formed as a result of a single break, and is represented by the gray-yellow half-and-half mosaics. The fact that they are found in the treated male series, and not in the treated female series, at once suggests that they arise from sperm in which the gametic X chromosome is already split at the time of irradiation. Otherwise, it would be difficult to explain their mosaic condition. They appeared at the rate of one in every 683, 1142, 1513, and 2648 flies, respectively, for the first four days or periods (table 5). These numbers, however, are not large enough to show whether the difference in rate for the different days is significant. It is of interest to note that they appeared at a decreasing frequency for the successive days, but when all types of mosaics arising from split chromosomes are considered, there is little or no indication of a decreasing trend, the rate being one in every 530, 571, 503, and 882, respectively, for the first four periods.

The second type of mosaic female is found among the "lethal mutations" class of flies. These were found in the treated male series, and all appeared

within the first three periods. It is not always possible to determine by breeding tests on fractionals whether the variation is due to a point-mutation, or to a deletion, because cells carrying the affected chromosome may not have been included within the germ glands. Nevertheless, they are important in indicating the split condition of the X chromosome in the sperm at the time of treatment.

Eversporting types of mosaics

Another class of variant produced by X-rays includes some of the so-called eversporting mosaics. The most common type of this class is caused by a chromosome rearrangement involving the locus of white, so that flies heterozygous for red and white show mottled-eyes. Sometimes adjacent genes are involved, especially the locus of facet, resulting in the production of mottled-eyed and variable notched-wing flies. Many of these cases have not as yet received an adequate explanation, but the writer has found two cases that are due to unstable translocations. One of these has been worked out both cytologically and genetically. It was found that a piece of about six map units of the left end of the *Theta* X chromosome had been broken off and translocated to a fourth chromosome. This piece carried the normal genes for white and facet, and its occasional loss from the attached fourth during somatogenesis resulted in the production of mottled-eyes and variable notched wings (PATTERSON 1932b). Still another case belonging to this category was found several years ago, and was partly worked out before the stock was lost. In this stock the flies heterozygous for gray and yellow showed yellow spots scattered over the body. Linkage tests showed that a small piece containing the normal gene for yellow had been broken off and translocated to a third chromosome. The loss of this piece during development produced the yellow spots.

This same type of eversporting mosaicism may occur as a result of spontaneous elimination in untreated material. A very good example is found in the scute-8 apricot stock. If homozygous females are crossed to yellow white males, about one in every sixty-six F_1 females shows one or more yellow spots on the body (4952 examined). Irradiation does not appreciably increase this rate, for in the treated series, one in every fifty-seven F_1 females had yellow spots (2165 examined). That the spotting is not due to a mutable gene is indicated by the fact that the scute-8 F_1 males are never spotted.

This case may be brought into line with the three cited above if we assume that the left end of the scute-8 X is occasionally lost during the course of development. This interpretation is made probable by a few tests that have been made with F_1 females. Three non-spotted and five spotted females were backcrossed to yellow white males. The three non-spotted

and four of the spotted females gave no spotted offspring. The fifth spotted female gave eighteen F_2 females, all showing yellow spots, but failed to yield any scute-8 apricot males. The stock established from this line continues to breed in this same manner. The loss of the left end of the scute-8 X creates a deficiency and hence, since it occurs in every X, the scute-8 apricot male zygote is non-viable. That the break is not followed by the translocation of the piece to one of the autosomes is made certain by the fact that none of the white-eyed females in the cultures are ever gray.

Mosaic males

We have already mentioned the fact that mosaic males are found in the treated series. These flies display various degrees of coarse and fine mosaicism, from types showing half the body gray and half yellow, with a sharp line of demarcation between the two halves, to types showing a fine mosaic of small gray and yellow areas (pepper and salt types). These flies arise as aberrant males and are therefore hyperploid. They have the untreated X, marked with the five recessive genes, and a deleted fragment of the treated X chromosome. The mosaic condition applies only to the yellow locus, for the other four recessives always show. The mosaic can be explained on the same basis offered above to account for some of the eversporting types of females, that is, the left or gray end of the deleted X is sometimes lost during the cleavage stages. If the elimination occurs once and at the first division, a half-and-half mosaic male would result, but if it took place at a later division, a male with a yellow spot would be produced. The fine mosaic type would result from several eliminations occurring in the late cleavage stages. It is possible that some of the mosaic males, as well as some of the aberrant males, have arisen from treated gametes in which the gray end had been translocated to another chromosome, rather than by a reattachment with the right-hand end of the deleted element. This cannot be determined genetically because of the fact that such males have no Y chromosome and are consequently sterile.

There are other types of mosaics than those obtained in this series of experiments. Thus by X-raying larval stages, heterozygous for various mutant characters, it is possible to produce "somatic mutations" that appear in the adult fly as mosaic or variant areas (PATTERSON 1929a, 1929b). Some of these areas are the result of induced point mutations, but most of them have been brought about through the elimination of a section of the chromosome that carried the dominant genes. The writer has also reported the finding of mosaics that resulted from somatic segregation of chromosomes, caused by X-raying egg and larval stages, heterozygous for yellow and singed (PATTERSON 1929c).

Mosaic flies caused by the loss of autosomal material are also known to oc-

cur. BRIDGES (1921) showed that the small fourth may be lost through non-disjunction. This gives rise to haplo-IV flies that have fine delicate bristles, a condition known as "Diminished." Recently MOHR (1932) has described and tested a fly that was normal on one side and haplo-IV on the other. DOBZHANSKY (1932) has reported a case (his translocation H) in which a small piece, including the locus of purple, had been broken out of a II chromosome and translocated to a Y chromosome. He obtained two females that were deficient at the locus of purple, showing that such hypoploid females may be viable. Finally, STERN (1927) has described two cases of mosaic spotting, caused by spontaneous eliminations of parts of the III chromosome. In one case the tissues of the mosaic spot were deficient for the left arm of the third, and in the other for half of the right arm of this same chromosome.

In general, however, the loss of either one of the two large autosomes, or even of more than a small piece thereof, is fatal. With respect therefore to the viability of the fly, the elimination of autosomal material stands out in sharp contrast to the loss of X-chromosomal material. This fundamental difference may have been the outcome of a long selective process. Through the evolution of the sex-determining mechanism, the fly has become adapted to the absence of one of the X chromosomes (but not to the absence of a large autosome) and consequently one can bring about the elimination of a very considerable portion of one of these chromosomes in an XX zygote without causing the death of the individual.

DISCUSSION AND CONCLUSIONS

In the majority of cases, the fundamental cause underlying the mechanism of mosaic formation is the process of chromatin elimination. Another important fact concerning mosaic formation relates to the condition of the chromosome at the time the irradiation is applied. The general rule is that if the chromosome is not split, a break or deletion will produce an aberrant male or female, depending upon the particular region eliminated; but if the chromosome has already split and is in the two-strand stage, a break or deletion in one of these strands will give rise to a mosaic fly. To a certain extent, one can obtain a desired type of variant by applying the irradiation to certain stages of the germ cells or larvae.

The results obtained in this and previously reported experiments indicate that, with few exceptions, breaks and deletions induced in the egg chromosome by X-raying virgin females give rise to aberrant flies only. We should expect this to be the case from the work of HUETTNER (1924) on maturation and fertilization. He found that the polar bodies are not given off until after the sperm has entered the egg. The ovarian egg has a large, reticular nucleus, but in eggs about ready to be fertilized the meta-

phase spindle of the first polar body is present. In treating the egg in the ovary, the irradiation is applied to chromosomes that in the main are in the tetrad or pretetrad condition, and, consequently, a deficiency induced in any chromosome will affect both of its potential strands. A mature egg that retains the broken element will, upon fertilization, develop into a fly that carries the deficiency in all of its cells, that is, it will be of the aberrant type. If mosaics with deficient chromosomes are produced at all, the break must have taken place in those eggs that had formed the first polar spindle, where there might be a chance for the gametic split to occur.

The production of mosaics from treated eggs is confined mainly to sex-mosaics of the half-and-half type. Such mosaics or gynandromorphs do not carry a broken chromosome (one exception, explained above), but are the result of the elimination of an entire somatic chromosome, usually at the first cleavage division, and therefore following maturation and after the gametic split had occurred. It has been found that the rate at which half-and-half gynandromorphs appear among F_1 flies derived from treated females is increased about three times over that at which they are found among the controls. It has also been observed (MORGAN and BRIDGES 1919, PATTERSON 1931) that the maternal and paternal X chromosomes are eliminated with equal frequency in gynandromorphs derived from untreated flies. In the case of gynandromorphs from treated mothers, the maternal and paternal chromosomes are likewise lost with about equal frequency.

This fact lead the writer (1931, p. 199) to suggest that at least part of the effect of irradiation on elimination must be indirect, probably operating through the cytoplasm of the egg. If this suggestion is valid, then the cytoplasm must eventually recover from this effect. In the present series of experiments little or no evidence was found which indicated that treating the egg increased the type of sex-mosaic which had male areas of less than half the size of the body. This type of gynandromorph occurred as frequently among the control flies as among the experimental flies. However, in some of the previously conducted experiments, especially when the *Theta* stock was used as the treated parent, evidence was found indicating that the effect persisted beyond the first cleavage division, for here the partial sex-mosaics were significantly increased as a result of the treatment.

If the cause of the elimination is brought about through the absorption of the rays by the cytoplasm, there might be a recovery from the effect causing elimination as development progressed. Recovery from the effects of radiation by organisms has been reported in the literature. Thus BOVIE and KLEIN (1918), and BOVIE and DALAND (1923) showed that paramecia, sensitized to heat by exposure to fluorite radiation, recover from the effects of the radiation after about five hours, and HANCE (1926) found that X-

radiation of these same organisms brings about a slight but constant depression in the division rate from which the organisms recover after from two to five days.

Irradiating the sperm cells by treating adult males results in the production, not only of aberrant flies, but also of mosaics, including gynandromorphs. But the increase in gynandromorphs over that found in controls is restricted to the half-and-half type. The partial sex-mosaics show no appreciable increase as a result of the irradiation. I have obtained a total of one hundred and nineteen half-and-half gynandromorphs among flies derived from treated males. Their distribution with reference to the elimination of the treated or untreated X chromosome is entirely different from that reported above for the treated female series. One hundred and thirteen of these had lost the treated X (or part) from their male parts, and only six had lost the untreated or maternal X. Undoubtedly, some half dozen of those in which the treated X was found to be missing were not caused by the irradiation but were the result of spontaneous eliminations. This leaves one hundred and seven cases that can safely be attributed to the direct effects of irradiation. In forty-five flies the male parts carried, in addition to the marked maternal X, a broken or deleted paternal X. In all such cases the irradiation must have affected only one of the two gametic strands. The remaining sixty-two cases gave the appearance of having lost one entire gametic strand of the treated X chromosome. This was proved to be true in some cases by the use of the *Theta* stock in which the gray fragment at the right end of the X chromosome served as a marker. In cases derived from treated non-*Theta* stock, it is possible that in some instances the treated X had been broken at a point lying to the right of the normal allelomorph of the last marker and the right-hand end of the chromosome, for in this event the presence of the broken chromosome could not be detected.

The mosaic females derived from treated sperm fall into two classes, the gray-yellow class and the fractional or lethal class. Both of these classes are important, because both indicate that the breaks which caused them took place in only one of the strands of the two-strand stage. This raises the question as to why X-rayed sperm give rise to both aberrant and mosaic flies. The ratio of aberrant females to mosaic females is about six to one. With reference to the condition of the gametic chromosome at the time of treatment, there are three possibilities, as follows: (a) The chromosome may not be split in any of the sperm, (b) it may be split in all sperm and (c) it may be split in some sperm but not in others. We may now consider what would follow on the basis of each of these assumptions.

If we assume that the chromosome is not split in any of the male gametes at the time of treatment, the appearance of aberrant flies can easily be

accounted for, but in order to explain the appearance of mosaic females, it would be necessary further to postulate some kind of delayed radiation effect which would bring about the break in one of the strands after the split had occurred. Aside from the fact that we have been unable to obtain any experimental proof of a delayed effect in breakage, there is the further objection that no such effect occurs in the egg chromosome, which is known to be in the one-strand stage at the time of treatment.

The second suggested possibility that the gametic split is present in all fully formed sperm also meets with a serious objection. It is true that some cytologists hold the view that the gametic split occurs in the prophase stages of the preceding division; nevertheless, the genetic evidence is not in harmony with that assumption. On the basis of this suggestion it would be necessary to assume that radiation sometimes breaks one strand and sometimes both strands. If the break is the result of a "direct electron hit," it would be difficult to explain the fact that in about six times out of seven both strands are hit simultaneously.

The simplest explanation to account for the facts of breakage is implied in the third possibility, for the genetic evidence indicates that the gametic split is present in only about one out of every seven fully formed sperms. Our complete lack of knowledge with reference to the exact nature of the effect of radiation in producing breaks in the chromosomes makes it difficult to decide definitely between these three alternatives. In view of all of the facts, however, the writer regards the third alternative as the most probable.

Another point of interest relates to the fate of the broken-off or eliminated piece of the chromosome. In all probability this piece simply disintegrates in the cytoplasm, although the possibility of its loss through the mechanism of a translocation must be considered. Obviously, such aberrant flies as the yellow apricot females, derived from treated male gametes, could not have arisen through a translocation of a part of the broken scute-8 chromosome to one of the autosomes. The irradiation must produce such translocations, but these can not be detected by examination of the F_1 flies, for the deficiency created at the locus of yellow in the broken X would still be covered by its normal allelomorph in the translocated fragment on the autosome.

The corresponding yellow apricot females, derived from treated female germ cells, might possibly arise from translocations. For here the break is induced in prematuration chromosomes and should a translocation occur there would be an equal chance that the resulting gametes would fail to receive the translocated piece. Such gametes upon fertilization by yellow X-bearing sperms would produce yellow aberrant females. But if this were the method, then there would be an equal number of gray hyperploid

females produced. It should be possible to detect at least some of these postulated females without having to resort to breeding tests. In over sixty thousand F_1 gray females from cultures that yielded sixty yellow aberrant females, not a single hyperploid was detected, although the flies were carefully examined with the view of detecting such variants. In view of these facts, it is very probably that the yellow aberrant females from treated mothers have been produced by a simple break, followed by the disintegration of the broken-off piece.

The class of gray-yellow mosaic females might possibly come from induced translocations. These flies are derived from treated sperm, and if the broken-off fragment from one of the strands were to become attached to an autosomal strand, it might segregate into the future gray part of the fly at the first somatic division. If this should happen, some of the sons of those mosaic females yielding gray offspring would reveal the presence of the translocated piece. Seven of the tested mosaic females gave numbers of gray offspring large enough to make the test adequate, but in no case were males carrying a translocated piece obtained. Such a male would have gray body color, but would show the remaining recessive characters present in the marked maternal X chromosome. This evidence supports the conclusions that the gray-yellow mosaic females result from simple breaks in the treated X chromosome.

SUMMARY

There is reported in the paper a series of new experiments which had as their object a more exact determination of the nature of the effects of X-radiation on the production of mosaic flies by breaks in the X chromosome. The scute-8 apricot stock used in the experiment is characterized by having an X chromosome with a long inverted section. This condition made it possible to obtain considerable numbers of aberrant and mosaic flies by breaking off the left end of the X chromosome—a result that is rarely attained when a normal X chromosome is treated. The main points brought out in the experiments are summarized in the following paragraphs.

1. The main cause underlying the production of mosaic flies is chromatin elimination. The elimination may involve the entire X chromosome but frequently includes only a part of that chromosome.

2. The type of fly resulting from breakage depends upon the condition of the chromosome at the time the break is induced. If the gametic element is not split at this time, the resulting fly will be of the aberrant type, and will reveal the deficiency in all of its tissues; but if the gametic split is present, the elimination of all or part of one of the strands will produce a mosaic individual.

3. It was found that if female germ cells were treated by X-raying vir-

gins, only the aberrant type of fly developed, following breakage of the X chromosome. This was taken to mean that the gametic split had not developed at the time of raying. The number of sex mosaics found among F₁ flies from treated mothers is significantly increased over that occurring among the controls. There is no conclusive evidence that these sex-mosaics carry a broken X chromosome, but they do show that their male parts lose the paternal X with the same frequency as the maternal X. This lead to the suggestion that the effect of radiation on the elimination of the X chromosome is in part indirect, probably operating through the cytoplasm.

4. X-ricing mature sperm cells result in the production of both mosaic and aberrant flies, in the ratio of one to six. This indicates that at the time of treatment the X chromosome is split in about one out of every seven sperms. Treating the male germ cells also increases the number of gynandromorphs. Over forty percent of these carry a broken X chromosome in their male parts, but most, if not all, of the remaining sex-mosaics have lost half the treated paternal X at the first somatic division. There is no evidence that the treated sperm cell affects the elimination of the maternal X chromosome brought into the zygote through the egg.

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