SEX LIMITED INHERITANCE
IN DROSOPHILA

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E S P

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INTRODUCTION

After Mendel's work was rediscovered in 1900, many researchers worked to confirm and extend his findings. Although a possible relationship between genes and chromosomes was suggested almost immediately[1], proof of that relationship, or even evidence that genes were physical objects, remained elusive. To many, the gene served only as a theoretical construct, conveniently invoked to explain observed inheritance patterns.

In 1910, when T. H. Morgan published the results of his work on an atypical male fruit fly that appeared in his laboratory, all this began to change. Normally *Drosophila melanogaster* have red eyes, but Morgan's new fly had white eyes. To study the genetics of the white-eye trait, Morgan crossed the original white-eyed male with a red-eyed female and obtained the following results:

	males	females
P	white eyes	red eyes
F_1	all red	all red
F_2	½ red	all red
	½ white	all red

Because the trait first seemed to occur only in males, Morgan referred to it as a "sex-limited" trait. However, after the first cross, he mated the original male with some of the F_1 red-eyed females and obtained approximately equal numbers of red- and white-eyed males and females among the progeny. Thus the trait proved to be sex-related, not sex-limited.

Beginning on page 2, Morgan presents a possible explanation of his results. His analysis can be difficult for a modern reader to follow because he represents the crosses using a symbology that is not in use today, and because he uses his symbology inconsistently (see footnote

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[1] For examples, see:

Cannon, W. A. 1902. A Cytological Basis for the Mendelian Law. *Bulletin of the Torrey Botanical Club,* 29: 657–661.

Sutton, Walter S. 1902. On the Morphology of the Chromosome Group in *Brachystola magna*, *Biological Bulletin*, 4: 24–39.

Sutton, W. S. 1903. The chromosomes in heredity. *Biological Bulletin*, 4:231–251.

on page 5). At one point, there is even a typographical error in the symbols that adds to the confusion (see footnote, page 3).

Morgan uses the letter "X" to represent the X chromosome, the letter "R" to represent the allele for red eyes, and the letter "W" to represent the allele for white eyes. He begins his analysis (page 2) by representing the X chromosome and the R and W alleles separately:

> When the white-eyed male (sport) is crossed with his red-eyed sisters, the following combinations result:
>
> $$\begin{array}{ccll}
> \text{WX} & — & \text{W} & \text{(male)} \\
> \text{RX} & — & \text{RX} & \text{(female)}
> \end{array}$$
> _____
> $$\begin{array}{cll}
> \text{RWXX (50\%)} & — & \text{RWX (50\%)} \\
> \text{Red female} & & \text{Red male}
> \end{array}$$

Here, the symbols above the line represent the gametes produced by the participants in the cross, and the symbols below the line represent the genotypes that will be produced when these gametes combine at random. A current approach would be to represent this with a Punnett square, as:
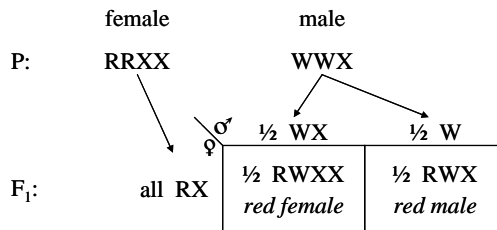
Morgan goes on to describe the cross between the males and females of the F_1 as:

> When these F_1 individuals are mated, the following table shows the expected combinations that result:
>
> $$\begin{array}{ccll}
> \text{RX} & — & \text{WX} & \text{(F_1 female)} \\
> \text{RX} & — & \text{W} & \text{(F_1 male)}
> \end{array}$$
> _____
>
> | RRXX | — | RWXX | — | RWX | — | WWX |
> |------|---|------|---|-----|---|-----|
> | (25%) | | (25%) | | (25%) | | (25%) |
> | Red | | Red | | Red | | White |
> | female | | female | | male | | male |

Again, a Punnett square can be used to represent this cross in a manner that is more familiar to a modern reader:

F$_1$: all RWXX   all RWX

	½ RX	½ W
½ RX	¼ RRXX *red female*	¼ RWX *red male*
½ WX	¼ RWXX *red female*	¼ WWX *white male*
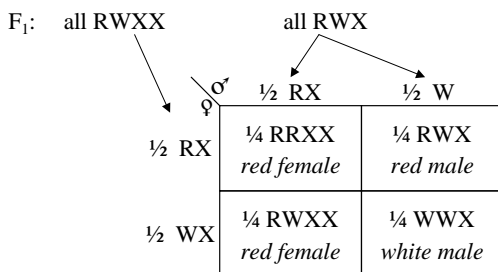
Although Morgan used separate symbols for the X chromosome and for the eye-color alleles, it is clear that he believes that they in fact have a physical relationship. At the beginning of the paper (bottom, page 2), he notes:

> In order to obtain these results it is necessary to assume . . . that, when the two classes of the spermatozoa are formed in the F$_1$ red male (RWX), R and X go together—otherwise the results will not follow (with the symbolism here used). This all-important point can not be fully discussed in this communication.

And, at the end of the paper (bottom, page 5), he concludes:

> It now becomes evident why we found it necessary to assume a coupling of R and X in one of the spermatozoa of the red-eyed F$_1$ hybrid (RXO). *The fact is that this R and X are combined, and have never existed apart.* (emphasis added)

Morgan is clearly interpreting his results on the assumption that the gene for eye color is physically attached to, or carried on, the X chromosome, although he does not make that claim explicitly in his paper.

Just one year earlier, Morgan had published a paper[1] in which he criticized Mendelian methods as they were generally used and he emphasized the hypothetical nature of the gene:

> In the modern interpretation of Mendelism, facts are being transformed into factors at a rapid rate. If one factor will not explain the facts, then two are invoked; if two prove insufficient, three will sometimes work out. The superior jugglery sometimes necessary to account for the result, may blind us, if taken too naïvely, to the common-place that the results are often so excellently "explained" because the explanation was invented to explain them. We work backwards from the facts to the factors, and then, presto! explain the facts by the very factors that we invented to account for them. I am

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[1] Morgan, T. H., 1909. What are "Factors" in Mendelian Explanations? *American Breeders Association Reports*, 5:365-368.

not unappreciative of the distinct advantages that this method has in handling the facts. I realize how valuable it has been to us to be able to marshal our results under a few simple assumptions, yet I cannot but fear that we are rapidly developing a sort of Mendelian ritual by which to explain the extraordinary facts of alternative inheritance. So long as we do not lose sight of the purely arbitrary and formal nature of our formulae, little harm will be done; and it is only fair to state that those who are doing the actual work of progress along Mendelian lines are aware of the hypothetical nature of the factor-assumption. But those who know the results at second hand and hear the explanations given, almost invariably in terms of factors, are likely to exaggerate the importance of the interpretations and to minimize the importance of the facts.

In this present paper, however, Morgan is providing the first evidence that genes are real, physical objects, located on chromosomes, with properties that can be manipulated and studied experimentally. The white-eyed fly provided the foundation upon which Morgan and his students would establish the modern theory of the gene. More X-linked mutants followed and soon Alfred H. Sturtevant, then a nineteen-year-old undergraduate, arranged them into the first genetic map[1].

Despite the success of Morgan and his students, a few scientists still doubted the chromosome theory of inheritance—that is, the idea that genes are real, physical objects that are carried on chromosomes. The skeptics noted that although the alleles for red and white eye color *behaved* in a manner wholly analogous to that of the X chromosomes, conclusive *proof* of the physical attachment of the alleles to the X chromosome had not yet been offered. Such a demonstration would require the establishment of a relationship between the abnormal, as well as the normal, assortment of alleles and chromosomes. Another of Morgan's students, Calvin Bridges, provided just that as proof of the chromosomal theory of inheritance

Bridges first published his work in 1913 as a short paper in *Science*[2], then in 1916 as a longer paper that appeared as the first article in the first volume of the new journal *Genetics*[3]. These papers are also

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[1] Sturtevant, A. H. 1913. The linear arrangement of six sex-linked factors in Drosophila, as shown by their mode of association. *Journal of Experimental Zoology,* 14: 43-59.

[2] Bridges, C. B. 1913. Direct proof through non-disjunction that the sex-linked genes of Drosophila are borne on the X-chromosome. *Science*, NS vol XL: 107–109.

[3] Bridges, C. B.. 1916. Non-disjunction as proof of the chromosome theory of inheritance. *Genetics* 1:1–52, 107-163.

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In 1915, Morgan and his students summarized their work in a monograph—*The Mechanism of Mendelian Heredity*. This book provided the foundation for modern genetics by laying out a comprehensive argument for interpreting the chromosomes as the material basis of inheritance.

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Robert J. Robbins
Seattle, Washington 2000

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SEX LIMITED INHERITANCE

IN DROSOPHILA

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In a pedigree culture of *Drosophila* which had been running for nearly a year through a considerable number of generations, a male appeared with white eyes. The normal flies have brilliant red eyes.

The white-eyed male, bred to his red-eyed sisters, produced 1,237 red-eyed offspring, (F_1), and 3 white-eyed males. The occurrence of these three white-eyed males (F_1) (due evidently to further sporting) will, in the present communication, be ignored.

The F_1 hybrids, inbred, produced:

> 2,459   red-eyed females,
> 1,011   red-eyed males,
>   782   white-eyed males.

No white-eyed females appeared. The new character showed itself therefore to be sex limited in the sense that it was transmitted only to the grandsons. But that the character is not incompatible with femaleness is shown by the following experiment.

The white-eyed male (mutant) was later crossed with some of his daughters (F_1), and produced:

> 129   red-eyed females,
> 132   red-eyed males,
>   88   white-eyed females,
>   86   white-eyed males.

The results show that the new character, white eyes, can be carried over to the females by a suitable cross, and is in consequence in this sense not limited to one sex. It will be noted that the four classes of individuals occur in approximately equal numbers (25 per cent.).

AN HYPOTHESIS TO ACCOUNT FOR THE RESULTS

The results just described can be accounted for by the following hypothesis. Assume that all of the spermatozoa of the white-eyed male carry the "factor" for white eyes "W"; that half of the spermatozoa carry a sex factor "X," the other half lack it, *i.e.*, the male is heterozygous for sex. Thus the symbol for the male is "WWX," and for his two kinds of spermatozoa WX–W.

Assume that all of the eggs of the red-eyed female carry the red-eyed "factor" R; and that all of the eggs (after reduction) carry one X each, the symbol for the red-eyed female will be therefore RRXX and that for her eggs will be RX–RX.

When the white-eyed male (sport) is crossed with his red-eyed sisters, the following combinations result:

WX	—	W	(male)
RX	—	RX	(female)

RWXX (50%)	—	RWX (50%)
Red female		Red male

When these F_1 individuals are mated, the following table shows the expected combinations that result:

RX	—	WX	(F_1 female)
RX	—	W	(F_1 male)

RRXX	—	RWXX	—	RWX	—	WWX
(25%)		(25%)		(25%)		(25%)
Red		Red		Red		White
female		female		male		male

It will be seen from the last formula that the outcome is Mendelian in the sense that there are three reds to one white. But it is also apparent that all of the whites are confined to the male sex.

It will also be noted that there are two classes of red females—one pure RRXX and one hybrid RWXX—but only one class of red males (RWX). This point will be taken up later. In order to obtain these results it is necessary to assume, as in the last scheme, that, when the two classes of the spermatozoa are formed in the F_1 red male (RWX), R

and X go together—otherwise the results will not follow (with the symbolism here used). This all-important point can not be fully discussed in this communication.

The hypothesis just utilized to explain these results first obtained can be tested in several ways.

VERIFICATION OF HYPOTHESIS

First Verification.—If the symbol for the white male is WWX, and for the white female WWXX, the germ cells will be WX–W (male) and WX–WX (female), respectively. Mated, these individuals should give

$$
\begin{array}{c}
\text{WX} \;-\; \text{W} \quad \text{(male)} \\
\text{WX} \;-\; \text{WX} \;\; \text{(female)} \\
\hline
\text{WWXX (50\%)} \;-\; \text{WWX (50\%)} \\
\text{White female} \qquad \text{White male}
\end{array}
$$

All of the offspring should be white, and male and female in equal numbers; this in fact is the case.

Second Verification.—As stated there should be two classes of female in the F_2 generation, namely, RRXX and RWXX. This can be tested by pairing individual females with white males. In the one instance (RRXX) all the offspring should be red—

$$
\begin{array}{c}
\text{RX} \;-\; \text{RX} \;\; \text{(female)} \\
\text{WX} \;-\; \text{W} \quad \text{(male)} \\
\hline
\text{RWXX} \;-\; \text{RWX}
\end{array}
$$

and in the other instance (RWXX) there should be four classes of individuals in equal numbers, thus:

$$
\begin{array}{c}
\text{RX} \;-\; \text{WX} \;\; \text{(female)} \\
\text{WX} \;-\; \text{W} \quad \text{(male)} \\
\hline
\text{RWXX} \;-\; \text{WWXX} \;-\; \text{RWX} \;-\; \text{WWX}
\end{array}
$$

Tests of the F_2 red females show in fact that these two classes exist.

Third Verification.—The red F_1 females should all be RWXX, and should give with any white male the four combinations last described. Such in fact is found to be the case.

Fourth Verification.—The red F_1 males (RWX) should also be heterozygous. Crossed with white females (WWXX) all the female

offspring should be red-eyed, and all the male offspring white-eyed, thus:

$$RX \quad — \quad W \quad \text{(red male)}$$
$$WX \quad — \quad WX \quad \text{(white female)}$$
$$\overline{}$$
$$RWXX \quad — \quad WWX$$

Here again the anticipation was verified, for all of the females were red-eyed and all of the males were white-eyed.

CROSSING THE NEW TYPE WITH WILD MALES AND FEMALES

A most surprising fact appeared when a white-eyed female was paired to a wild, red-eyed male, *i.e.*, to an individual of an unrelated stock. The anticipation was that wild males and females alike carry the factor for red eyes, but the experiments showed that all wild males are heterozygous for red eyes, and that all the wild females are homozygous. Thus when the white-eyed female is crossed with a wild red-eyed male, all of the female offspring are red-eyed, and all of the male offspring white-eyed. The results can be accounted for on the assumption that the wild male is RWX. Thus:

$$RX \quad — \quad W \quad \text{(red male)}$$
$$WX \quad — \quad WX \quad \text{(white female)}$$
$$\overline{}$$
$$RWXX\,(50\%) \quad — \quad WWX\,(50\%)$$

The converse cross between a white-eyed male WWX[1] and a wild, red-eyed female shows that the wild female is homozygous both for X and for red eyes. Thus:

$$WX \quad — \quad W \quad \text{(white male)}$$
$$RX \quad — \quad RX \quad \text{(red female)}$$
$$\overline{}$$
$$RWXX\,(50\%) \quad — \quad RWX\,(50\%)$$

The results give, in fact, only red males and females in equal numbers.

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[1] Here, the original reads "RWX" — not "WWX" as it should. This is clearly a typographical error, since the immediately following diagram of the cross shows the male producing only WX and W gametes. (Note added for ESP digital-reprint publication.)

GENERAL CONCLUSIONS

The most important consideration from these results is that in every point they furnish the converse evidence from that given by Abraxas as worked out by Punnett and Raynor. The two cases supplement each other in every way, and it is significant to note in this connection that in nature only females of the sport *Abraxas lacticolor* occur, while in *Drosophila* I have obtained only the male sport. Significant, too, is the fact that analysis of the result shows that the wild female *Abraxas grossulariata* is heterozygous for color and sex, while in *Drosophila* it is the male that is heterozygous for these two characters.

Since the wild males (RWX) are heterozygous for red eyes, and the female (RXRX[1]) homozygous, it seems probable that the sport arose from a change in a single egg of such a sort that instead of being RX (after reduction) the red factor dropped out, so that RX became WX or simply OX. If this view is correct it follows that the mutation took place in the egg of a female from which a male was produced by combination with the sperm carrying no X, no R (or W in our formulae). In other words, if the formula for the eggs of the normal female is RX–RX, then the formula for the particular egg that sported will be WX; *i.e.*, one R dropped out of the egg leaving it WX (or no R and one X), which may be written OX. This egg we assume was fertilized by a male-producing sperm. The formula for the two classes of spermatozoa is RX–O. The latter, O, is the male-producing sperm, which combining with the egg OX (see above) gives OOX (or WWX), which is the formula for the white-eyed male mutant.

The transfer of the new character (white eyes) to the female (by crossing a white-eyed male, OOX to a heterozygous female (F_1)) can therefore be expressed as follows:

$$
\begin{array}{llll}
\text{OX} & \text{---} & \text{O} & \text{(white male)} \\
\text{RX} & \text{---} & \text{OX} & (F_1 \text{ female})
\end{array}
$$

RXOX —	RXO —	OOXX —	OOX
Red	Red	White	White
female	male	female	male

It now becomes evident why we found it necessary to assume a coupling of R and X in one of the spermatozoa of the red-eyed F_1

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[1] Morgan uses his symbology inconsistently at different points within this paper. Here he refers to the wild type female as RXRX. but earlier (page 2) he had been using RRXX. (Note added for ESP digital-reprint publication.)

hybrid (RXO). The fact is that this R and X are combined, and have never existed apart.

It has been assumed that the white-eyed mutant arose by a male-producing sperm (O) fertilizing an egg (OX) that had mutated. It may be asked what would have been the result if a female-producing sperm (RX) had fertilized this egg (OX)? Evidently a heterozygous female RXOX would arise, which, fertilized later by any normal male (RX–O) would produce in the next generation pure red females RRXX, red heterozygous females RXOX, red males RXO, and white males OOX (25 per cent.). As yet I have found no evidence that white-eyed sports occur in such numbers. Selective fertilization may be involved in the answer to this question.

Postscript: The Cross in Modern Symbols

Modern symbolism combines the symbols for genes and chromosomes by placing superscripts, representing alleles, on an "X", representing the X chromosome. Alleles for recessive mutants are represented with a lower-case letter, while the normal allele is represented by the same letter with a superscript "+".

To represent Morgan's findings in modern symbols, let:

X^{w^+} = an X chromosome with the dominant, red-eye allele,

X^w = an X chromosome with the recessive, white-eye allele,

Y = the Y chromosome, with no allele for eye color.

Since *Drosophila* females have two X chromosomes, whereas males have one X and one Y, Morgan's original cross can be diagrammed as below.