The Birth of Genetics

The study of heredity and

the techniques of genetic analysis

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History of Modern Earth and Life Sciences

The analysis of heredity

Genetics, as a study of the phenomena of heredity, can be thought of as an experimental practice that cuts across many different fields of biology. As an experimental practice, or craft, it relies on the fundamental methodology of hybridization, or sex-crossing. That is, it relies on procedures of interfering with the normal processes of breeding, as well as making inferences from counterfactual-assumptions.

We will see that the analysis of heredity practiced in genetics is a form of *methodological reductionism*, which perhaps includes *epistemological reductionism* but does not need to imply *ontological reductionism*. If this is the case, we do not need to be concerned to articulate a program of reducing the organism to the gene, and we can instead ask about the changing concept of the gene through various forms of genetic analysis.

The hereditarians

In the 19th century, there was a lively debate about what constituted a *heritable characteristic*, and whether or not acquired – or learned – characteristics could be passed on through the mechanisms of inheritance.

Galton conceived of inheritance as a statistical relation over characteristics between populations of successive generations. This definition gives rise to a research program treating the *data* of hereditary transmission. In general, in this tradition the traits were seen to have continuous differentiation.

Finally, A. Weismann's theory of cellular heredity – with the nucleus of the germ cell carrying the *hereditary substance* – used the results of cytology (the study of cells) to explain heredity. This cytological theory, however, originally provided no mechanism for inheritance.

Darwin's theory of pangenesis

In *The Variation of Animals and Plants under Domestication* (1886), C. Darwin put forward a theory of heredity – which he called pangenesis – that was quite influential up to around 1900.

Pangenesis was the theory that all the cells in an organism shed minute particles that he called "gemmules," which are able to circulate throughout the body and finally congregate in the germ cells. These gemmules are then transmitted to the next generation and are responsible for the transmission of characteristics from parent to offspring. If any cells of the parent undergo changes as a result of environmental change, they will consequently transmit modified gemmules to their offspring. This was a way of *accounting* for the inheritance of acquired characteristics.

The theory of was set aside after F. Galton failed to transfer pigmentation differences between developing rabbits by blood transfusion.

Gregor Johann Mendel (1822–1884)

- Mendel was an ethnic German, born in the Austrian Empire (now, Czech Republic), to a farming family.
- He was a fiar, but attended university at both Olomauc and Vienna. (His physics professor was Doppler.)
- He carried out his experiments in breeding at St. Thomas' Abbey.
- He was a physics teacher and later head of the Abbey.
- Most of his published work was in meteorology.
- We will look at some results from *Experiments on Plant Hybridization*, 1865.

Mendel's laws of hybridization in pea plants

Mendel was interested in how hybridization might be related to the emergence of new species. He carried out a series of breeding experiments on pea plants, involving some 10,000 plants over the course of 8 years.

He believed that the key to heredity lay in the question of variation and advanced the novel proposition that heredity is particulate, or *discrete*, in opposition to the blended theories of inheritance put forward by Darwin and others.

In 1865 he published a paper which made a new argument for the idea that heredity does not operate on acquired characteristics, and that traits are transmitted unchanged from one generation to the next.

The *Pisum sativum* experiment

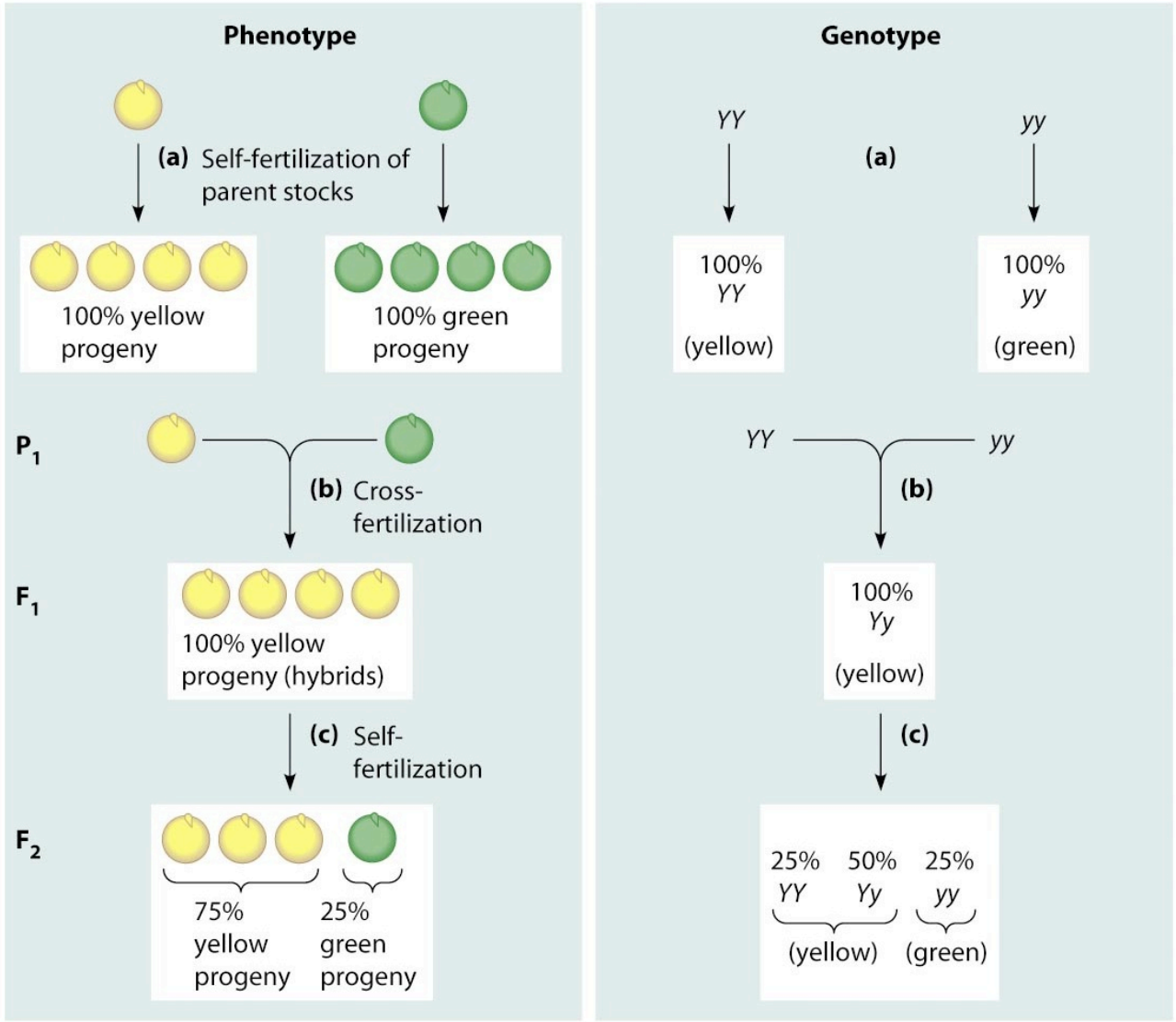
He chose *Pisum sativum* (pea) as a model system that showed clear pairs of contrasting traits (which he called "elements"), such as stem height, seed shape and color, and bred plants having opposite traits over a number of generations.

He first bred true lines of each character, and then cross-bred these and counted the results. He was interested the ratios, not the absolute numbers.

He found that in the first generation (F1) one of the traits, which he called dominant, would be found in 100% of the offspring, but in the next generation (F2), the other trait, which he called recessive, would reappear in numbers that *approximated* the rato 3:1, dominant to recessive.

In order to explain these results he supposed there was some *underlying object of analysis*, which he called the factor or rudiment (*Anlage*, related to our later *genotype*), that could be distinguished from the plant itself (later our *phenotype*).

Simplification of Mendel's law of heredity



The reception of Mendel's ideas

Mendel's paper was distributed to 134 libraries and scientific institutions. 40 reprints of the paper were made and Mendel sent some of these to prominent biologists. Nevertheless, the paper was neglected by geneticists for almost 30 years.

There are a number of reasons why his contemporaries were not interested in his work:

- Mendel was writing about hybridization, not inheritance. He was interested in the production of species through hybridization, a degenerating research program at the time.
- His contemporaries were interested in the origin of species, but Mendel gave no account of how new species could be produced by crossing hybrids in this way.
- He did not believe that the laws that he had discovered were universal.
- Mendel did not belong to a social network of biologists.

The rediscovery

In 1900, three botanists – Carl Correns (1864–1933), Hugo de Vries (1848–1935) and Erich Tschermak (1871–1962) – claimed to have independently rediscovered Mendel's ratios, and then to have found his 1856 paper.

In fact, however, many people had reported numbers that were approximations of Mendel's ratios, but they did not see the significance of this. What seems clear from the evidence is that Correns and Tschermak saw that there was something significant in the numbers they were seeing, and then in searching the literature, they found Mendel's work. De Vries had produced numbers that could have been used to show the ratios, but it was only after he read a copy of Mendel's paper in 1900, that he understood the significance of these numbers.

That is, the Mendelian ratios are not a simple observational fact, but a *theory-laden fact*.

De Vries' "mutations"

Hugo de Vries (1848–1935) was a Dutch botanist who worked in genetics after rediscovering Mendel's laws (and paper). He disagreed with the mechanism of *natural selection* for explaining evolution and offered, instead, a theory of rapid changes, which he called *mutations*. These, he thought, would lead to rapid changes in species – an idea known as saltationism.

He carried out a series of experiments on *Oenothera lamarkiana* – evening primrose. He planted seeds in the botanical gardens at Amsterdam, and observed the results. Very quickly he found varieties that were different from the original stock. He found one variety, *O. gigas*, which was robust and bred true, claiming that these were new forms that were complete and bred true.

New “species”

Oenothera lacta

De Vries believed that he had obtained new species in this way.

de Vries, *Species and variation* … (1905)

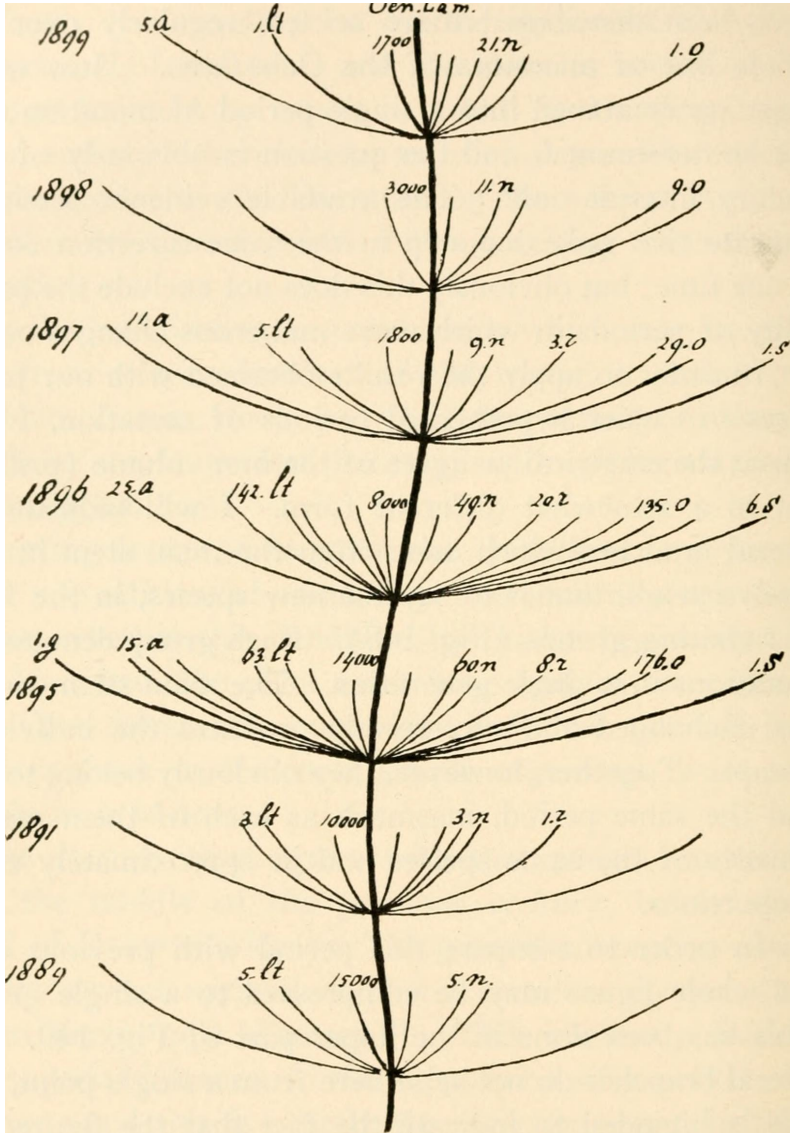
“They come into existence at once, fully equipped, without preparation or intermediate steps. No series of generations, no selection, no struggle for existence was needed. It was a sudden leap into another type, a sport in the best acceptation of the word. It fulfilled my hopes, and at once gave proof of the possibility of the direct observation of the origin of species, and the experimental control thereof.”

The mutation theory

de Vries, *Mutation Theory* (1903)

"I. New elementary species arise suddenly, without transitional forms... II. New elementary species are... absolutely constant from the moment they arise... VI. The mutations, to which the origin of new species is due appear to be indefinite, that is to say, the changes may effect all organs and seem to take place in any direction..."

Such mutations are *different* from the modern concept of mutation as occuring in the genetic material.



Bateson's Mendelism

William Bateson (1861–1926) was a Cambridge natural scientist and zoologist, who helped found the department of genetics. He supported evolution as a biological fact, but he did not accept the mechanism of natural selection. He argued, instead, that species are created by hybridization or drastic mutations. This was partly because it was believed by physicists at the time that the earth was fairly young. He wrote a number of books arguing for the saltationist position.

In 1900, Bateson became a Mendelian and had Mendel's paper translated into English and republished. He and his colleagues discovered *semidominance*; showed that there are Mendelian traits in animals as well as plants; that some genes are linked; etc. In the early part of the 20th century, the Darwinists and the Mendelians were opposed: They had different ideas (gradual vs. sudden change, continuous vs. discrete traits), they had different research methods (observation vs. experimentation), they represented different research traditions.

Drosophila melanogaster, the common fruit fly

- *Drosophila* has had a long career in science; they are ubiquitous and breed easily and quickly.
- The fruit fly first came into genetic labs in 1901 as a control for other experiments.
- Gradually, however, researchers noticed that they show a large number of easily observable mutations which display Medelian traits.
- The fruit fly was made most famous by the so-called “Fly Room” at Columbia University and remains an essential tool for genetic research and instruction.

Thomas Morgan (1866–1945), and the "Fly Boys"

Morgan took a PhD in zoology from Johns Hopkins, and taught at Columbia University before becoming the founding director of the devision of biology at Caltech. He had a number of students at Columbia, of whom the most famous were Alfred Sturtevant (1891–1970), Calvin Bridges (1889–1938), and later Hermann Joseph Muller (1890–1967).

Morgan started out to try to prove de Vries correct, but his work quickly lead him down a path of studying Mendelian mechanisms in *Drosophila*. He took on a number of students who worked with him in Columbia and who took with them the experimental methods of *Drosophila* crossing to their own labs. This was an incredibly productive time and they all worked collaboratively to develop the chromosome theory of inheritance. Researchers came from all over the world to learn the techniques of genetic analysis developed in the "Fly Room."

Morgan and the "boys"

Marine Biological Laboratory in Woods Hole, Massachusetts

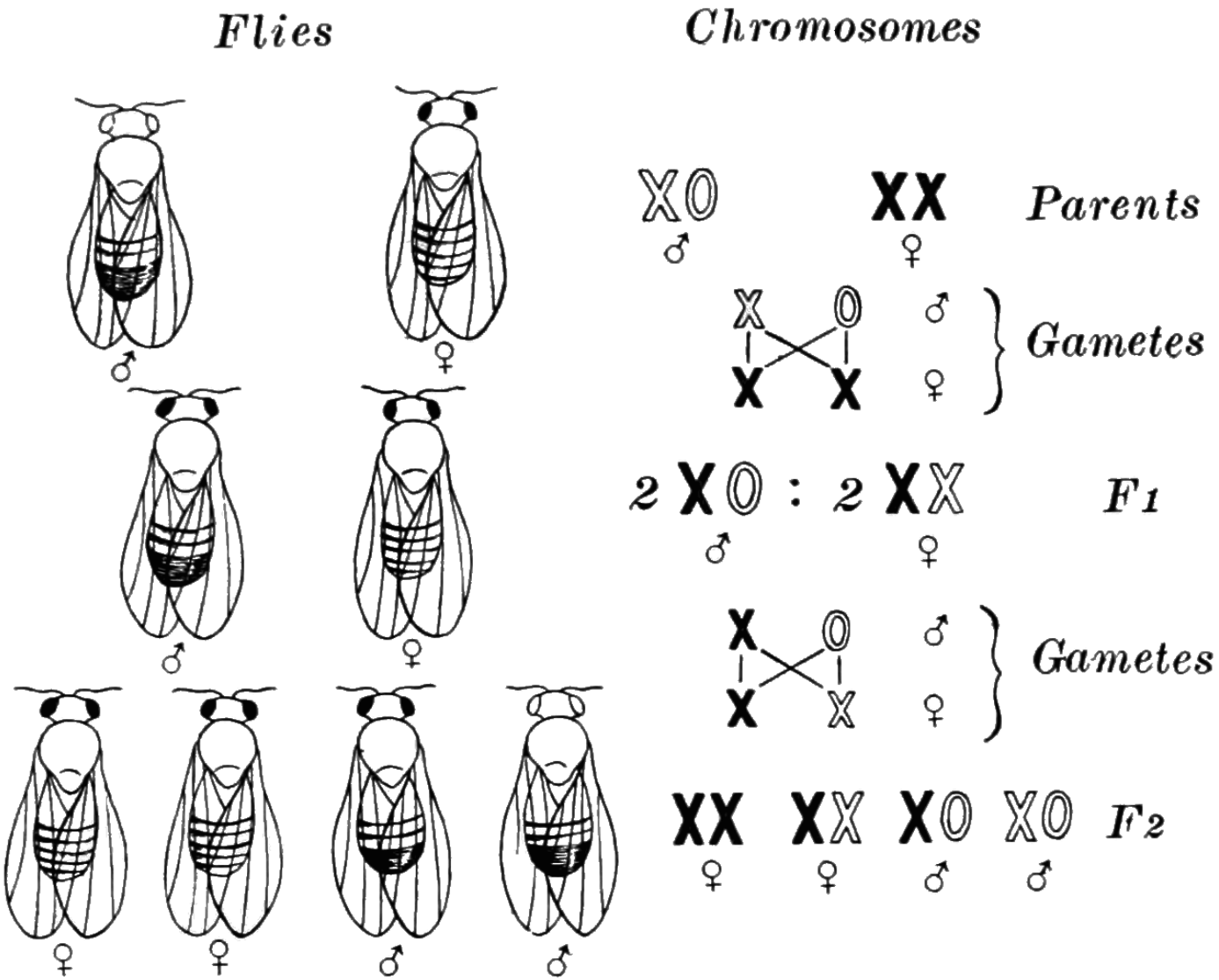
White eyes

Morgan was initially skeptical about Mendel's ideas and began working on *Drosophila* to see if he could find evidence for de Vriesian mutation. In the course of these experiments, he noticed a white-eyed male, which he called a "mutation." As he studied and crossed this white-eyed male he noticed that all of the F1 were wild type, but in the F2 generation, white-eyed males appeared again – as would be expected. When he crossed these white-eyed F2 males with wild-eyed F1 females, half of the males and half of the females were white-eyed, and when he crossed these white-eyed females with wild-eyed males, all the males were white-eyed and all the females were wild-eyed.

This lead to the realization that there was some kind of sex linkage that was effecting the results. That is, Morgan assumed that the factor for eye color segregated with the factor for sex.

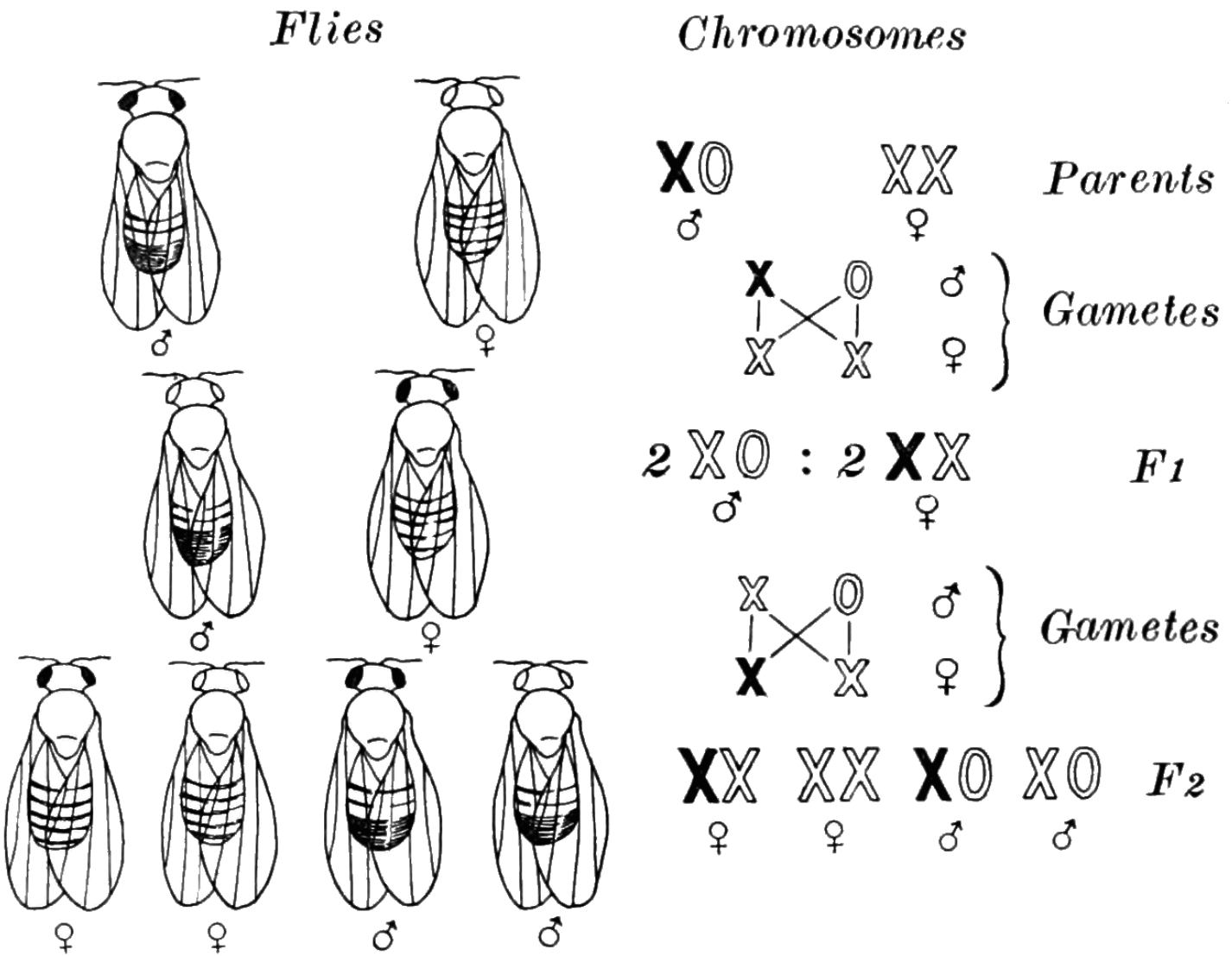
This was the impetus for a change in research direction and Morgan and his younger colleagues began to study *linkage*.

Sex-linkage in white-eyed *Drosophila*, I



Wild-eyed females crossed with white-eyed males

Sex-linkage in white-eyed *Drosophila*, II



White-eyed females crossed with wild-eyed males

Linkage analysis

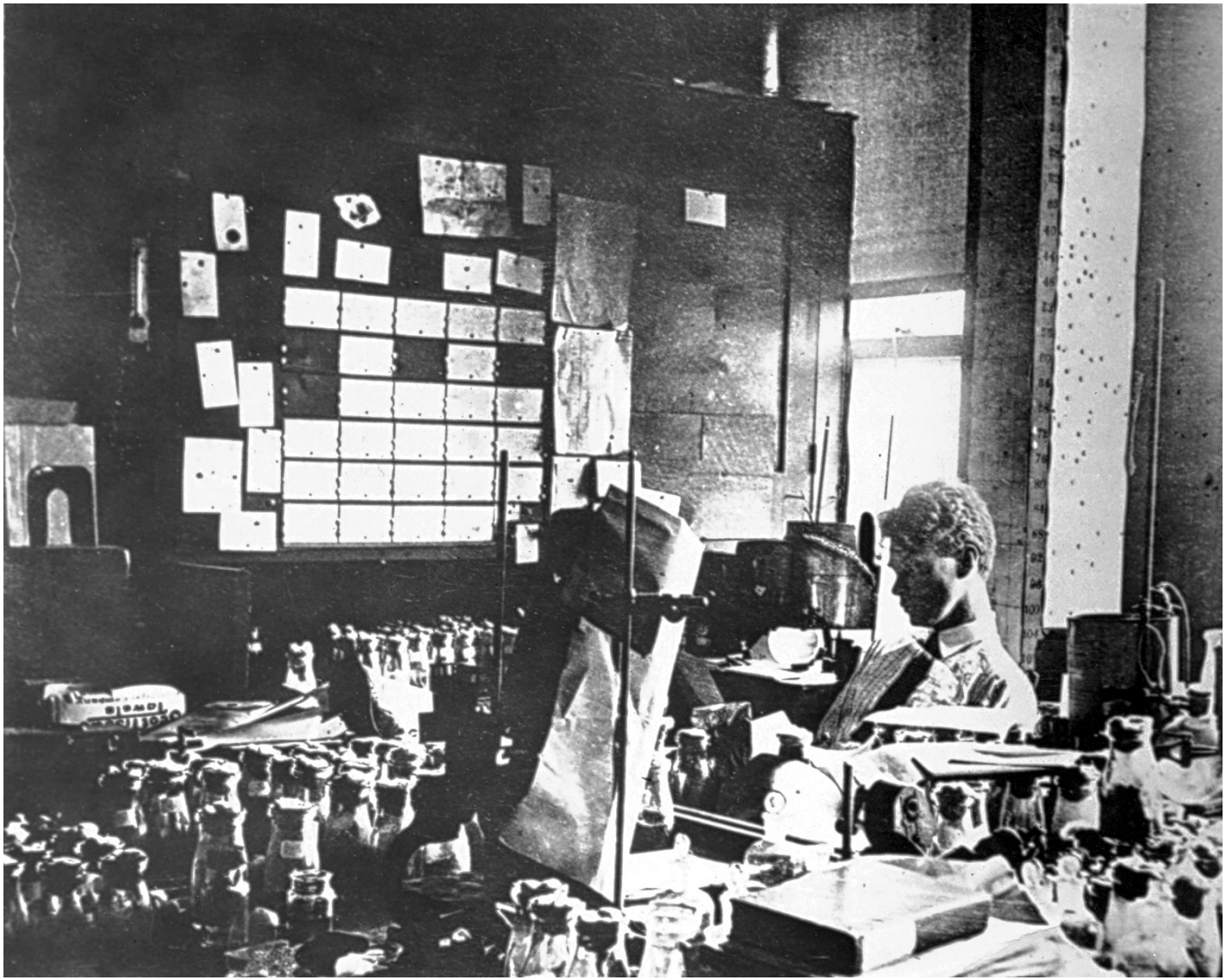
The realization that the factor for white-eyes was linked to sex, lead to the *supposition* that it was physically located on the sex chromosome. This assumption – along with the observation of crossover in meiosis – provided the basis for a far-ranging research program to map the genes to the chromosome.

The first step in this program was to establish a baseline by measuring the "distance" between two genes – as the ratio (percentage) over a large number of crosses of the actual rate of recombination to the expected rate for unlinked genes. This involved separating and counting the progeny of crosses in which recombination has and has not occurred.

In order to measure the linkage between different genes, pure strains of *Drosophila* had to be bred, which was itself a long, drawn out process. Bridges and Muller proved to be particularly good at this.

Morgan in the Fly Room

Drosophila were kept in empty milk bottles capped with cotton gauze. They were fed banana pulp and could be knocked out with ether so that they could be inspected, counted and sorted into new bottles.



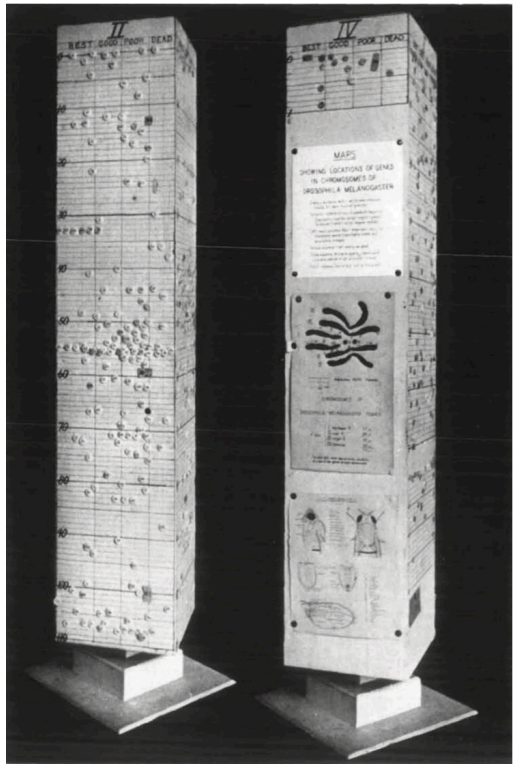
Calvin Bridges in the Columbia Fly Room

The chromosome theory

Drosophila have only 4 chromosomes, so the "fly boys" thought it would be relatively easy to map the genes to this structure.

Constructing the framework for chromosomes 2 and 3, in fact, took two years. First the "distance" between two genes – say *pink* and *ebony* – were established, and then other genes were related to these. It turns out that chromosomes also have physical structure that complicates this process, and this also had to be worked out through these analytical techniques.

In all of this work the fundamental technique was *genetic analysis* – that is, crossing and back crossing specially prepared stocks of flies and counting the results.



Bridges' "Totem pole"

The reception of the theory

A flood of papers from the "Fly Room" and *The Mechanism of Mendelian Heredity* (1915) by Morgan, Sturtevant, Muller and Bridges convinced most biologists that Mendelian genetics coupled with chromosome theory was the way forward in studying heredity. Morgan lectured widely, many young researchers were trained at Columbia and then later Caltech, and the fly group freely gave stocks of specially bred flies to other researchers.

This produced a new school of geneticists who took a pragmatic and experimental approach to biology. Although many of the older generations of naturalists objected to the "unnatural" constraints of laboratory practice, the younger researchers gravitated to these highly productive methods. The merger of cytology and genetic analysis gave the new genetics a basis in physical reality that the previous theories of heredity had lacked.

Genes and chromosomes

The argument that genes are *physically located* on the chromosomes came from the lab of the maize geneticist Barbara McClintock (1902–1992). Although the chromosomes of maize are more complicated than those of *Drosophila*, they are also generally larger. McClintock had already worked out the hypothetical "locations" of a number of important genes. She set her PhD student Harriet Creighton (1909–2004) the task of correlating these with cytological markers on the chromosome to confirm that the crossover was the same between the two.

In 1931, Morgan was at Cornell University to give a series of lectures. When he found out what McClintock and Creighton were working on, he insisted that they should publish right away. Although this was Creighton's PhD work, and they were planning to get more data, Morgan wrote a letter to to the editor of *Proceedings NAS*, telling them to expect a paper soon. (In 1934, the large chromosomes of the *Drosophila* salivary gland where discovered.)

Biology as a laboratory science

Morgan, *Critique of the Theory of Evolution* … (1916)

"The objection has been raised, in fact, that in the breeding work with *Drosophila* we are dealing with artificial and unnatural conditions. It has been more than implied that results obtained from the breeding pen, the seed pan, the flower pot and the milk bottle do not apply to evolution in the 'open', nature 'at large' or to 'wild' types. To be consistent, this same objection should be extended to the use of the spectroscope in the study of the evolution of the stars, to the use of the test tube and the balance by the chemist, of the galvanometer by the physicist. All these are unnatural instruments used to torture Nature's secrets from her. I venture to think that the real antithesis is not between unnatural and natural treatment of Nature, but rather between controlled or verifiable data on the one hand, and unrestrained generalization on the other."

The dissemination of *Drosophila* and genetics

It was the custom of the drosophilists to share information and fly stocks with each other. Sharing fly stocks was a sign of membership in a special community, a guarantee of participation.

In 1911–1912, Morgan persuaded professors at small colleges in the US to take and breed fly stocks. In 1922, Muller brought flies to his colleagues in the Soviet Union. In the 10s, Columbia was the only large center. During the 1920s and 30s, large labs started in Cold Spring Harbor, Berlin, and University of Texas, Austin. In 1928, Morgan, Bridges, and Sturtevant moved from Columbia to Caltech. By the end of the 30s, all large universities kept stocks of *Drosophila*.

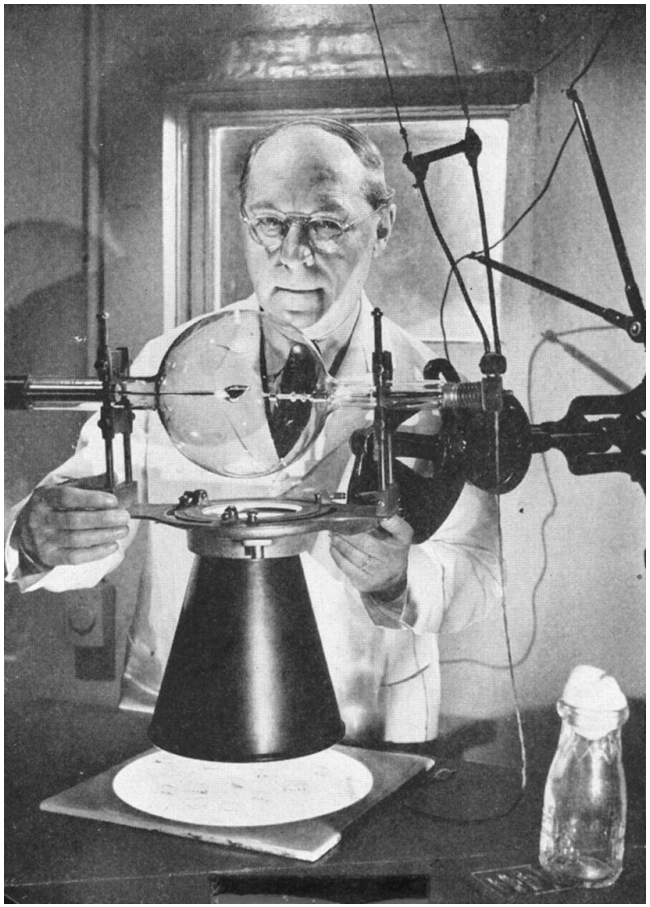
The model experimental systems that were produced with these stocks were freely exchanged and a large percentage of the drosophilists' correspondence was taken up discussing the exchange of stocks. Morgan's group continued to dominate this exchange into the 30s.

The fly lab at University of Texas, Austin

T.S. Painter sits to the left, W.S. Stone stands in the back, C.P. Oliver sits in front, and Muller views flies through a jeweler's loupe.

The fly lab at Cold Spring Harbor, Long Island, New York

X-rays and mutation



In 1926, now at University of Texas, Muller carried out at series of experiments on the effect of x-ray radiation on the rate of mutations in *Drosophila*. A quantitative correlation between the dose of radiation and the number of lethal mutations quickly emerged.

There was a media sensation when he announced these results at a conference in Berlin, and when his results were repeated by others he became something of a scientific celebrity.

Drosophila and the genetics of development

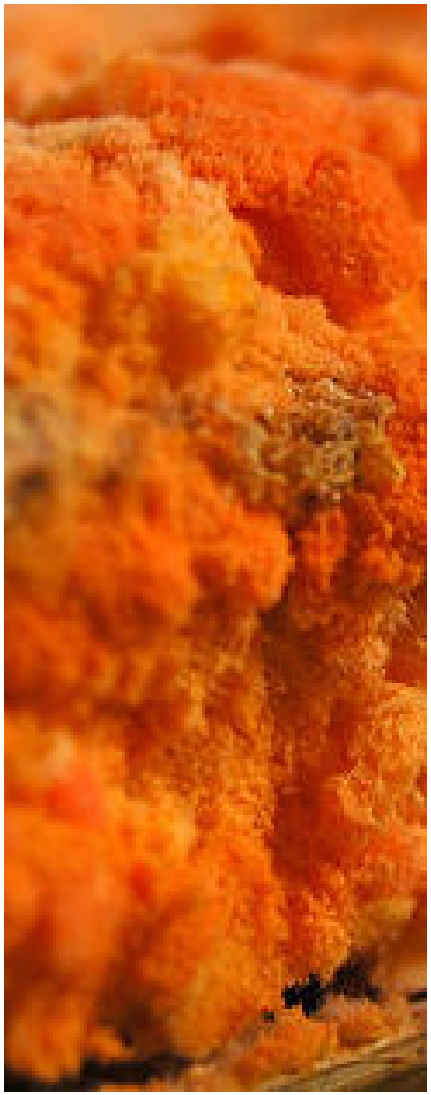
In the 1930s, George Beadle (1903–1989) and Boris Ephrussi (1901–1979), working in Morgan's fly group at Caltech, began to study the genetics of development in *Drosophila* by transplanting tissue – an imaginal disk of the eye – from one fly larva into another fly larva, using a micropipette, in order to grow the transplanted tissue in the host larvae.

They developed a delicate experimental technique to investigate the role of genes in the embryological development of eye color. In fact, they showed that although transplanted eyes still became eyes – although not properly located – they generally, although not always, took on the coloration of the host genes not that of the transplanted genes. They argued that this means that the mechanism of development is controlled by the overall – we would say, epigenetic – context, not simply the chromosomal material of the transplanted imaginal disk.

Beadle and Ephrussi at work

Microscope A, used by one person, had a stand and a mechanism for the change of objectives. Microscope B, facing Microscope A at 45° and used by a different person, examined a test tube mounted on an adjustable stand.

Neurospora



Neurospora is a mold – used to make oncom – that is usually cultured on a medium consisting of sugar, inorganic salts, and the vitamin biotin. The fungus has a short life cycle, and reproduces both asexually and sexually – that is, sexual reproduction gives rise to spores. Hence, it could be subjected to *genetic analysis*. In addition, *Neurospora* possesses only one set of *unpaired* chromosomes, so that any mutation is immediately expressed.

It can also be cultivated on a *minimal medium* of carbon, salt and biotin. On this medium, the fungus can manufacture for itself the other substances that it needs – amino acids, vitamins and proteins.

Neurospora takes over

The fact that not all transplanted imaginal disks showed autonomous development indicated that the genetics of *metabolic chains* might be investigated, but *Drosophila* proved to be a complicated an overly complicated system for these studies.

Now at Stanford, Beadle began working on *Neurospora* with Edward Tatum (1909–1975). They irradiated the mold to produce mutants that could not live without the addition of specific amino acids, starting with arginine. They produced four different strains of the mold that could not produce arginine and showed that each of these had lost the ability to produce a certain *enzyme* that is involved in the production of arginine. In this way, they set out an experimental system for demonstrating the effects of genes on metabolism at a molecular level.

The one-gene one-enzyme hypothesis

This work led them to frame the hypothesis that each individual gene is responsible for the production of one, and only one, enzyme. This was the basis of a highly productive research program in biochemical genetics, that helped lay the foundations for molecular biology.

The current position is that one gene produces one protein, or rather polypeptide (protein component).

Enzyme

A protein capable of producing certain chemical changes by catalytic action. In the 19th century, what we call enzymes were often known as “ferments.”

What is a gene?

We tend to think we have a clear idea of what a gene is, but this is actually tricky to pin down. In fact, we generally have two different things in mind, and it is not clear that they are the same, or map one-to-one to each other.

Gene-p refers to something, or set of things, that has the function of producing a certain trait in the phenotype – including the genetic material of the phenotype, the genome. But the idea that there is actually a certain *thing* that functions in this way is unclear, and we speak of such *gene-p*s only from an *instrumentalist* perspective.

On the other hand, when we try to take a *realist* perspective we mean *gene-d*, and refer to some molecular sequence in the chromosome, in the genome. But, in fact, *gene-d* is indeterminate with respect to the phenotype, because the *context in which it operates* – the epigenome, and the organism in general – is also crucial.

Overview

- We have discussed the rise of classical genetics focusing on Mendel and the Columbia Fly Room.
- We have discussed the rise of developmental, or biochemical genetics.
- We have underlined some philosophical questions pertaining to the nature of the gene, or the gene concept.