CHAPTER 5

Thomas Hunt Morgan & the White-eyed Mutant

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INTRODUCTION

In 1910, the lively ragtime music of Scott Joplin was sweeping the nation. Harry Houdini amazed crowds with his spectacular escapes from straitjackets and locked trunks. Cities were booming. Major industry had increased dramatically in the late 1800s, and with it the demand for more workers to operate factories. Many people had moved from rural to urban areas to find jobs. In New York City, residents were accustoming themselves to this growth and to a new underground train system, a subway, opened six years earlier to help accommodate their needs. City residents were also still fascinated with "aeroplane" flights. The Wright Brothers had been the first to fly at Kitty Hawk, North Carolina, only seven years earlier. *The World*, one of the city's newspapers, capitalizing on the excitement surrounding manned flights, had offered a $10,000 prize for the first person to fly from Albany to New York non-stop.

On the upper west side of New York City, on the sixth floor of Schermerhorn Hall on the campus of Columbia University, was a 16- by 23-foot room that would soon become renowned worldwide (Figure 5.1). It was Thomas Hunt Morgan's lab—or what passed for his lab. It was crowded with eight large desks, including those for undergraduates involved in his research. Papers were piled on the desks, shelves were filled with bottles, and the air smelled of yeast and fermenting bananas. Morgan (Figure 5.2) had gained widespread recognition for his experiments in embryology. He was also noted for his vigorous skepticism, especially about the ideas of Darwin and Mendel.

Morgan was pursuing many research projects. In one study on experimental evolution using fruit flies, he had recently encountered a white-eyed male. In a population of flies whose eyes were normally red, the white-eyed individual was certainly remarkable. Granted, individuals with unusual traits—"sports of nature"—did appear occasionally. But the traits often were lost again in subsequent generations. If the white-eyed trait was inherited, however, it might reflect a mutation—a significant, long-term genetic change in the population. If so, it held for Morgan a potential clue about how new species could originate. At the same time, the trait exhibited a strange and equally remarkable pattern of inheritance. So far, only males had been found with the white-eyed trait. Why? What feature of development, heredity, or species formation could account for this?

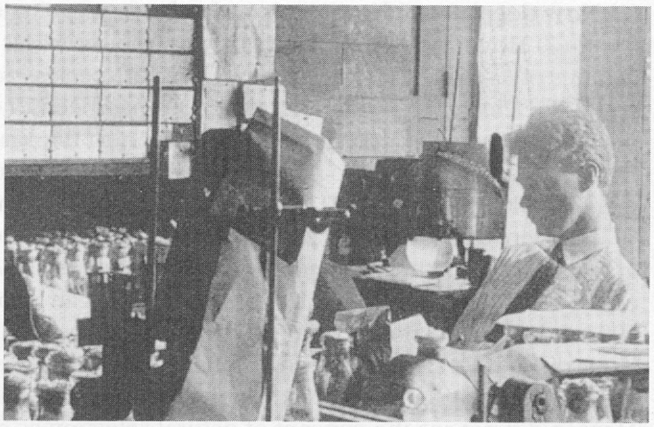

FIGURE 5.1 Thomas Hunt Morgan's lab in Schermerhorn Hall, Columbia University, New York (around 1920). Calvin Bridges, who originally started working with Morgan by washing bottles as an undergraduate, sits at his desk. *Source:* Courtesy of the American Philosophical Society Library, Stern Papers.

FIGURE 5.2 Thomas Hunt Morgan at work in his office (sometime between 1915 and 1920). *Source:* American Philosophical Library, Columbia University Department of Biology Photograph Collection.

THOMAS HUNT MORGAN AND THE LIFE SCIENCES, 1900–1910

Morgan's background influenced how he perceived the problem of the white-eyed fly. Most of Morgan's research had been related to a central question in biology at the time: What determines the form of an organism? The question had three parts: (1) How does a complex organism *develop* from a single cell and acquire its specific form? (2) How does an organism *inherit* from previous generations specific traits or features of its form? (3) How do new forms or species *evolve* on a larger historical time scale? The challenge throughout the 1800s had been to explain all three processes at once. Each question posed ways for Morgan to think about his white-eyed mutant: How did the new eye color originate? Was it an accident of embryological development? Could it be inherited? Did it represent a trait distinguishing a new species?

Darwin, of course, had provided one solution to the puzzle of organismal form: gradual evolution through natural selection. But his views were not uniformly accepted, even by biologists working after 1900. Morgan strongly criticized Darwinism in 1903. Selection, he noted, was only a negative process. It edited or reduced variation. How did new traits emerge in the first place? Biologists needed to search for the causes of variation that would explain how a new lineage evolved. In addition, Morgan did not see the concept of natural selection as rigorous or testable. Morgan's criterion of "scientific" proof was experiment in the laboratory. No one had demonstrated evolution or the creation of a new species in a lab (though Morgan might have been impressed with later studies by H. B. D. Kettlewell—see Chapter 1).

The premier area of study in biology at the turn of the century was development—how a fertilized egg is dramatically transformed into an embryo and how an embryo is further transformed into a complex adult organism (see also Chapter 4). When Morgan encountered the white-eyed mutant, he had already studied development extensively. For example, he had examined how the developing organism's form is affected by the initial orientation of the egg and by the concentration of salts in the fluid surrounding the egg. He had looked at how egg fragments (rather than whole eggs) developed when fertilized. Morgan also had a strong interest in how sex was determined. What made one organism male, another female? He had summarized his views in a 1909 research paper. Morgan's previous research offered several ideas for viewing the white-eyed trait in terms of development.

Despite the long-standing focus on development, the study of inheritance was expanding rapidly in the early 1900s. The research was closely linked to agriculture. As cities grew and population increased, demand for food rose. At the same time, because people had migrated to the cities, there were fewer hands to manage the farms. Farmers needed to increase crop yields. They turned to fertilizers, new methods of plowing, and better animal nutrition. But as U.S. Secretary of Agriculture James Wilson noted in 1910, these improvements based on the "environment" relied on costly expenditures every year. Farm profits could be vastly increased, he argued, by changing the plants themselves. Genetic improvement would be more permanent and, ultimately, less costly. Both public and private groups recognized the opportunity and invested heavily in agricultural research. Money flowed from the U.S. Department of Agriculture, from state agricultural stations, and from private agencies such as the Rockefeller Foundation, the Kellogg

Foundation, and The Carnegie Institution of Washington. With more funds available, research on heredity accelerated.

The rediscovery in 1900 of Gregor Mendel's work on inheritance in pea plants sparked new research. Mendel's notions about hybrids suggested how to search for better crops and domesticated animals. Some researchers thought that they might be able to modify the Mendelian factors of inheritance and began to look for them at the level of the cell. Morgan, however, was as skeptical of Mendelism as he was of Darwinism. Mendelians believed that heredity was controlled by unit particles, with one trait dominant over another. Morgan saw this as flying in the face of the subtle variety that he observed in organisms. Given his own studies on how the environment could influence development, Mendelism seemed too rigid. More importantly, Mendel's "factors" were unobservable. Many of the complex patterns of inheritance could be explained instead by the selective fertilization of gametes; that is, some gametes were more likely to be fertilized than others. Morgan considered Mendel's concepts too simple for the complexity of organisms that he knew well.

FRUITFUL FLIES

Morgan reportedly remarked (more than once) that he had done three kinds of experiments: "those that were foolish; those that were damn foolish; and those that were worse than that." He might well have used any of these phrases to assess one line of his investigations in the four years leading up to 1910. Beginning in 1906, Morgan began trying to induce the mutations that he thought fueled evolution. He tried various treatments: salts, sugars, acids, and alkali—the kinds of factors that he knew from his previous research could influence embryological development. If they could change the form of one organism, he reasoned, then they might be able to change the form of the entire species' lineage. But Morgan was not having much success. His failure was hardly due to foolishness, though—just bad luck.

While his search for mutants continued, Morgan was busy with other projects as well. He was thinking about the problem of sex determination. He was looking at regeneration in embryos. At the same time, like any university professor, he was also teaching classes.

Morgan's classes typically involved an independent research project, as was customary at the time. In 1907, a graduate student in one of his courses, Fernandes Payne, planned to study whether he could gradually induce blindness in organisms living several generations in the dark. Morgan would have endorsed such a study, given its experimental approach to an evolutionary question. The critical problem for a one-year course was time: how could he examine enough generations to make the study worthwhile? Payne's teacher at college had worked with fruit flies (also called vinegar flies, pomace flies, and sometimes banana flies), and they seemed an appropriate organism to study. He would be able to study at least ten generations in 9 months. Payne found nothing remarkable in his experiments, but Morgan had found a new research organism. The following year, Morgan began to incorporate fruit flies into his own work on mutations and experimental evolution.

One may wonder why Morgan would have found fruit flies worth researching. They provided no obvious clues to human physiology. Nor were they one of the agricultural organisms currently the target of so much research on genetic improvement. But fruit flies have great advantages for researchers. They do not take up much space—something to consider when your lab is small. They can be easily collected from the wild, even in the city. Caring for them is cheap and easy—an advantage when you have a busy schedule. In fact, Morgan kept the flies in half-pint milk bottles that he "borrowed" from the Columbia University cafeteria. The flies fed on yeast that grew on bits of overripe banana. The fly larvae also needed a surface on which to pupate, and so Morgan folded leftover envelopes and inserted them in the milk bottles. All in all, Morgan invested little time, money, or trouble for his "foolish" experiment. Fruit flies may have seemed trivial, but the choice made practical sense.

Morgan tried to induce mutations in fruit flies with the same treatments he had been using—salts, sugars, acids, and alkali. He exposed them to radium. A year later, he began subjecting large populations of flies to intense selection pressure, hoping to amplify the effect of mutations. Morgan was not having much success. In early 1910, when an old colleague visited his lab, Morgan waved his hand at the rows of bottles on the shelves, exclaiming, "There's two years of work wasted. I've been breeding these flies for all that time and have got nothing out of it."

A PUZZLING WHITE-EYED MUTANT

But soon thereafter, Morgan began to find flies with unusual traits. Some had a different coloration, others had a different body shape. In May, Morgan found a male with anomalous white eyes (Figure 5.3). Perhaps he was unveiling the clues to understanding evolution. The change in eye color was not dramatic enough to mark a new species. Still, it was outside the range of normal variation. Morgan had to ask whether each trait was a "sport of nature"—one of those random variants that was not inherited. Morgan wanted to know how the white-eyed trait, like others, would fare in future generations. So he bred the individual with sister females from the same population.

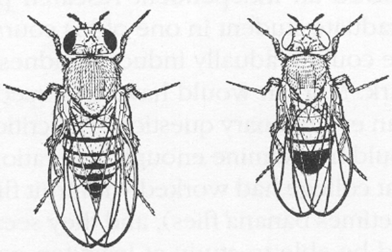

FIGURE 5.3 Mutant fly. Normal red-eyed female on left, white-eyed male on right. Note the different shapes and colors of the abdomens, which allowed Morgan and his students to determine the sex of each fly. *Source:* Thomas Hunt Morgan, *The Theory of the Gene* (Yale University Press, 1926), p. 60.

The white-eyed trait did not become more prevalent in the offspring. Nor did it generate eyes that were an intermediate pink, a mixture of half-red and half-white (color blending had occurred in some flower crosses). Instead, Morgan puzzled over the following results:

red-eyed female(s) x white-eyed male:
1,237 red-eyed (male and female)
3 white-eyed (all male)

Three white-eyed males appeared among a large sample of over a thousand (a proportion of less than one-half of 1 percent). Morgan had plenty of options to consider. Should the three white-eyed offspring be viewed as having received the trait from the white-eyed parent? If the white eye was due to a lack of pigment, then could the small number reflect a dilution in the concentration of the pigment chemical in the sperm cell? Did the three males indicate that the trait would eventually proliferate throughout the population and form a new species or subspecies? Or were the three flies merely "sports of nature," perhaps like the original white-eyed male in the previous generation?

The trait appeared lost in the first generation. But the appearance of traits from generations earlier than one's immediate parents was a well-documented hereditary phenomenon. Morgan allowed the first-generation offspring to breed among themselves. He found the trait reappeared much as Mendel would have predicted(!):

F_1 red-eyed females x F_1 red-eyed males:
2,459 red-eyed females
1,011 red-eyed males
782 white-eyed males

Morgan interpreted this as a Mendelian three-to-one ratio, though the ratio was not perfect. (Would you agree with his interpretation?)

Morgan's attention, however, was drawn by a distinctly non-Mendelian feature of the results, evident when the flies were sorted and counted by sex. As Morgan emphasized when he published his results, "*No white-eyed females appeared.*" That is, *all the white-eyed flies were male.* What could possibly yield this Mendelian ratio split so dramatically and discretely across sexes?

Even though Morgan was looking primarily at evolution, his findings introduced questions about sex determination. Like many researchers encountering unexpected results, Morgan needed to draw on knowledge in a related field by talking with colleagues who might know something or by reading the published scientific literature. In this case, Morgan could "consult" himself, since, coincidentally in this case, he had researched sex determination.

The question of how sex was determined was still largely unsolved for Morgan. He was certainly aware of the work of his former graduate student, Nettie Stevens (Chapter 4), who claimed that sex was determined by the presence or absence of a Y chromosome. In fruit flies, she had observed that XX chromosome pairs occur exclusively in females, while XY pairs or X singles occur only in males. Stevens's views were shared by Edmund Wilson, chairman of the Zoology Department at Columbia, whose office was just down the hall from Morgan's. Morgan and Wilson were close friends and undoubtedly exchanged thoughts on matters such as this. But Morgan had interpreted Stevens's results slightly differently. In 1907, Morgan had suggested that sex was determined quantitatively through biochemical reactions of the chromatin—the material that made up the chromosomes. That is, above some threshold amount of chromatin, the zygote would become a female (or male), while below that threshold, the opposite sex would develop. Individuals with an XX pair of chromosomes would have more chromatin than X or XY individuals, and hence be one particular sex. Morgan had recently reiterated this view in a long 1909 publication.

Morgan would have been troubled by the implications of Stevens's hypothesis for his white-eyed fly. If sex was indeed determined by chromosomes, and the eye-color trait was related to sex, then traits like eye color must themselves be related to the chromosomes. Yet there were far more traits than there were chromosomes, and far more combinations of traits than combinations of chromosomes. Further, to imagine that material units carried predefined traits, as Mendelians claimed, implied that organisms were predetermined. Morgan knew, however, how the environment also affects growing organisms. If Morgan was going to pursue chromosomal notions of sex, he would have to rethink his own notions about sex determination and Mendelian inheritance.

Morgan could thus apply several ideas from his experience to the problem of the white-eyed mutant. The answer would not announce itself, however. He had to carefully think through the alternatives, which included:

—Sex and white eye result from some gametes being fertilized while others are not (selective fertilization).

—The white-eyed trait appears only in association with the Y chromosome in males.

—The eye-color trait is associated with the X and Y chromosomes in some other way.

—Sex and white eye are each determined by a quantitative biochemical threshold of chromatin or some other compound.

PROBLEM

Select the hypothesis you think is most plausible. Review how it could explain the available evidence. Suggest an investigation that would allow you to further confirm or demonstrate the explanation. Identify the results you would expect. Would your prospective investigation allow you to rule out other plausible explanations?

Consider using diagrams or physical objects to help organize your thinking.

A RELUCTANT CONCLUSION?

Morgan ultimately concluded that the white-eyed trait was coupled to a sex factor similar to the X chromosome. At first, this may not seem plausible, because only males had exhibited the white-eyed trait, while females also had X chromosomes but did not exhibit the trait. To reason through this, you have to track chromosomes and eye color simultaneously (though Morgan himself continued to think in terms of X and Y factors, not chromosomes). The original white-eyed mutant, Morgan concluded, had the white-eyed factor, ***W***, *coupled* with the X factor for sex. The trick was to follow the coupled X–***W*** *pair* of factors through the generations and know when the white-eyed trait would appear.

In detail, the original white-eyed male would be XY but also have an X–***W*** couple. When he produced gametes, the X and Y sex factors would separate, and half the offspring would receive the coupled X–***W*** trait. Which half? Because the other parent, an XX female, could contribute only an X factor (or chromosome), the offspring with the father's coupled X–***W*** would all be XX, or females. But the trait would not be expressed because these females would also have inherited a dominant red-eyed trait along with the X factor from the red-eyed mother. In other words, red-eyed traits would also be coupled to the X factor, making X–***R*** couples. The female offspring would be X–***W***, X–***R***.

When the first-generation offspring mated with each other, the X–***W*** couple (now in the F_1 females) would combine again with a Y factor from the F_1 males. The result, X–***W*** and Y, would be a white-eyed male. (Because there was no dominant red-eyed factor, the males would be white-eyed.)

Why were there no white-eyed females? Some F_2 females would indeed have the X–***W*** couple. But they also would have inherited an X–***R*** couple from an F_1 male. They would be female, XX, but red-eyed, ***RW*** (with ***R*** dominant). Overall, you could trace the traits just as you would in a Mendelian cross. The key was to treat eye color and the sex factor (or chromosome) as a single unit, not two.

PROBLEM

At this point Morgan had found only white-eyed males. Were white-eyed females possible according to his hypothesis? If so, predict a cross that would yield such a female.

For further guidance, consider: What would be the hereditary composition of a white-eyed female? Work backwards to determine a combination of gametes that might create a white-eyed female. Which parents from Morgan's cultures would produce such gametes?

CHALLENGE

What would a white-eyed female indicate about the explanations based on biochemical thresholds or selective fertilization?

Morgan's results indeed fit elegantly with the chromosome hypothesis of sex determination and with the chromosome hypothesis of Mendelian factors. But Morgan was not thoroughly convinced. As noted earlier, Morgan had exceptionally high standards of experimental evidence. In addition, you might imagine that he would not easily have abandoned the objections to Mendel that he had held for so many years.

Not long afterwards, however, a mutant with a yellow body appeared. Alfred Sturtevant, one of Morgan's students, showed that the yellow-body trait was inherited the same way as the white-eye trait. Moreover, the inheritance of the two traits could be "coupled" (later, "linked") with each other, not just with the sex factor. Here was evidence that two traits seemed to be carried together by the same (X) chromosome. The results would have answered Morgan's earlier objection that a chromosome could not carry more than one trait. The chromosomal theory of inheritance would also explain why the eye-color factor and sex factor did not segregate independently from each other during reproduction: they would be literally linked together chromosomally. You might imagine Morgan's somewhat reluctant conclusion: Mendel's scheme worked, after all, and sex and other traits were determined by the chromosomes. Geneticist William Bateson described Morgan as having "a thick head," but how could Morgan have dismissed the evidence from experiments in his own lab?

EPILOGUE

In retrospect, the appearance of the white-eyed mutant was a significant turning point for Morgan—and for biology as well. Morgan soon shifted the focus of his research to the immediate problems presented by the white-eyed fly: genetics. And it remained there for the next two decades. Morgan not only accepted Mendelism but became one of its strongest proponents. The fruit fly offered a productive avenue of research for him and his students. They capitalized on the many funds available for agricultural research, and the subsequent work of the "Morgan Group" was funded almost exclusively by the Carnegie Institution. The office became even more crowded as jars of fruit flies accumulated on the desks and shelves. The room was often noisy with chatter. The otherwise modest office became a center of genetics research known internationally simply as "the Fly Room." The humble fruit fly also gained renown. Even now, the fruit fly is one of the most studied organisms in biology, along with humans, *E. coli* bacteria, white mice, Rhesus monkeys, and the roundworm *C. elegans.*

In their subsequent work, Morgan and his students extended the evidence that genetic information is located on the chromosomes. This has since been recognized as their most significant contribution. In addition, they established that each gene has a specific position on the chromosomes. They argued that genes were arranged linearly and that their relative positions or distances could be "mapped." Their proposals generated a spirited debate. By 1926, however, Morgan was able to summarize the resolution of these controversies in a now landmark book, *The Theory of the Gene.* He was awarded a Nobel Prize in 1933 for leading the work linking chromosomes and heredity.

Morgan's research had traveled a quite unexpected path. The work first focused on experimental evolution with fruit flies, led through questions about development and sex determination, and then passed into the nature of genetics at the cellular level, where it spawned a major and enduring field of research. During this transition, views held at the turn of the century had also changed dramatically. Morgan had answered many questions about inheritance without also answering questions of development and evolution.

In the decades that followed, several biologists who studied under Morgan made significant discoveries in both these areas. Theodosius Dobzhansky, for example, studied fruit fly populations in the wild, documenting the relationship among species chromosomally. His conclusions about evolutionary change are still central today. George Beadle, another of Morgan's former graduate students, teamed up with Edward Tatum to study how genes were expressed biochemically in the cell—

a key process for understanding development. After working with fruit flies for a while, they switched to studying a mold and later introduced the notion that each gene is associated with a specific enzyme or protein. In other words, genes become traits through a functional protein or enzyme.

Nearly a century after Morgan, biologists are beginning to integrate the fields of genetics, evolution, and development more completely—and the fruit fly is once again central. Recent studies have focused on a gene identified by Morgan's group, named *eyeless*. In mutant flies that lack the normal gene, the eye is absent or partial. Researchers have now identified the developmental significance of the gene. It appears to be a regulatory or control gene. That is, it triggers the expression of all the other genes that lead to the development of the eye. When it is absent, no eye develops. The *eyeless* gene also appears to be similar to a corresponding gene in mice, suggesting that fruit flies and mice have a common evolutionary origin. Researchers further explored this evolutionary relationship by transplanting the mouse's gene into fruit fly larvae, where it induced the development of a *fruit fly* eye (not a mouse eye) on a leg! Such spectacular cross-species gene transplants hold clues to understanding how regulatory genes act in development and how changes in them may lead to evolution. Biologists are at last developing a comprehensive explanation that unifies evolution, development, and heredity. And the fruit fly is once again proving to be a "fruitful" organism for study.

QUESTIONS AND ACTIVITIES

1. What does this case show about the following aspects of doing biology?
   — chance or accident
   — the role of theoretical perspective in interpreting evidence
   — the posing of problems
   — the cost of research and funding research
2. In his published paper, Morgan characterized his three white-eyed males in the first-generation offspring as "due evidently to further sporting." Was this an adequate explanation? How fully does a researcher have to address all his or her results in a formal scientific report? Did Morgan have a responsibility to report those results at all, since they were incidental to his conclusions?
3. The case of the white-eyed mutant highlights how chance events can dramatically shift the direction of research. How should this affect how research is funded? If you were a science policy maker, how would you decide which specific researchers or research projects to fund?
4. According to Morgan's initial hypothesis, the F_2 females would have differed in hereditary makeup, even though they all had red eyes. How would you demonstrate whether the individuals that appeared the same possibly had different genetic compositions?

5. Morgan's original system of notation (which he later revised) allows us to glimpse his thoughts as they were still being formed. In his original publication, he described the white-eyed mutant as WX–W and the red-eyed wild female as RX–RX. Here, he followed the XX/X pattern of sex rather than the XX/XY pattern. He also assumed that all individuals had two Mendelian factors for eye color, so that males had an uncoupled factor for eye color. He described the first two crosses as follows:

WX–W (male)
RX–RX (female)

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

and

RX–WX (F_1 female)
RX–W (F_1 male)

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

He rearranged the factors in symbolizing offspring, uniting Xs with each other and Rs with Ws.

At one point Morgan crossed a red-eyed male from the original wild population with a white-eyed female (yes, they were possible). Morgan's results showed roughly one-half red-eyed females, one-half white-eyed males. Morgan assumed that the white-eyed males had inherited one white-eye factor from the mother:

RX–W (red male)
WX–WX (white female)

RWXX (50%)	WWX (50%)
Red female	White male

But where had the other white-eye factor come from, if the wild flies were all red-eyed? Morgan published his conclusion: All wild males must be hybrids (heterozygous) for eye color, namely RW. Consider the implications of this hypothesis: The white-eye color allele would never express itself in a wild population, though it was present in every male. This posed a severe problem, which Morgan did not solve at first.

Describe how Morgan's conclusion was affected by his notation system. Devise an alternative system that addresses the problems it introduces. Based on your notation system, describe how the eye-color factors differ from standard Mendelian factors.

SUGGESTED READING

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