GENETICS NOTES

by

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Seventh Edition

FOREWORD

The first edition of these Notes was written exactly 25 years ago. It has been an incredible quarter century for genetics. At that time microbial genetics was in its infancy. The gene had not been proven to be DNA, although there was emerging evidence. In the first edition I alluded to the forthcoming chemical attack on the gene, but no one (at least, not I) dreamed that the attack would be so quickly successful.

The unfolding story of the chemistry of the gene was reflected in successive editions. Through the sixth edition, the structure of DNA and how this so elegantly explains the central mysteries of genetics was kept secret and not revealed until late in the book, after the classical groundwork had been laid. But it was increasingly apparent that the secret had been widely leaked, so I have now started the DNA story near the beginning.

This edition is somewhat longer than previous ones have been. Partly this reflects the increase of knowledge in molecular genetics. But I have also expanded the sections on population, quantitative, and evolutionary genetics, since these topics seem to me to be the least adequately dealt with in most genetics textbooks.

These Notes are intended to be self-contained, but they are a bit thin—skeleton thin in some parts. The pages have wide margins so you can write notes, clarifications, and additional material. I have given references, mostly to books that are more complete and detailed. These are assembled by chapter at the end of the book.

Most of the chapters are followed by problems, so you have a chance to test your understanding of the material and your ability to apply this knowledge. There is a glossary, an index, and a statistical appendix. Also at the end, there are answers to the problems. I mention this especially, since one unusually systematic student studied the book diligently, starting at the beginning and working all the problems, and didn't discover the answers until he had reached the end.

The chromosome photographs in Chapters 3, 4, and 15 were provided by Klaus and Eeva Patau. I thank many colleagues and other friends, too numerous to mention individually, for comments and suggestions. Robert DeMars and Millard Susman have

been particularly helpful. My special thanks go to students who in various ways, direct and indirect, have revealed those parts which were vague, ambiguous, or simply wrong. Since so much of this edition has been rewritten, I again need your help.

J. F. C.

January, 1976

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MENDELIAN INHERITANCE

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GENETICS BEFORE 1900

Eighteenth-century plant hybridizers, especially Kolreuter who published his results in the 1760's, were familiar with the pollination process, but there was considerable uncertainty as to whether only one pollen grain was sufficient for fertilization. But by the time of Mendel's work there was enough evidence that he developed his analysis in the correct belief that a single egg and pollen unite to initiate embryonic development.

Similarly, it was known that in animals a single egg and sperm unite. The early breeders were also aware that, despite the great disparity in size between the male and female germ cells, they usually contribute equally to the inheritance.

The cell theory was well established by Mendel's time, but the nuclear details of cell division were vague. The period between the publication of Mendel's paper in 1865 and its rediscovery in 1900 was one of great advance in the knowledge of chromosome behavior, so that when Mendel's principles became known it was immediately realized that the chromosomes provided the material basis for these principles. It was also during this period that Miescher discovered nucleic acid, although the identification of DNA as the chemical basis of heredity was not firmly established until the 1950's.

The prevailing view of heredity in the pre-Mendelian era was a **blending** theory. The hereditary material was thought of as being analogous to a fluid. Under this concept the progeny of a black and a white animal would be uniformly gray. The further progeny from crossing the hybrids among themselves would also be gray; for the black and white hereditary material, once blended, could never be separated again—just as a mixture of black and white paint cannot be separated.

Mendel's great contribution was to replace the blending theory with a **particulate** theory. Mendel first presented his rules of inheritance in 1865, but they remained unknown for many years. Their rediscovery in 1900 by deVries, Correns, and von Tschermak, independently in three different countries, marks the beginning of modern genetics.

MENDEL'S EXPERIMENTS

Mendel chose to work with garden peas because they were readily hybridized and the characters could be easily observed.

Seven character differences were selected for study: round vs. wrinkled peas, yellow vs. green peas, tall (6 feet) vs. short (1 foot) plants, and four others.

When he crossed a tall with a short variety the hybrids were all tall (regardless of which type was used as female parent and which the male, confirming observations of earlier workers). Then he allowed the hybrids from each cross to be self-pollinated and observed the subsequent generation. He found 787 tall and 277 short plants, roughly 3:1.

When the plants of this generation were self-fertilized as was done in the previous generation, Mendel found that all the short plants produced only short offspring. On the other hand, the tall plants were of two types. About 1/3 of them produced only tall offspring; the remaining 2/3 produced both tall and short plants in the proportions of roughly 3/4 and 1/4.

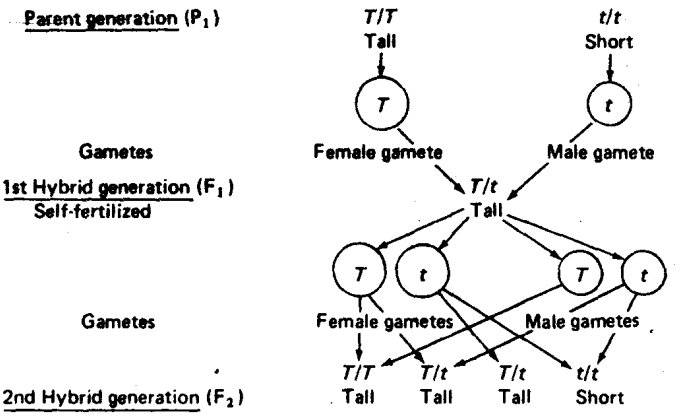
The same results occurred in crosses involving the other six characters.

MENDEL'S HYPOTHESIS AND HOW IT WAS TESTED (Mendel's First Law)

From the results just described, Mendel was able to formulate the remarkable hypothesis that has come to be known as **Mendel's First Law**, or the **Law of Segregation.** The principle is that heredity characters (such as tallness or shortness) are determined by particulate factors (now called genes); that these factors occur in pairs; and that in the formation of the gametes these factors are segregated so that only one of the pair is transmitted by a particular gamete. When the male and female gametes fuse to form the zygote, the double number is restored.

In addition to the principle of segregation, Mendel discovered **dominance.** He noted that the hybrid between the tall and short strain was tall, even though it must have contained both a tall and a short factor. Because the tall character seemed to dominate in the hybrid, Mendel designated the factor for tallness as **dominant** and the alternative **recessive.**

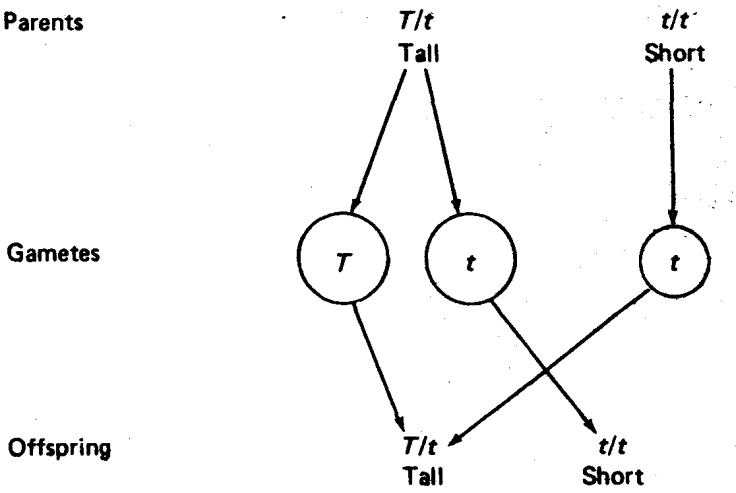
It is a convention, started by Mendel, to designate dominant factors with capital letters and recessives with corresponding lowercase letters. Using these symbols, the crosses between tall and short plants may be diagrammed as follows:



By combining the two kinds of male and female gametes in all possible ways, the relative proportions of offspring types are obtained. The hypothesis leads to an expectation of 3/4 tall and 1/4 short plants, a ratio of 3:1. Among the tall plants, 1/3 have two *T* factors, and hence if self-fertilized would produce only tall offspring; the other 2/3 have one *T* and one *t* factor and when self-fertilized would be expected to produce both tall and short progeny. So the theory accounts for all the results described in the previous section.

Mendel's law is not a specification of the physical nature of the character determiners but is essentially a statement of the rules they follow. The hypothesis can be tested by seeing if the rules are followed in further crosses. That is what Mendel did. He computed the proportion of tall and short plants to be expected from types of crosses other than those already done and compared the expectations with observed results from experimental tests.

The first test make was what is today called a **testcross**. Mendel crossed the F_1 hybrid (*T*/*t*) back to the short parent (*t*/*t*). This cross may be diagrammed as follows:



The expectation in this cross is ½ tall and ½ short. The actual results were 87 tall and 79 short. Here, as in all the other tests, the results were as close to a 1:1 ratio as would be expected according to the laws of chance.

PROBABILITY AND MENDELIAN EXPECTATIONS

According to the Mendelian hypothesis, the gametes are combined by the rules of chance with certain fixed probabilities. The situation is analogous to that of tossing coins or throwing dice. Common experience has demonstrated that the larger the number of trials, the more uniform are the results. If half a dozen coins are tossed, it is not an especially unlikely event to have them all come up heads; but if a large number were tossed, it is almost certain that both heads and tails would be found in approximately equal proportions.

The same thing is true of Mendelian class frequencies. When a ratio of 3/4 to 1/4 is expected in a group of half a dozen animals, almost anything might happen, and it does in practice. On the other hand, with large numbers of offspring, the numbers become more and more accurately predictable. One reason for Mendel's success was that he used large numbers of experimental plants and hence got easily recognizable ratios.

In many situations that one meets in genetics the probability of future events is predictable. From Mendel's hypothesis it can be stated that the probability is 3/4 that a given F_2 plant will be tall, or that the probability is 1/4 that it will be short. Likewise, in certain human families a geneticist can say that the probability is 1/2, or 1/4, that a child will be brown eyed, or be color-blind, or have some other trait whose manner of inheritance is known. Mathematical methods have been developed to determine the probability of a given discrepancy between theoretical and observed ratios. The practicing geneticist makes a great deal of use of such theory in testing hypotheses, and some procedures will be taken up later.

It does not surprise a geneticist who knows that the probability of a black pig is 3/4 to find in a litter of eight that only two or three are black; such discrepancies between expectation and observation are frequent occurrences when small numbers are involved. On the other hand, the geneticist would be very much surprised to find a proportional discrepancy between observed and expected if there had been 150 in the group of offspring. It becomes clear why geneticists have chosen such forms as peas, corn, and fruit flies for their research. Since they are always dealing with probabilities and ratios they must have large enough numbers to test these adequately.

SOME DEFINITIONS

An egg or sperm cell, or the equivalent structure in a plant, is a **gamete.** The fusion of two gametes at fertilization results in the formation of a **zygote.** A zygote in which both factors are alike (for example, T/T or t/t) is called a **homozygote**; one in which they are different is called a **heterozygote** (for example, T/t). The adjectives **homozygous** and **heterozygous** are used to describe these two conditions.

The hereditary factors are now called **genes.** The gene that shows its trait in the heterozygous condition is the dominant factor; that which is concealed is the recessive factor. Two such factors forming a contrasting pair are called **alleles.** The genetic makeup (T/T, T/t, or t/t) is the **genotype.** The character determined by the genetic makeup is the **phenotype.** For example, the two classes T/T and T/t, both being tall, have the same phenotype, but different genotypes.

ABSENCE OF DOMINANCE

Since the time of Mendel's experiments many examples have appeared where the heterozygote is intermediate between the two homozygotes, rather than like one or the other as would be

expected if the character were completely dominant. A conspicuous example is the coat color in Shorthorn cattle. The genotypes and phenotypes are as follows:

Genotypes	Phenotype
R/*R*	Solid color (Red in Shorthorns)
R/*r*	Mottled (Roan)
r/*r*	White

The probability of the occurrence of various kinds of offspring of two roan parents, as determined by the usual method, would be: red, 1/4; white, 1/4; roan, 1/2. In a very large family these expected proportions would be approximately realized.

FURTHER EXPERIMENTS OF MENDEL (Mendel's Second Law)

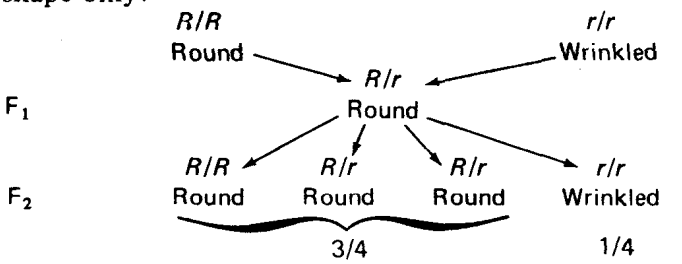
Mendel's first law, the law of segregation, applies to the behavior of a single pair of factors. The second law describes the simultaneous behavior of two or more pairs of genes.

Mendel made several hybridizations in which two or three pairs of factors were studied simultaneously. For example, he crossed plants producing round yellow seeds with plants producing wrinkled green seeds and observed the F_1, F_2, and F_3 generations. In the first hybrid generation all the seeds produced were round and yellow. This was to be expected, since the genes for the round and yellow characters were dominant over their respective alleles. When these plants were self-pollinated, 556 seeds were obtained, of which 315 were round and yellow, 101 wrinkled and yellow, 108 round and green, and 32 wrinkled and green. These are approximately in the proportions 9/16 round yellow, 3/16 wrinkled yellow, 3/16 round green, and 1/16 wrinkled green, a ratio of 9:3:3:1. Other similar crosses yielded these same ratios.

From these data Mendel formulated his second law, or the **Law of Independence.** The principle is a very simple one: it states that the members of one pair of genes segregate independently of other pairs. From this hypothesis he could deduce the results of other crosses and test for agreement with the data actually obtained.

If the characters are behaving independently, it means that the results of an experiment involving several sets of characters may be obtained by mutiplying together the proportions expected for each factor considered by itself. This may be illustrated for the data just mentioned. Letting *R* stand for round, *r* for wrinkled, *Y* for yellow, and *y* for green, the cross may be diagrammed as follows:

Considering shape only:



Considering color only, in exactly the same manner, the expectation in the F_2 generation is 3/4 yellow and 1/4 green. Multiplying these,

(3/4 Round + 1/4 Wrinkled)
x (3/4 Yellow + 1/4 Green)

9/16 Round Yellow + 3/16 Round Green + 3/16 Wrinkled Yellow + 1/16 Wrinkled Green.

Mendel checked this hypothesis by predicting the offspring in other crosses. For example, he crossed the F_1 hybrid with the wrinkled green parent. Considering the shape only, he would expect 1/2 round and 1/2 wrinkled. Considering color only, he would expect 1/2 yellow and 1/2 green. Combined, according to the hypothesis of independence, he would expect

(1/2 yellow + 1/2 green) x (1/2 round + 1/2 wrinkled) = 1/4 round yellow + 1/4 round green + 1/4 wrinkled yellow + 1/4 wrinkled green.

The actual numbers obtained were

55 round yellow	49 wrinkled yellow
51 round green	52 wrinkled green

Again, as before, Mendel tried out various other matings involving the other characters. Also, he tried crosses involving three pairs of contrasting characters, and again the rule of independence held. He could predict the combined results by multiplying together the expected proportions for the three pairs of characters considered individually.

The principle of independent assortment makes it easy to compute the expected results of a cross involving any number of pairs of factors by merely multiplying together the results for each pair considered individually.

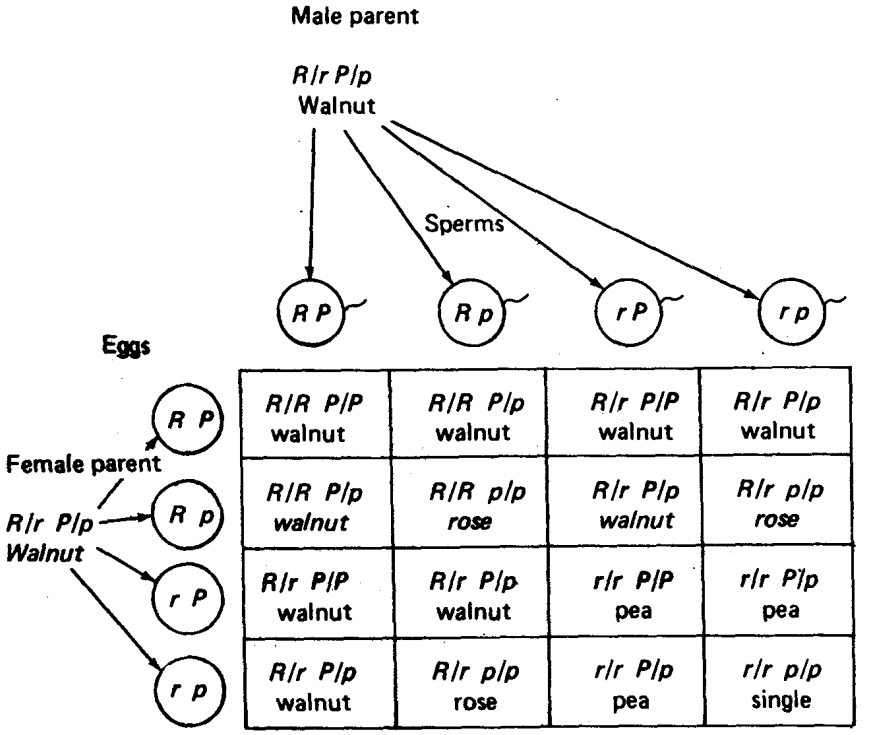
THE PUNNETT SQUARE

A system of diagramming crosses first employed by R.C. Punnett has now become time-honored through its dogged, if not enthusiastic, use by generations of genetics students. It can best be described with an example, and I have chosen one used by Punnett himself in 1905.

In chickens two pairs of genes are involved in comb shape. We shall designate the dominant factors by *R* (for rose comb) and *P* (for pea comb) and their corresponding recessives by *r* and *p*. The various genotypes and their associated phenotypes are as follows, where a dash indicates that either allele may be present.

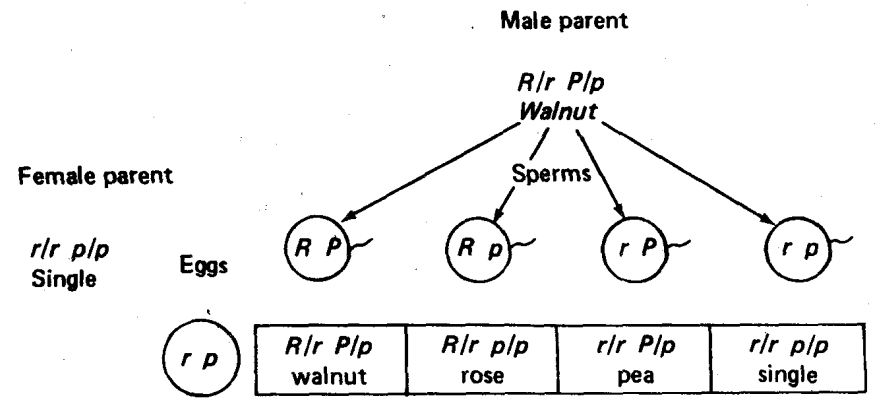
Genotype	Phenotype
R/- P/-	Walnut comb
R/- p/p	Rose comb
r/r- P/-	Pea comb
r/r p/p	Single comb

Consider first a cross between two birds, each heterozygous for both factors (i.e., of genotype *R/r P/p*). Since each gamete produced has one, and only one, representative of each pair of genes there are four possible kinds from each parent: *RP, Rp, rP,* and *rp*. These can be combined as shown in the square below.



Counting the squares, we obtain the familiar phenotypic ratio of nine walnut, three rose, three pea, one single.

As a second example, consider a backcross between a doubly heterozygous male (*R/r P/p*) and a single combed (*r/r p/p*) female.



All four phenotypes are expected with equal frequency.

MUTATION

Thus far we have treated hereditary factors as if they were absolutely stable and unchanging. This is not strictly true; if it

were there would be no evolution. On rare occasions a gene does change to another allele. For example, a gene producing yellow peas may change to one producing green. Such a rare change in a gene is called a **mutation** and the changed gene is called a **mutant.** A mutant gene is just as stable as it was in the original state, and is inherited in the same way.

The rate of mutation is such that a particular gene mutates only once in a hundred thousand generations or more. Nevertheless, there are so many genes (perhaps 10,000 pairs per cell) that the occurrence of a mutation in some one of them is a fairly common event. The mutation rate can be increased by radiation and by various chemicals.

HOW WELL HAS MENDEL'S WORK STOOD UP?

Mendel's most fundamental contribution was to replace the blending theory of inheritance with a particulate theory. His first law, the law of segregation, has become the basic rule of inheritance in sexually reproducing organisms. The second law, the law of independent assortment, has numerous exceptions. We shall see in Chapter 3 that genes are located in the cell nucleus, in the **chromosomes.** The law of independence applies to genes located in independent chromosomes, or, if in the same chromosome, only if the genes are very far apart. Genes near each other in the same chromosome are **linked** in inheritance. The analysis of genetic linkage has been responsible for much of what we know about genetics, as will be discussed in Chapter 8.

Mendel's pea-breeding experiments told us how the genes are transmitted, but they told very little about the nature of the gene. How the remarkable properties of constancy, self-replication, and mutation can be accounted for by the discoveries of molecular biology is the subject of the next chapter.

PROBLEMS

1. Usually, though not invariably, human eye color is inherited as if brown eyes were due to a dominant factor and blue to the corresponding recessive. Assume that this is correct in this and the following problems. A man with blue eyes marries a brown-eyed woman whose mother had blue eyes. What proportion of the children would be expected to have blue eyes?
2. A brown-eyed man marries a blue-eyed woman. The first child is blue eyed. What is the man's genotype?
3. Which is more likely, two brown-eyed parents producing a blue-eyed child or two blue-eyed parents producing a brown-eyed child?
4. A brown-eyed man marries a blue-eyed woman and they have eight children, all with brown eyes. Can you be sure whether the man is homozygous or heterozygous? Which is more likely? If the ninth child has blue eyes, will that settle the question?

5. What offspring would be expected from mating a roan cow with a roan bull? A roan with a white? A red with a white?

6. What would be the easiest way to determine whether a rose combed rooster is homozygous or heterozygous?

7. Which would be easier to get rid of in a flock of chickens, a recessive factor for single comb or a dominant factor for feathered legs?

8. In mice the genotype *y/y* is gray (agouti), *Y/y* is yellow, and *Y/Y* dies as a small embryo. What offspring would be expected from a cross between a yellow and a gray? Between two yellows? In which cross would you expect the larger size of litter?

9. In man the gene for ability to taste phenyl-thio-carbamide (*A*) is dominant to the gene for inability (*a*). The brown-eye gene (*B*) is dominant to the blue (*b*). What proportion of the offspring of two parents each of genotype *A/a B/b* would be blue-eyed tasters? blue-eyed nontasters?

10. What offspring would be expected from two parents of genotypes *A/a B/b* and *a/a b/b*?

11. What proportion of the children of two parents of genotypes *A/a B/B* and *a/a b/b* would be expected to be brown-eyed tasters? Blue-eyed tasters?

12. In cocker spaniels, the genotype *A/- B/-* is black, *a/a B/-* is liver, *A/- b/b* is red, and *a/a b/b* is lemon. A black cocker is mated to a lemon one and produces a lemon pup. If this black dog is mated to another of his own genotype what proportions would be expected among the offspring?

13. In cattle, polled is dominant to horned, and roan is the result of the heterozygous condition of the genes for red and white. What proportion of the offspring of a roan, heterozygous polled bull and a roan, horned cow would be expected to be roan and horned?

14. How many kinds of gametes can be produced by an individual of genotype *A/a B/b C/C d/d E/e F/F*?

15. What proportion of the offspring of two parents, each of genotype *A/a B/b C/c* will be *a/a b/b c/c*?

16. What proportion of the offspring of the cross *A/a B/b C/c* x *A/a B/b C/c* would be expected to be homozygous?

17. One hypothesis for the inheritance of handedness is that two loci are involved. At the first locus *L/-* produces left cerebral dominance and *l/l* right. At the second *C/-* causes the dominant hand to be contralateral (opposite) to the side of the dominant cerebral hemisphere and *c/c* causes the hand and brain dominance to be ipsilateral (on the same side). On

this hypothesis which of the following would be left-handed: *C/- L/-*, *C/- l/l*, *c/c L/-*, and *c/c l/l*?

18. Give an example of genotypes such that two left-handed parents would produce only right-handed children. Only left-handed. Both.

2 THE CHEMICAL NATURE OF THE GENE

WHAT IS A GENE?

The great British geneticist and statistician, R. A. Fisher, once said that the gene can be regarded from either of two viewpoints: (1) as a hypothetical entity by which we can make sense of breeding experiments, or (2) as a very tiny piece of meat. The first corresponds to the Mendelian view. Mendel's experiments showed that the principles of heredity can be formulated as very simple rules based on the behavior of particles which are transmitted from cell to cell and from parent to offspring. The nature of the particles, and even whether such particles exist, was unknown.

The history of genetics from the rediscovery of Mendel's laws in 1900 until the present time has been the gradual replacement of the Mendelian view by Fisher's second view. By 1950 there was strong evidence that the gene is DNA (for **Deoxyribonucleic Acid**) and, thanks to the happy insight of James Watson and Francis Crick, the chemical structure of DNA has been known since 1953. The "tiny piece of meat" that Fisher talked about is a segment of DNA.

For many purposes, such as animal and plant breeding and the study of human pedigrees, it is sufficient to regard the gene simply as an unanalyzed particle, and to be concerned solely with the rules of transmission. But, we are not content with this, and the most exciting recent advances in genetics are concerned with the nature and behavior of the gene itself.

WHAT THE GENE MUST BE ABLE TO DO

At the time of Mendel's experiments it was known that all organisms are composed of cells and that all the cells in the body are derived from a single cell. It was also known that the sperm (or pollen) and egg form the bridge between generations. From this knowledge and from the rules of inheritance and mutation, we can infer that the gene must be able to do at least four things. These are:

1. The gene must store and carry genetic information from cell to cell and from generation to generation. Furthermore, it must carry an enormous amount of information, for the set of genes that you inherited from your parents determined that the fertilized egg developed into you, not some other person, or an elephant, or a dinosaur, or an eggplant, or a slime mold.

2. It must copy itself every time the cell divides. Moreover, it must copy itself with great precision, for the error rate is typically less than one per million copyings.
3. When it does make an error, the error must be copied in each successive cell division. In other words, there is mutation. This is a very unusual property in nonliving systems, but of vital importance for life, for without mutation there could be no natural selection as we understand it.
4. The information stored in the gene must be such that it can be decoded and translated into action. Somehow, the gene influences development to produce the character; or, in genetic parlance, the genotype (together with the environment) produces the phenotype.

We shall soon see that the structure of DNA immediately suggests mechanisms for the first three properties, and points the way to understanding the fourth.

THE STRUCTURE OF DNA

The double-helical structure of DNA, proposed by Watson and Crick, has turned out to be correct in almost every detail. The molecule is a very long, thin, twisted, double thread. The backbone of the molecule is a chain of alternating sugar and phosphate groups. The sugar is a 5-carbon type, **deoxyribose**. There are two of these chains, bridged at each sugar by a pair of **bases**. These are of four kinds: two large **purines (adenine** and **guanine)**, and two small **pyrimidines (thymine** and **cytosine)**. I will abbreviate them **A, G, T,** and **C**. Between the two sugar-phosphate chains there is room for one purine and one pyrimidine, but the space is too large for two pyrimidines and too small for two purines. Furthermore, because of their chemical structures, A and T can be held together by weak chemical bonds (hydrogen bonds) and so can G and C, but not other combinations. The structure is like a stepladder in which the sugar-phosphate chains are the uprights and the pairs of