Joel, This is a preprint. It will be published in American Zoologist this summer with the papers of those who participated in the symposium. My best

See p. 146 for Newsletter

SCIENCE AS A WAY OF KNOWING

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SCIENCE AS A WAY OF KNOWING

III—GENETICS

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genetics—which shortly became the central paradigm of the biological sciences.

WHAT DO GENES DO?

Nevertheless the crude probes available before 1953 made possible important discoveries in gene function. Among the probes were those developed for studying enzymes. During the first half of the 20th century one of the most vigorous fields of cell biology and biochemistry was the study of enzymes. Enzymes were viewed as one of the major factors making life possible. The sorts of reactions that were known or suspected to occur in cells simply could not take place without these organic catalysts.

In one of those strange episodes in the history of ideas, genes and enzymes were first linked at a time when very little was known about either.

An English physician, Archibald E. Garrod (1857–1936), had a patient, a baby, with a rare disease—alkaptonuria. It was so named because the urine of patients has alkapton bodies, which consist largely of homogentisic acid. That substance becomes dark red or black when oxidized. A clue to the patient's problem was stains on its diapers (or, since the baby was British, its nappys).

Garrod knew that the baby's parents were first cousins and he wondered if alkaptonuria might be an inherited disease. In 1902 (!) he consulted Bateson, who suggested that the disease might be due to recessive alleles.

Garrod (1908*a*, 1908*b*; Harris, 1963) spoke of alkaptonuria and similar ailments as "inborn errors of metabolism." Bateson continued to be interested and wrote in 1913*a* (p. 233):

> Alkaptonuria must be regarded as due to the absence of a certain ferment which has the power of decomposing the substance alkapton. In a normal body that substance is not present in the urine, because it has been broken up by the responsible ferment; but when the organism is deficient in the power to produce that ferment, then the alkapton is excreted undecomposed and the urine is coloured by it.

The hypothesis, then, is "one allelomorph, one ferment." Thirty years later, with the terminology brought up to date, this was to become one of the most important hypotheses guiding genetic research.

Neither Garrod nor alkaptonuria is mentioned in any of the books written by the Morgan school in the years of active discovery. Even if Morgan knew of Garrod's hypothesis he may have ignored it. Morgan was so pro experimental science and anti all else—including non-experimental science—that he would have viewed Garrod's hypothesis as useless, for he had written:

> It is the perogative of science, in comparison with the speculative procedures of philosophy and metaphysics, to cherish those theories that can be given an experimental verification and to disregard the rest, not because they are wrong, but because they are useless.

Sturtevant in his history (1965*a*, p. 134) notes,

> There are other examples of a widespread failure to appreciate first-rate discoveries in genetics, and it is perhaps worthwhile to examine some of these briefly. Perhaps the most remarkable examples are the work of . . . and of Garrod on biochemical genetics . . . .
>
> Garrod was concerned with biochemical processes, and few geneticists were well enough grounded in biochemistry to be willing to make the moderate effort required to understand what he was talking about.

But possibly an important part of the answer lies elsewhere. When research programs were developing rapidly and productively, as they were for the *Drosophila* workers, there is little stimulus to look for new things to do. It was not until the 1930s, with transmission genetics satisfactorily explained, that geneticists began an intensive study of the sorts of problems that interested Garrod.

METABOLIC PATHWAYS IN CELLS

George W. Beadle (born 1903), Edward L. Tatum (1909–1975), and Boris Ephrussi (1901–1979) were leaders in the quest for information on how genes act. By the late

HOW'S THAT FOR CARCPOL PROOF READING

1930s there was considerable information about cell metabolism. That fundamental reaction of all life,

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$$

had been resolved into several dozen separate reactions, each controlled by a specific enzyme.

The elucidation of this one metabolic pathway had required the efforts of many scientists for many years. One of the major problems was the speed of the reactions, often requiring a fraction of a second. How was one to study a reaction that would be over before the investigator knew it had started? The standard way was to use chemical substances ("enzyme poisons") that would block the action of a specific enzyme. The result would be that the substrate for that enzyme would then accumulate in the cell and could possibly be detected and identified.

Assume, for example, that one metabolic pathway in cells involves molecule A being changed into molecule B and then B into molecule C and then down the alphabet to molecule Z. We will assume that the change from A to B is controlled by enzyme A-ase and from B to C by B-ase and from Y to Z by Y-ase. All we know at first is that the cell changes molecule A to molecule Z. That is, the conversion may be accomplished by a single enzyme in a single reaction.

One of the first enzyme poisons we try is cyanide. We observe that no Z is formed and, instead, a previously undetected molecule, M, is found. What can we conclude? Can we say that the cell converts A to Z in two steps: A is converted to M and then M to Z? That may have been said a few generations earlier but, as the complexity of intracellular metabolism came to be understood in the 1930s, the conclusion would be no more than "there are at least two intermediary steps from A to Z."

Other poisons could be tried, and with time more and more could be learned about normal metabolism by throwing these chemical wrenches into the biochemical gears of the cell.

Some early studies of Beadle and Ephrussi on the way that eye color genes of *Drosophila* produce their effects had indicated that gene action might be mediated by enzymes. Enough was discovered to suggest that the hypothesis "one gene, one enzyme" might be a fruitful approach. The biochemistry of *Drosophila* proved to be too complex to test that hypothesis and for the first time that noble animal let a geneticist down.

So a long-standing experimental technique was invoked: if the experiment cannot be done with one organism, search for another one that is suitable. By this time Beadle was at the California Institute of Technology with Morgan. Before Morgan left Columbia, Bernard Dodge of the New York Botanical Garden gave him a culture of the red bread mold, *Neurospora crassa*, in the belief that it might be of use in genetic experiments. Morgan never used *Neurospora* but it was still being cultured in his laboratory when Beadle and Tatum sought an organism for their research.

Neurospora crassa

Beadle and Tatum (1941) reasoned that lethal mutations change alleles so that they are incapable of producing an enzyme essential for the life of the organism. Thus they intended to induce lethal mutations with radiations and to study their biochemical effects. This might appear to your students to be a considerable problem since, if the lethal kills the individual, there would not appear to be much to investigate. But Beadle and Tatum solved that problem in what was surely one of the most innovative and productive lines of experimentation in the late 1930s and 1940s. Others must have thought so too because Beadle and Tatum shared a Nobel Prize for this work.

For reasons that will shortly become apparent they first had to determine exactly the minimum variety of molecules required for normal growth—the minimal medium. The menu was surprisingly simple: air, water, inorganic salts, sucrose, and the vitamin biotin. *Neurospora* is, of course, composed of innumerable organic compounds, all interacting as the life of that organism. Yet from those few raw materials it is able to synthesize all of the amino acids, proteins, fats, carbohydrates, nucleic

acids, vitamins, and other substances of its body.

As an example of the many experiments done by Beadle and Tatum, we will discuss those concerned with the synthesis of the amino acid arginine. The working hypothesis was that specific genes control the production of specific enzymes that catalyze the reactions that lead to the formation of arginine. Presumably these genes could mutate to allelic forms that would either be unable to make the enzyme or not be able to make it in sufficient quantity. Since arginine is essential for the life of *Neurospora,* such mutations would be lethal.

Beadle and Tatum then devised a method for the production of these lethal mutations, for identifying them as related to the synthesis of arginine, and for maintaining them in culture in order to work out the metabolic pathway of arginine synthesis. This may sound impossible, especially when we realize that for most of its life cycle *Neurospora* is monoploid and hence any lethal mutations could not be carried as heterozygotes.

This was their game plan. First, X-rays were used to induce mutations. They assumed that all sorts of mutations would be produced, but by chance some might be involved with the production of arginine. When we remember how rare any specific mutation would be, the chance of obtaining the desired mutations would be exceedingly small.

Spores from the irradiated *Neurospora* were then placed on the minimal growth medium. Most of them grew, showing that whatever mutations may have occurred none was so serious as to prevent the *Neurospora* from synthesizing all of its substance from the few chemicals in the minimal medium. Other spores did not germinate, and among these might be some biochemical mutants that could not produce the enzymes necessary for normal growth and development. And somewhere among them might be genes involved in the synthesis of arginine. How could one find them? The spores were not germinating, so they were for practical purposes "dead."

The solution of this apparently insolvable difficulty was elegant in its simplicity and effectiveness. If the spores could not grow because they could not synthesize their own arginine, why not give it to them? And that is precisely what Beadle and Tatum did. Again most of the spores did not grow but a precious few did. Among these precious few might be mutants of genes involved in arginine synthesis.

The next, and critical, step in the analysis was to make sure that whatever was wrong with the spores was inherited. It could not be concluded that, just because the otherwise "lethal" spores could grow on arginine, that a mutational event was the cause.

The life cycle of *Neurospora* makes it ideal for some sorts of genetic analysis. The colonies are monoploid for nearly their entire life. There are two mating types, *A* and *a*, which cannot be distinguished except by their mating behavior. If colonies of *A* and *a* are grown together, parts of each will fuse and *A* nuclei will unite ("fertilize") with *a* nuclei to form diploid zygotes. Meiosis occurs immediately and 4 monoploid spores are formed. These divide, by mitosis, to produce 8 monoploid spores. These 8 spores are enclosed in an elongate spore sac (ascus). They are arranged in the sac in a linear order that reflects the two meiotic divisions and the single mitosis. The spore sacs can be opened under a microscope and the individual spores removed and placed in culture media. Thus one can obtain all of the products of meiosis of a single zygote.

The presumed mutant strains were crossed to normal strains. Meiosis occurred immediately afterwards and monoploid spores were formed. These were then isolated. Half were found to grow on the minimal medium and half only if arginine was added. These results were consistent with the hypothesis that the wild-type *Neurospora* had a gene **A**, which was necessary for the synthesis of arginine. The radiation treatment had caused a mutation of **A** to **a** and **a** was unable to play some essential role in arginine synthesis.

The experimental procedure appeared to be working and numerous genetic strains were isolated that required arginine for

growth. Were all the genetic strains alike or had different genes mutated to alleles that could not synthesize arginine? Can your students suggest how one could go about answering that question?

There were two possible answers:

First, all of the mutant strains could be due to changes at a single gene locus.

Second, many different loci could have mutated. In this case one would suspect that many genes are involved in arginine synthesis: $\mathbf{A}_1$, $\mathbf{A}_2$, $\mathbf{A}_3$, $\mathbf{A}_x$, etc. Any one of these could have mutated to $\mathbf{a}_1$, $\mathbf{a}_2$, etc. In all these mutants the same phenotype would be observed—inability to grow on minimal medium without arginine.

Crosses could test the alternatives. If a single locus is involved, a cross of two strains would produce spores unable to grow without arginine. Alternatively, if different loci are involved, some of the spores will grow as wild-type colonies for the following reason. Assume that different genes are involved and we are crossing $\mathbf{a}_1 \times \mathbf{a}_2$. If a mutation had occurred at only one locus in each strain, which is overwhelmingly probable (why?), the mutated strain would have a normal allele at the other locus. Thus, mutant strain $\mathbf{a}_1$ would be expected to have $\mathbf{A}_2$. Strain $\mathbf{a}_2$ would be expected to have $\mathbf{A}_1$. Thus a cross of $\mathbf{a}_1\mathbf{A}_2 \times \mathbf{A}_1\mathbf{a}_2$ would produce diploid zygotes with a genotype $\mathbf{A}_1\mathbf{a}_1\ \mathbf{A}_2\mathbf{a}_2$. Meiosis then occurs and the monoploid spores are produced. If the two loci are on different chromosomes the isolated spores should give these results:

- ¼ should be $\mathbf{A}_1\mathbf{A}_2$ and grow on minimal medium.
- ¼ should be $\mathbf{A}_1\mathbf{a}_2$ and will require arginine since $\mathbf{a}_2$ cannot function.
- ¼ should be $\mathbf{a}_1\mathbf{A}_2$ and require arginine since $\mathbf{a}_1$ is not functioning.
- ¼ should be $\mathbf{a}_1\mathbf{a}_2$ and require arginine since neither allele can function.

If the loci are on the same chromosome, the frequency of the four genotypes will depend on the amount of crossing-over.

Early on in the experiments, Beadle and Tatum discovered seven genetically different mutants, each requiring supplemental arginine if it was to grow normally. Various interpretations of the data were possible but Beadle and Tatum preferred the hypothesis that the synthesis of arginine required that at least seven normal genes be present—each producing an essential enzyme. When any one of these genes mutated in such a way that its specific enzyme could not be produced, the synthesis of arginine was blocked. There was no reason to believe, of course, that there are only seven steps in the synthesis of arginine in *Neurospora*. We can conclude only that seven was the minimum number.

It was possible to extend the analysis by taking advantage of what was already known about the synthesis of arginine. In 1932 the biochemist Hans A. Krebs had discovered that in some vertebrate cells arginine is formed from citrulline, citrulline from ornithine, and ornithine from an unknown precursor. A specific enzyme is required for each transformation.

If *Neurospora* has a similar metabolic pathway, one should be able to determine how the seven mutant strains are involved. This could be done by seeing which, if any, of the seven would grow if either citrulline or ornithine was used to replace arginine. Your students should be able to predict what conclusions could be drawn if a mutant strain, normally requiring supplemental arginine, would grow if citrulline was substituted or if ornithine was substituted.

Many experiments were done. Four of the mutant strains would grow if either ornithine, citrulline, or arginine was added. This suggested that these four mutants were involved in reactions before the ornithine stage. If ornithine was added, the remaining enzymatic steps, being normal, could carry the reactions to arginine.

Two of the strains would not grow if only ornithine was added but they would grow if either citrulline or arginine was added. In these cases the block was between ornithine and citrulline. Since two genetically different strains were both blocked between ornithine and citrulline, it is reasonable to conclude that there are at least two steps between these molecules.

Finally, one strain was found that would

grow only if arginine was added. This suggests that some enzyme between citrulline and arginine was deficient or defective.

Thus, Beadle and Tatum were able to conclude that, for *Neurospora* to synthesize arginine, a minimum of seven enzyme-controlled reactions are required and a minimum of seven kinds of molecules are involved. Two of these are known: ornithine and citrulline.

The hypothesis that a function of genes is to control the production of specific enzymes was supported. One could not conclude that this is the only thing genes do. Beadle and Tatum had designed their experiments solely to detect enzymes involved in metabolic pathways.

Much as Sutton had linked cytology and genetics in the early 1900s, Beadle and Tatum effectively linked genetics and biochemistry in the early 1940s. Their type of experimentation was used immediately by numerous other investigators on other molds, yeasts, and bacteria. This approach led directly to the molecular biology of today.

While all this was going on still another attempt to study genetics at the molecular level was underway. This was a line of investigation that began in the 1920s and ultimately led to the positive identification of the gene as DNA. That will be our final topic, bringing us to the formulation of the current paradigm of genetics by Watson and Crick in 1953.

THE SUBSTANCE OF INHERITANCE

The dynamics of scientific discovery elude us to this day. There is no way of predicting the who?, the what?, and the where? Important discoveries are nearly always made by scientists active in the field. The breakthrough may be made by an outstanding scientist or by a novice. Neither Mendel, Sutton, Morgan, Watson nor Crick was a leader in the field of inheritance to which each made such notable contributions. The revolution in biology that followed from Watson and Crick (1953*a*, 1953*b*) was due in part to scientists from other fields (mainly physics) deciding that the problems in biology were more exciting than their own (Fleming, 1968; Judson, 1979). Many prominent molecular geneticists of today remember being made aware of new possibilities for genetic research by a slender book written by Schrödinger (1945), himself a physicist.

It could be that it is easier for those not steeped in the data and traditions of a field to see problems and solutions clearly than for those fully engaged in their Kuhnian normal science. As Hanson says (1965, p. 30):

> Physical science is not just a systematic exposure of the senses to the world; it is also a way of thinking about the world, a way of forming conceptions. The paradigm observer is not the man who sees and reports what all normal observers see and report, but the man who sees in familiar objects what no one else has seen before.

Some important discoveries are the outcome of deliberate attempts to find answers to specific questions. In other cases discovery is more of an accident. The elegant experiments of Beadle and Tatum are examples of experiments planned to test a specific hypothesis. The road to DNA was not nearly so straight. The zero milestone cannot be identified but we can start in 1928 with some observations in another field that were to lead, a quarter of a century later, to the description of the chemical structure of DNA.

TRANSFORMATION IN PNEUMOCOCCUS

Pneumonia in human beings and many other mammals is caused by the pneumococcus bacterium (properly known as *Diplococcus pneumoniae*). As in many disease-causing microorganisms, there are numerous genetic strains. These are called Type I, Type II, etc. The specificity is based on the chemical composition of the bacterium's polysaccharide coat. The strains are identified immunologically. If they are injected into rabbits, antibodies are formed against the polysaccharide antigens.

If capsulated cells are grown on culture plates, they form colonies that are *smooth* and shiny. Some of the colonies may have

a different appearance—they are *rough*. These changes were observed long before the cause was known—the change from *smooth* to *rough* is the result of a gene mutation. There was considerable medical interest in this phenomenon because the *smooth* cells cause pneumonia but the *rough* mutant does not. It was discovered that the *smooth* cells have the polysaccharide capsules but the *rough* cells do not.

The road to DNA begins in 1928 with F. Griffith, a Medical Officer with the British Ministry of Health. His publications give no evidence of an interest in genetics; he was a medical bacteriologist concerned with diseases of human beings. He knew that if he injected mice with capsulated Type II *smooth* (capsulated) cells, they would die. Type II *rough* (non-capsulated) cells would not cause the death of his mice. However, heat-killed *smooth* cells did not kill the mice. Therefore, it was not the polysaccharide coat that was the cause of death.

The next experiment is the crucial one for us. Griffith gave four mice a double injection of Type II cells: living *rough* cells plus dead *smooth* cells. Survival was expected, since the *rough* cells are not pathogenic and the pathogenic *smooth* cells had been killed. Nevertheless, all four mice died after five days. Type II *smooth* cells were found in their blood. Thirty control mice injected only with living *rough* cells remained healthy.

This was an unbelievable result—but the experiment was repeated and confirmed. It appeared that the ability to synthesize a capsule had been transferred from the dead capsulated cells to the living non-capsulated cells. Any geneticist of 1928 who might have known of these experiments would have shuddered and rededicated himself to *Drosophila melanogaster*.

During those years geneticists ignored microorganisms almost entirely and microbiologists ignored genetics. It was not suspected by either group that microorganisms possessed a genetic system remotely similar to that of higher organisms. Joshua Lederberg, who as a young student worked in the Zoology Department at Columbia University and who was to find that "adaptation" in bacteria is a mutational event, was far in the future.

A later generation of geneticists might have suspected that a mutation from *rough* to *smooth* had occurred but another experiment by Griffith showed this not to be so. This time the living and the dead cells were of different Types. The living cells without capsules (*rough*) were Type II and the killed cells with capsules (*smooth*) were Type I. Eight mice were injected and two died. Their blood was found to contain virulent capsulated cells of Type I. Somehow the Type II non-capsulated cells had been transformed to Type I. This was not a transitory change. They were cultured and thereafter remained Type I. The change was permanent, and hence in a broad sense genetic. In today's terms we also might suspect the transformation to virulence to be due to mutation. But this second experiment rules out that possibility since, had the living Type II cells mutated from capsule-less to capsulated, they would still have been Type II. However, the capsulated cells were like the dead cells, Type I.

This line of research was taken up by many bacteriologists, including M. H. Dawson and Oswald T. Avery of the Rockefeller Institute in New York. They became convinced that transformation must be due to some chemical substance and it was reasonable to suspect the polysaccharide of the capsule. Nevertheless that proved not to be so. Alloway, another member of the Rockefeller group, summed up the problem in 1932 as follows (with my paraphrasing):

> The polysaccharide when added in chemically purified form, has not been found effective in causing transformation of non-capsulated organisms derived from *Diplococcus* of one Type into capsulated forms of the other Type. When non-capsulated cells change into the capsulated form they always acquire the property of producing the specific capsular substance. The immunological specificity of the encapsulated cell depends upon the chemical constitution of the particular polysaccharide in the

capsule. The synthesis of this specific polysaccharide is a function peculiar to cells with capsules. However, since the non-capsulated cells under suitable conditions have been found to develop again the capacity of elaborating the specific material, it appears in them this function is potentially present, but that it remains latent until activated by specific environmental conditions. The fact that a non-capsulated strain derived from one Type of *Diplococcus*, under the conditions defined in this paper, may be caused to acquire the specific characters of the capsulated forms of a Type other than that from which it was originally derived, implies that the activating stimulus is of a specific nature.

There is nothing in this quotation, or in the writings of other bacteriologists of the period, to suggest that transformation might be a genetic phenomenon. It seemed more probable that some sort of physiological modification had occurred. Many bacteriologists at the time suspected that some sort of Lamarckian evolution was responsible for this phenomenon known as "adaptation." It was much later that it was found that mutation and selection would account for the phenomena observed.

DNA Is the Transforming Substance

But if "the activating stimulus is of a specific nature," hard work and luck might discover what it is. It was found that the transforming principle could be extracted from capsulated cells and that transformation could occur *in vitro*—no need that mice be used. After a decade Avery, MacLeod, and McCarty (1944) reported that they had purified the transforming substance and that it was almost certainly DNA. The overall elemental composition of the transforming principle agreed closely with that of DNA. The molecular weight was judged to be about 500,000. The substance was highly active—one part in 600 million was effective. Treatment with trypsin and chymotrypsin left activity intact indicating that it was not protein. Ribonuclease, which denatures RNA, was also without effect. However, a then available crude deoxyribonuclease destroyed the activity of the purified transforming substance.

What does this all mean? This is how Avery, MacLeod, and McCarty interpreted their experiments (see also McCarty, 1985):

> Various hypotheses have been advanced in explanation of the nature of the changes induced. In his original description of the phenomenon Griffith suggested that the dead bacteria in the inoculum might furnish some specific protein that serves as a 'pabulum' and enables the [non-capsulated] form to manufacture a capsular carbohydrate.
>
> More recently the phenomenon has been interpreted from a genetic point of view. The inducing substance has been likened to a gene, and the capsular antigen which is produced in response to it has been regarded as a gene product. In discussing the phenomenon of transformation Dobzhansky has stated that "If this transformation is described as a genetic mutation—and it is difficult to avoid so describing it—we are dealing with authentic cases of induction of specific mutations by specific treatments . . . ."

It is, of course, possible that the biological activity of the substance described is not an inherent property of the nucleic acid but is due to minute amounts of some other substance adsorbed to it or so intimately associated with it as to escape detection. If, however, the biologically active substance isolated in highly purified form as the sodium salt of deoxyribonucleic acid actually proves to be the transforming principle, as the available evidence strongly suggests, then nucleic acids of this type must be regarded not merely as structurally important [at the time biochemists could not discover any function for the nucleic acids] but as functionally active in determining the biochemical activities and specific characteristics of [the bacterial]

cells. Assuming that the sodium deoxyribonucleate and the active principle are one and the same substance, then the transformation described represents a change that is chemically induced and specifically directed by a known chemical compound. If the results of the present study on the chemical nature of the transforming principle are confirmed, then nucleic acids must be regarded as possessing biological specificity the chemical basis of which is as yet undetermined.

Was DNA only an inducing agent or was it something else? Most geneticists would probably have agreed with Dobzhansky that DNA could not be the genetic material. The evidence was fairly convincing. Enough was known about DNA to realize that it was a rather simple molecule—composed of a few bases, a simple sugar, and phosphate. Presumably an extremely complex substance would be required to control the life of cells. Proteins were a far more likely candidate than DNA to be the gene. They could be huge and were composed of a number of amino acids about equal to the number of letters in our alphabet. Just as the combinations of a few letters can give us the uncounted numbers of words in the languages of the world, that same number of amino acids should be adequate to supply all the genetic variation required.

CORE OR COAT?

The answer came in less than a decade: DNA *is* the gene, not a mutagenic agent. One of the more important experiments was done in 1952 by A. D. Hershey and Martha Chase. By that time much more sophisticated experimentation was possible. In large part as a result of the work on the atom bomb in World War II many sorts of radioactive substances had been produced that could be used to study intracellular reactions. Methods were developed for culturing many different sorts of microorganisms and, for many reasons, they were becoming the favorite experimental organisms for geneticists. There was also very much more research being done. The extraordinary contributions of scientists to the war effort were recognized in Washington and the work of scientists began to be supported on a lavish scale. It was estimated that in the 1950s the number of active scientists was equal to all the scientists who had ever lived. Big Science was national policy and a national activity.

Hershey and Chase took advantage of the peculiar life cycle of bacteriophage to ascertain whether or not DNA contains the information for that organism. Bacteriophages, or phages, are incapable of an independent life. They are parasites of bacteria, upon which they depend for their own reproduction.

If the bacterium *Escherichia coli* is infected with a phage called T_2, the bacterium is killed in about 20 minutes. Before entrance of the phage, the bacterial cell was synthesizing its own specific molecules: bacterial proteins, bacterial nucleic acids, and so on. The phage changes all this. It assumes control of the bacterial synthetic machinery and diverts it to producing phage molecules instead of *E. coli* molecules. About 100 phages are made in about 20 minutes. The bacterium bursts and liberates the phages. They can then enter (they must if they are to live and reproduce) other bacterial cells and repeat the process.

There are many kinds of phages that maintain their genetic identity and other specific characteristics. Structurally they are simple, being composed of a protein coat and a DNA core. The protein of the phage coat is chemically very different from the DNA core. The coat contains sulfur but little or no phosphorus. The reverse is true for DNA. Radioactive isotopes of both phosphorus and sulfur were available to Hershey and Chase.

The experiment was as follows. One group of bacteria was grown in a medium with ^{32}P, which became incorporated in the bacterial molecules. Later, phages were introduced. When the bacteria then began to synthesize new phages, the latter's DNA became tagged with the ^{32}P. The protein coat would have little or no label.

In a parallel experiment bacteria were grown in a medium containing ^{35}S. This became incorporated in some of the bac-

terial proteins. Later phages were introduced and in this case the protein coats of the phages became labelled with ^{35}S.

These two sorts of phages, one labelled for the protein coat and the other for the DNA, were then used in separate experiments. They were introduced into cultures of bacteria and Hershey and Chase found that the labelled DNA entered the bacterial cells. The labelled protein remained on the outside. These observations, together with others, suggested that the phage attaches itself to the cell wall of the bacterium and injects its DNA core, the coat remaining on the outside.

The phages in both experiments reproduced and destroyed the bacterial cells. The experiments had shown that the entire genetic information on "how to make phage" is contained in the phage DNA.

The work surveyed in this chapter, together with a very much larger amount going on at the same time, leads to this tremendous thought: the once mysterious gene, which though invisible could be mapped and followed through the generations with precision, is revealed as an identifiable molecule—DNA. Just as E. B. Wilson had said in 1895.

REFERENCES TO THE GENE TO 1953

G. E. Allen (1975*a*, 1975*b*, 1983), Alloway (1932), Astbury (1949), Avery (1943, letter to his brother in Moore, 1972*b*, pp. 249–251), Avery, MacLeod, and McCarty (1944), Babcock (1949–1951), Beadle (1945, 1946*a*, 1946*b*, 1951, 1959, 1963, 1966), Beadle and Beadle (1967), Beadle and Tatum (1941), Beckwith and Zipser (1970), Borek (1965), Braun (1953), Cairns, Stent, and Watson (1966), Carlson (*1966, 1967*a*, 1967*b*, 1971, 1974, 1981), Caspari and Ravin (1969), Chargaff (1968), Coburn (1969), Cohen (1965), Davidson (1968), Dawson (1930), Demerec (1933, 1955, 1967), Dunn (1951, *1965*a*, 1969), East (1929), Edsall (1962), Ephrussi (1942), Fleming (1968), Garrod (1908*a*, 1908*b*), Gilbert (1978), Glass (1965), Goldschmidt (1938, 1955), Griffith (1928), Haldane (1954), Harris (1963), Hershey and Chase (1952), Hess (1970), Ingram (1963), Jacob and Monod (1961*a*, 1961*b*), Judson (1979), Keller (1983), Kendrew (1966), Lechevalier and Solotorovsky (1965), Lewis (1967), Luria (1970), McCarty (1985), McElroy and Glass (1957), Moore (1972*a*, 1972*b*), Morgan (*1926*a*), Muller (1929, *1947, *1951, 1966), Nardone (1968), Nature (1974), Olby (1968, 1970*a*, 1970*b*, 1971), Pauling (1970), Ravin (1965, 1977), Russell (1930), Schrödinger (*1945), Sonneborn (1968), Srb and Horowitz (1944), Stadler (*1954), Stent (1968*a*, 1968*b*, 1969, *1970), Stern (1970), Sturtevant (*1948, *1965*a*, 1970), Sturtevant and Beadle (*1939), Tatum (1959), Watson (1965, 1968), Watson and Crick (1953*a*, 1953*b*), Whitehouse (*1965), Wright (*1941), Zamecnik (1960).

THE END

This essay, as part of the symposium *Science as a Way of Knowing—Genetics,* has sought to provide a background for the papers by the symposium speakers and to provide materials for teachers using the science as a way of knowing approach. For the most part, the speakers will be dealing with events that occurred after 1953. These events have been so staggering in their importance and different in their problems and procedures that we must recognize that a new paradigm now guides the investigators.

The old paradigm of the Chromosomal Theory of Heredity, or transmission genetics, held the attention of geneticists to the mid-1930s but by then it was so well established that geneticists sought new challenges. It was during the 1930s and 1940s the groundwork was laid for an attack at the molecular level on what genes are and what they do. Molecular genetics is very different from classical genetics, which is the concern of this essay.

And that raises a difficult problem for what should be taught in the first-year biology course in the colleges and universities when the time available is severely limited. Can Mendel, Sutton, and Morgan hold the attention of students who live in a world where genetic engineering is about to perform its miracles? Should students be taught about these classical experiments and concepts?

I think they should and there is no need

for an either/or structuring of the curriculum. The basic argument of the *Science as a Way of Knowing* approach is that students are best served if they are provided with the conceptual framework of the field. Full appreciation of the events of today is possible only if that conceptual framework is understood.

There is a practical matter also. Few students in first-year courses have the background necessary to understand the tremendously sophisticated experiments and data of modern molecular genetics. In many instances they may be able to *memorize* the material but I am talking about something else—*understanding*. Classical genetics, on the other hand, is approachable to a considerable degree by students in first-year courses. They really can understand the questions, the data, and the reasons for the conclusions. This is another of our goals—having students understand how science works.

Nevertheless we serve our students poorly if we leave them ignorant of the general results and especially the implications of the science of the day. My recommendation, therefore, is to emphasize classical genetics and then discuss the main conclusions of molecular genetics, stressing its implications for better health and better food. And, most certainly, there should be consideration of some of the more difficult ethical questions that are being raised by molecular genetics.

Remember also that everything does not have to be included in a first-year course. Something of importance and interest should be left for the more advanced courses. Biologists, alone among scientists, seem to believe that all the cream has to come that first year. It really does not.

My suggestions may not have much appeal for some university scientists for according to Sydney Brenner (*Nature* 317: 209, 1985):

> For most young molecular biologists, the history of their subject is divided into two epochs: the last two years and everything else before that. The present and very recent past are perceived in sharp detail but the rest is swathed in a legendary mist where Crick, Watson, Mendel, Darwin—perhaps even Aristotle—coexist as uneasy contemporaries.

Too bad, if so. We have to do better for our students.

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REFERENCES

Ackerknecht, E. H. 1953. *Rudolf Virchow, doctor, statesman, anthropologist.* Univ. of Wisconsin Press, Madison.

Allen, G. E. 1966*a*. Thomas Hunt Morgan and the problem of sex determination. Proc. Amer. Philosophical Soc. 110:48–57.

Allen, G. E. 1966*b*. T. H. Morgan and the emergence of a new American biology. Quart. Rev. Biol. 44: 168–188.

Allen, G. E. 1969. Hugo de Vries and the reception of the "mutation theory." Jour. History Biology 2:55–87.

Allen, G. E. 1974*a*. Opposition to the Mendelian-chromosome theory: The physiological and developmental genetics of Richard Goldschmidt. Jour. History Biology 7:49–92.

Allen, G. E. 1974*b*. Morgan, Thomas Hunt. Dictionary of Scientific Biography 9:515–526.

Allen, G. E. 1975*a*. The introduction of *Drosophila* into the study of heredity and evolution. Isis 66: 322–333.

Allen, Garland E. 1975*b*. *Life science in the twentieth century.* Wiley, New York.

Allen, G. E. 1976. Wilson, Edmund Beecher (1856–1939). Dictionary of Scientific Biography 14:423–436.

Allen, Garland E. 1978. *Thomas Hunt Morgan; the man and his science.* Princeton Univ. Press, Princeton.

Allen, G. E. 1979. Naturalists and experimentalists: The genotype and phenotype. Studies in the History of Biology 3:179–209.

Allen, G. E. 1983. T. H. Morgan and the influence of mechanistic materialism on the development of the gene concept. Amer. Zool. 23:829–843.

Allen, G. E. 1985. Heredity under an embryological paradigm: The case of genetics and embryology. Biol. Bull. 168(Suppl.):107–121.

Allen, Roy M. 1940. *The microscope.* Van Nostrand, New York.

Alloway, J. L. 1932. The transformation *in vitro* of R pneumococcus into S forms of different specific types by the use of filtered pneumococcus extracts. Jour. Exper. Medicine 55:91–99.

Aristotle. [1943]. *Generation of animals.* [Translated by A. L. Peck. Loeb Classical Library. Harvard Univ. Press, Cambridge.]

Aristotle. [1955]. *Organon.* [Translated by H. P. Cooke and H. Tredennick. Loeb Classical Library. Harvard Univ. Press, Cambridge.]

Astbury, W. T. 1949. Adventures in molecular biology. Harvey Lectures 46:3–44.

Avery, O. T., C. M. MacLeod, and M. McCarty. 1944. Studies on the nature of the substance inducing transformation of pneumococcal types. Jour. Exper. Medicine 79:137–158.

Ayala, Francisco J. and John A. Kiger, Jr. 1984. *Modern genetics.* 2nd ed. Benjamin/Cummings, Menlo Park.

Babcock, E. B. 1949–1951. The development of fundamental concepts in the science of genetics. Portugaliae Acta Biologica. Serie A, Volume R, pp. 1–46. B. Goldschmidt.

Bailey, L. H. 1895. *Plant-breeding.* Macmillan, New York.

Baker, Henry. 1742. *The microscope made easy.* Dodsley, London.

Baker, H. 1756. A supplement to the account of a distempered skin, published in the 424th number of the Philosophical Transactions. Philosophical Transactions 49(Pt. 1):21–24.

Baker, J. R. 1948–1955. The cell theory: A restatement, history, and critique. Quarterly Jour. Microscopic Science 89:103–125; 90:87–108; 93: 157–190; 94:407–440; 96:449–481.

Balbiani, E. G. 1881. Sur la structure du noyau des cellules salivaires chez les larves de Chironomus. Zool. Anzeiger 4:637–641, 662–666.

Baltzer, F. 1964. Theodor Boveri. Science 144:809–815.

Baltzer, Fritz. 1967. *Theodor Boveri. Life and work of a great biologist, 1862–1915.* Univ. of California Press, Berkeley.

Barlow, Nora (ed.) 1958. *The autobiography of Charles Darwin, 1809–1882; with original omissions restored; edited with appendix and notes by his grand-daughter.* Collins, London.

Barthelmess, Alfred. 1952. *Vererbungswissenschaft.* Karl Alber, Freiburg.

Bateson, Beatrice. 1928. *William Bateson, F.R.S. Naturalist.* Cambridge Univ. Press, London.

Bateson, William. 1894. *Materials for the study of variation treated with especial regard to discontinuity in the origin of species.* Macmillan, London.

Bateson, W. 1900*a*. Hybridisation and cross-breeding as a method of scientific investigation. Jour. Royal Horticultural Soc. 24:59–66.

Bateson, W. 1900*b*. Problem of heredity as a subject for horticultural investigation. Jour. Royal Horticultural Soc. 25:54–61.

Bateson, William. 1902. *Mendel's principles of heredity. A defence.* Cambridge Univ. Press, Cambridge.

Bateson, W. 1906. An address on Mendelian heredity and its application to man. Brain 29:157–179.

Bateson, W. 1908. The methods and scope of genetics. An inaugural lecture delivered 23 October 1908. Cambridge Univ. Press, Cambridge.

Bateson, William. 1909. *Mendel's principles of heredity.* Cambridge Univ. Press, Cambridge. [Reprinted with additions, 1913.]

Bateson, William. 1913*a*. Above with additions.

Bateson, William. 1913*b*. *The problems of genetics.* Yale Univ. Press, New Haven.

Bateson, W. 1914. Address of the President of the British Association for the Advancement of Science. Science 40:287–302.