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Genes and Chemical Reactions in Neurospora

The concepts of biochemical genetics began with Garrod's "inborn errors" and have evolved gradually.

George W. Beadle

On this occasion of sharing the high honor of a Nobel award with Edward L. Tatum for our "discovery that genes act by regulating chemical events," and with Joshua Lederberg for his related "discoveries concerning the organization of the genetic material of bacteria," it seems appropriate that I sketch briefly the background events that led to the work on *Neurospora* that Tatum and I initiated in 1940. I shall leave to my corecipients of the award the task of describing in detail the developments in *Neurospora* that followed our first success, and the relation of this to the rise of bacterial genetics, which has depended largely on studies of genetic recombination following conjugation and transduction.

I shall make no attempt to review the entire history of biochemical genetics, for this has been done elsewhere (*1–4*).

Anthocyanins and Alcaptonuria

Soon after de Vries, Correns, and Tschermak "rediscovered" Mendel's 1865 paper and recognized its full significance, investigators in the exciting new field, which was to be called genetics, naturally speculated about the physical nature of the "elements" of Mendel and the manner of their action. Renamed genes, these units of inheritance were soon found to be carried in the chromosomes.

One line of investigation that was destined to reveal much about what genes do was started by Wheldale (later name Onslow, by marriage) in 1903. It began with a genetic study of flower pigmentation in snapdragons. But soon the genetic observations began to be correlated with the chemistry of the anthocyanin and related pigments that were responsible. The material was favorable for both genetic and chemical studies, and the work has continued to yield new information ever since and almost without interruption. Many workers and many species of plants have been involved (*1–5*).

It became clear very soon that a number of genes were involved and that they acted by somehow controlling the onset of various identifiable and specific chemical reactions. Since an understanding of the genetics helped in interpreting the chemistry and vice versa, the anthrocyanin work was well known to both geneticists and biochemists. It significantly influenced the thinking of both fields and thus had great importance in further developments.

A second important line of investigation was begun even earlier by the Oxford physician-biochemist Sir Archibald E. Garrod. At the turn of the century he was interested in a group of congenital metabolic diseases in man, which he later named "inborn errors of metabolism." There are now many diseases so described; in fact, this has come to be recognized as a category of diseases of major medical importance.

One of the first "inborn errors" to be studied by Garrod was alcaptonuria. Its most striking symptom is blackening of urine on exposure to air. It had been recorded medically long before Garrod became interested in it, and important aspects of its biochemistry were understood. The substance responsible for blackening of the urine is alcapton or homogentisic acid (2,5-dihydroxyphenylacetic acid). Garrod suggested early that alcaptonuria behaved in inheritance as though it were differentiated by a single recessive gene.

By 1908 a considerable body of knowledge about alcaptonuria had accumulated. This was brought together and interpreted by Garrod in his Croonian lectures and in the two editions of his book, *Inborn Errors of Metabolism,* which were based on them (*6*). It was his belief that alcaptonuria was the result of inability on the part of affected individuals to cleave the ring of homogentisic acid as do normal individuals. He believed this to be due to absence or inactivity of the enzyme that normally catalyzes this reaction. This in turn was dependent on the absence of the normal form of a specific gene.

Thus, Garrod had clearly in mind the concept of a gene-enzyme-chemical-reaction system in which all three entities were interrelated in a very specific way. In the 1923 edition of *Inborn Errors* (*6*) he wrote: "We may further conceive that the splitting of the benzene ring of homogentisic acid in normal metabolism is the work of a special enzyme, that in congenital alcaptonuria this enzyme is wanting. . . ."

Failure to metabolize an intermediate

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compound when its normal pathway is thus blocked by a gene-enzyme defect was a part of the interpretation and accounted for the accumulation and excretion of homogentisic acid. Garrod recognized this as a means of identifying an intermediate compound that might otherwise not appear in sufficient amounts to be detected.

He also clearly realized that alcaptonurics would be used experimentally to explore the metabolic pathways by which homogentisic acid was formed. He summarized a large body of evidence indicating that when normal precursors of homogentisic acid are fed to alcaptonurics there is an almost quantitative increase in homogentisic acid excretion. In this way evidence was accumulated that phenylalanine, tyrosine, and the keto acid analog of the latter were almost certainly the direct precursors of homogentisic acid.

Despite the simplicity and elegance of Garrod's interpretation of alcaptonuria and other inborn errors of metabolism as gene defects which resulted in inactivity of specific enzymes and thus in blocked reactions, his work had relatively little influence on the thinking of the geneticists of his time. Bateson's *Mendel's Principles of Heredity* and a few other books of its time discuss the concept briefly. But up to the 1940's, no widely used later textbook of genetics that I have examined even so much as refers to alcaptonuria. It is true that a number of other workers had seriously considered that genes might act in regulating chemical reactions by way of enzymes (*1–5*). But there was no other known instance as simple as alcaptonuria. It is interesting—and significant, I think—to note that it was approximately 50 years after Garrod proposed his hypothesis before it was anything like fully verified through the resolution into six enzymatically catalyzed steps of phenylalanine-tyrosine metabolism via the homogentisic acid pathway, and by the clear demonstration that homogentisate oxidase is indeed lacking in the liver of an alcaptonuric (*7*). Perhaps it is also well to recall that it was not until 1926 that the first enzyme was isolated in crystalline form and shown in a convincing way to consist solely of protein.

Eye Pigments of Drosophila

I shall now shift to a consideration of an independent line of investigation which ended up with conclusions very much like those of Garrod and which led directly to the work with *Neurospora* that Tatum and I subsequently began.

In 1933, Boris Ephrussi came to the California Institute of Technology to work on developmental aspects of genetics. During his stay he and I had many long discussions in which we deplored the lack of information about the manner in which genes act on development. This we ascribed to the fact that the classical organisms of experimental embryology did not lend themselves readily to genetic investigation. Contrariwise, those plants and animals about which most was known genetically had been little used in studies of development.

It would be worth while, we believed, to attempt to remedy this situation by finding new ways experimentally to study *Drosophila melanogaster*—which, genetically, was the best understood organism of the time. Tissue-culture techniques seemed to offer hope. In the spring of 1935 we joined forces in Ephrussi's section of l'Institut de Biologie Physio-chimique in Paris, resolved to find ways of culturing tissues of the larvae of *Drosophila.*

After some discouraging preliminary attempts, we followed Ephrussi's suggestion and shifted to a transplantation technique. It was our hope that in this way we could make use of nonautonomous genetic characters as a means of investigating gene action in development.

Drosophila larvae are small, and we were told by a noted Sorbonne authority on the development of Diptera that the prospects were not good. In fact, he said, they were terrible.

But we were determined to try, so we returned to the laboratory, made micropipettes, dissected larvae, and attempted to transfer embryonic buds from one larva to the body cavity of another. The results were discouraging. But we persisted and finally one day discovered that we had produced a fly with three eyes. Although our joy was great over this small success, we immediately began to worry about three points: First, could we do it again? Second, if we could, would we be able to characterize the diffusible substances responsible for interactions between tissues of different genetic types? And, third, how many nonautonomous characters could we find?

We first investigated the sex-linked eye-color mutant vermilion because of the earlier finding of Sturtevant that in gynandromorphs genetically vermilion eye tissue often fails to follow the general rule of autonomy (*8*).

Gynandromorphs may result if, in an embryo that begins development as a female from an egg with two X chromosomes, one X chromosome is lost during an early cleavage, giving rise to a sector that has one X chromosome and is male. If the original egg is heterozygous for a sex-linked gene—say vermilion—and the lost chromosome carries the normal allele, the male sector will be genetically vermilion, whereas the female parts are normal or wild type. (Other sex-linked characters like yellow body or forked bristles can be used as independent markers to reveal genetic constitution in most parts of the body.)

Yet in Sturtevant's gynandromorphs, in which only a small part of the body, including eye tissue, was vermilion, the appearance of that tissue was usually not vermilion but wild type—as though some substance had diffused from wild-type tissue to the eye and caused it to become normally pigmented.

It was on the basis of this observation that Ephrussi and I transplanted vermilion eyes into wild-type larvae. The result was as expected—the transplanted eyes were indeed wild type.

At that time there were some 26 separate eye-color genes known in *Drosophila.* We obtained stocks of all of them and made a series of transplants of mutant eyes into wild-type hosts. We found only one other clear-cut nonautonomous eye character. This was cinnabar, a bright red eye color like vermilion but differentiated by a second chromosome recessive gene. We had a third less clear case, claret, but this was never entirely satisfactory from an experimental point of view because it was difficult to distinguish claret from wild-type eyes in transplants.

The vermilion and cinnabar characters are alike in appearance; both lack the brown pigment of the wild-type fly but retain the bright red component. Were the diffusible substances that caused them to develop brown pigment when grown in wild-type hosts the same or different? If the same, reciprocal transplants between the two mutants should give mutant transplanted eyes in both cases. If two separate and independent substances were involved, such reciprocal transplants should give wild-type transplanted eyes in both instances.

We made the experiment and were much puzzled that neither of these results was obtained. A cinnabar eye in a vermilion host remained cinnabar, but a vermilion eye in a cinnabar host became wild-type.

To explain this result we formulated the hypothesis that there must be two diffusible substances involved, one formed from the other, according to the scheme:

precursor → v^+ substance → cn^+ substance → pigment . . .,

where v^+ substance is a diffusible material capable of making a vermilion eye become wild type and cn^+ substance is capable of doing the same to a cinnabar eye (*9*).

The vermilion (*v*) mutant gene blocks the first reaction, and the cinnabar (*cn*) mutant gene interrupts the second. A vermilion eye in a cinnabar host makes pigment because it can, in its own tissues, convert the v^+ substance into cn^+ substance and pigment. In it, the second reaction is not blocked.

This scheme involves the following concepts: (i) a sequence of two gene-regulated chemical reactions, one gene identified with each; (ii) the accumulation of intermediates prior to blocked reactions; (iii) the ability of the mutant blocked in the first reaction to make use of an intermediate accumulated as a result of a genetic interruption of the second reaction. The principle involved is the same as that employed in the cross-feeding technique later so widely used in detecting biosynthetic intermediates in microorganisms.

What was later called the one-gene–one-enzyme concept was clearly in our minds at this time, although, as I remember, we did not so designate it.

Ours was a scheme closely similar to that proposed by Garrod for alcaptonuria, except that he did not have genes that blocked an adjacent reaction in the sequence. But at the time we were unaware of Garrod's work, partly because geneticists were not in the habit of referring to it and partly because we had failed to explore the literature. Garrod's book was available in many libraries.

We continued the eye-color investigations at the California Institute of Technology, Ephrussi having returned there to spend part of 1936. Late in the year, Ephrussi returned to Paris and I went for a year to Harvard; we continued to work along similar lines. We identified the source of diffusible substances—fat bodies and malpighian tubercules—and began to devise ways of determining their chemical nature. In this I collaborated to some extent with Kenneth Thimann.

In the fall of 1937 I moved to Stanford, where Tatum shortly joined me, to take charge of the chemical aspects of identifying the eye-color substances. Yvonne Khouvine worked in a similar capacity with Ephrussi. We made progress slowly. Ephrussi and Khouvine discovered that under certain conditions feeding tryptophan had an effect on vermilion eye color. Following this lead, Tatum found—through accidental contamination of an aseptic culture containing tryptophan and test flies—an aerobic *Bacillus* that converted tryptophan into a substance highly active in inducing formation of brown pigment in vermilion flies. He soon isolated and crystallized this, but its final identification was slowed down by what later proved to be a sucrose molecule esterified with the active compound.

A. Butenandt and his co-workers (*10*) in Germany, who had been collaborating with Kühn on an analogous eye-color mutant in the meal moth *Ephestia,* and Amano *et al.* (*11*), working at Osaka University, showed that v^+ substance was kynurenine. Later, Butenandt and Hallmann (*12*) and Butenandt *et al.* (*13*) showed that our original cn^+ substance was 3-hydroxykynurenine.

Thus was established a reaction series of the kind we had originally conceived. When the known chemicals are substituted, it is as follows:

Tryptophan
↓
N-Formylkynurenine
↓
Kynurenine
↓
3-Hydroxykynurenine
↓
Brown pigment

A New Approach

Isolating the eye-pigment precursors of *Drosophila* was a slow and discouraging job. Tatum and I realized this was likely to be the case in most attempts to identify the chemical disturbances underlying inherited abnormalities; it would be no more than good fortune if any particular example chosen for investigation should prove to be simple chemically. Alcaptonuria was such a happy choice for Garrod, for the chemistry had been largely worked out and the homogentisic acid had been isolated and identified many years before.

Our idea—to reverse the procedure and look for gene mutations that influence known chemical reactions—was an obvious one. It followed logically from the concept that, in general, enzymatically catalyzed reactions are gene-dependent, presumably through genic control of enzyme specificity. Although we were without doubt influenced in arriving at this approach by the anthocyanin investigations, by Lwoff's demonstrations that parasites tend to become specialized nutritionally through loss of ability to synthesize substances that they can obtain readily from their hosts (*14*), and by the speculations of others as to how genes might act, the concepts on which the idea was based developed in our minds fairly directly from the eye-color work Ephrussi and I had started five years earlier.

The idea was simple: select an organism like a fungus that has simple nutritional requirements. This will mean that it can carry out many reactions by which amino acids and vitamins are made. Induce mutations by radiation or other mutagenic agents. Allow meiosis to take place, in order to produce spores that are genetically homogeneous. Grow these on a medium supplemented with an array of vitamins and amino acids. Test them by vegetative transfer to a medium with no supplement. Those that have lost the ability to grow on the minimal medium will have lost the ability to synthesize one or more of the substances present in the supplemented medium. The growth requirements of the deficient strain could then be readily ascertained by a systematic series of tests on partially supplemented media.

In addition to the above specifications, we wanted an organism well suited to genetic studies, preferably one on which the basic genetic work had already been done.

Neurospora

As a graduate student at Cornell, I had heard B. O. Dodge of the New York Botanical Garden give a seminar on inheritance in the bread mold *Neurospora.* So-called second-division segregation of mating types and of albinos was a puzzle to him. Several of us who had just been reviewing the evidence for four-strand crossing over in *Drosophila* suggested that crossing over between the centromere and the segregating gene could well explain the result.

Dodge was an enthusiastic supporter of *Neurospora* as an organism for genetic work. "It's even better than *Drosophila,*" he insisted to Thomas Hunt Morgan, whose laboratory he often visited. He finally persuaded Morgan to take a collection of *Neurospora* cultures with him from Columbia to the new Biology Division of the California Institute of Technology, which he established in 1928.

Shortly thereafter, when Carl C. Lindegren came to Morgan's laboratory to become a graduate student, it was suggested that he work on the genetics of *Neurospora* as a basis for his thesis. This was a fortunate choice, for Lindegren had an abundance of imagination, enthusiasm, and energy and at the same time had the advice of E. G. Anderson, C. B. Bridges, S. Emerson, A. H. Sturtevant, and others at the institute who at that time were actively interested in problems of crossing over as a part of the mechanism of meiosis. In this favorable setting, Lindegren soon worked out much of the basic genetics of *Neurospora.* New characters were found, and a good start was made toward mapping the chromosomes.

Thus, Tatum and I realized that *Neurospora* was genetically an almost ideal organism for use in our new approach.

There was one important unanswered question. We did not know the mold's nutritional requirements. But we had the monograph of Nils Fries, which told us that the nutritional requirements of a number of related filamentous fungi were simple. Thus, encouraged, we obtained strains of *Neurospora crassa* from Lindegren and from Dodge. Tatum soon discovered that the only growth factor required, other than the usual inorganic salts and sugar, was the recently discovered vitamin biotin. We could not have used *Neurospora* for our purposes as much as a year earlier, for biotin would not then have been available in the quantities we required.

It remained only to irradiate asexual spores, cross them with a strain of the opposite mating type, allow sexual spores to be produced, isolate them, grow them on a suitably supplemented medium, and test them on the unsupplemented medium. We believed so thoroughly that the gene-enzyme-reaction relation was a general one that there was no doubt in our minds that we would find the mutants we wanted. We had only one worry—that their frequency might be so low that we would get discouraged and give up before finding one.

We were so concerned about the possible discouragement of a long series of negative results that we prepared more than a thousand single spore cultures on supplemented medium before we tested them. The 299th spore isolated gave a mutant strain requiring vitamin B_6, and the 1090th one required vitamin B_1. We made a vow to keep going until we had ten mutants. We soon had dozens.

Because of the ease with which all the products of a single meiotic process in *Neurospora* could be recovered, it was a simple matter to determine whether our newly induced nutritional deficiencies were the result of mutations in single genes. If they were, crosses with the original should yield four mutant and four nonmutant spores in each spore sac. They did (*15, 16*).

In this long, roundabout way, first in *Drosophila* and then in *Neurospora,* we had rediscovered what Garrod had seen so clearly so many years before. By now we knew of his work and were aware that we had added little if anything new in principle. We were working with a more favorable organism and were able to produce, almost at will, inborn errors of metabolism for almost any chemical reaction whose product we could supply through the medium. Thus, we were able to demonstrate that what Garrod had shown for a few genes and a few chemical reactions in man was true for many genes and many reactions in *Neurospora.*

In the fall of 1941 Francis J. Ryan came to Stanford as a National Research Council fellow and was soon deeply involved in the *Neurospora* work. A year later David M. Bonner and Norman H. Horowitz joined the group. Shortly thereafter Herschel K. Mitchell did likewise. With the collaboration of a number of capable graduate students and a group of enthusiastic and able research assistants, the work moved along at a gratifying pace.

A substantial part of the financial support that enabled us thus to expand our efforts was generously made available by the Rockefeller Foundation and the Nutrition Foundation.

I shall leave to Tatum the task of summarizing our subsequent investigations and their results.

One Gene—One Enzyme

It is sometimes thought that the *Neurospora* work was responsible for the one-gene–one-enzyme hypothesis—the concept that genes in general have single primary functions, aside from serving an essential role in their own replication, and that in many cases this function is to direct specificities of enzymatically active proteins. The fact is that it was the other way around—the hypothesis was clearly responsible for the new approach.

Although we may not have stated it explicitly, Ephrussi and I had some such concept in mind. A more specific form of the hypothesis was suggested by the fact that of all the 26 known eye-color mutants in *Drosophila,* there was only one that blocked the first of our postulated reactions and one that similarly interrupted the second. Thus, it seemed reasonable to assume that the *total* specificity of a particular enzyme might somehow be derived from a single gene. The finding in *Neurospora* that many nutritionally deficient mutant strains can be repaired by supplying single chemical compounds was a verification of our prediction and, as such, reinforced our belief in the hypothesis, at least in its more general form.

As I hope Tatum will point out in detail, there are now known a number of instances in which mutations of independent origin, all abolishing or reducing the activity of a specific enzyme, have been shown to involve one small segment of genetic material (*17*). To me these seem to lend strong support to the more restricted form of the hypothesis.

Regardless of when it was first written down on paper, or in what form, I myself am convinced that the one-gene–one-enzyme concept was the product of gradual evolution, beginning with Garrod and contributed to by many, including Moore, Goldschmidt, Troland, Haldane, Wright, Grüneberg, and many others (*1–4, 18*). Horowitz and his coworkers (*19*) have given it, in both forms referred to above, its clearest and most explicit formulation. They have summarized and critically evaluated the evidence for and against it, with the result that they remain convinced of its continued value.

In addition, Horowitz has himself made an important application of the concept in arriving at a plausible hypothesis as to how sequences of biosynthetic reactions might have evolved (*20*). He points out that many biologically important compounds are known to be synthesized in a stepwise manner —a process in which the intermediate compounds, as such, seem not to serve useful purposes. How could such synthetic pathways have evolved if they serve no purpose unless they are complete? Simultaneous appearance of several independent enzymes would of course be exceedingly improbable.

Horowitz proposes that the end product of such a series of reactions was at first obtained directly from the environment, it having been produced there in the first place by nonbiological reactions such as have been postulated by a num-

ber of persons, including Darwin, Haldane, Oparin, and Urey and demonstrated by Miller, Fox, and others (*21*). It is then possible reasonably to assume that the ability to synthesize such a compound biologically could arise through a series of separate single mutations, each adding successive enzymatically catalyzed steps in the synthetic sequence, starting with the one immediately responsible for the end product. In this way each mutational step could confer a selective advantage by making the organism dependent on one less exogenous precursor of a needed end product. Without some such mechanism, by which no more than a single gene mutation is required for the origin of a new enzyme, it is difficult to see how complex synthetic pathways could have evolved. I know of no alternative hypothesis that is equally simple and plausible.

Place of Genetics in Modern Biology

In a sense, genetics grew up as an orphan. In the bginning, botanists and zoologists were often indifferent and sometimes hostile toward it. "Genetics deals only with superficial characters," it was often said. Biochemists likewise paid it little heed in its early days. They —especially medical biochemists—knew of Garrod's "inborn errors of metabolism" and no doubt were aware of their significance in the biochemical sense and as diseases, but the biological world was inadequately prepared to appreciate fully the significance of Garrod's investigations and his thinking. Geneticists, it should be said, tended to be preoccupied mainly with the mechanisms by which genetic material is transmitted from one generation to the next.

Today, happily, the situation is much changed. Genetics has an established place in modern biology. Biochemists recognize the genetic material as an integral part of the systems with which they work. Our rapidly growing knowledge of the architecture of proteins and nucleic acids is making it possible—for the first time in the history of science—for geneticists, biochemists, and biophysicists to discuss basic problems of biology in the common language of molecular structure. To me, this is most encouraging and significant.

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CURRENT PROBLEMS IN RESEARCH

The Interpretive Cortex

The stream of consciousness in the human brain can be electrically reactivated.

Wilder Penfield

There is an area of the surface of the human brain where local electrical stimulation can call back a sequence of past experience. An epileptic irritation in this area may do the same. It is as though a wire recorder, or a strip of cinematographic film with sound track, had been set in motion within the brain. The sights and sounds, and the thoughts, of a former day pass through the man's mind again.

The purpose of this article is to describe, for readers from various disciplines of science, the area of the cerebral cortex from which this neuron record of the past can be activated and to suggest what normal contribution it may make to cerebral function.

The human brain is the master organ of the human race. It differs from the brains of other mammals particularly in the greater extent of its cerebral cortex. The gray matter, or cortex, that covers the two cerebral hemispheres of the brain of man is so vast in nerve cell population that it could never have been contained within the human skull if it were not folded upon itself, and refolded, so as to form a very large number of fissures and convolutions (Fig. 1). The fissures are so deep and so devious that by far the greater portion of this ganglionic carpet (about 65 percent) is hidden in them, below the surface (Fig. 2).

The portion that is labeled "interpretive" in Figs. 1 and 3 covers a part of both temporal lobes. It is from these two homologous areas, and from nowhere else, that electrical stimulation has occasionally produced physical responses which may be divided into (i) experiential responses and (ii) interpretive responses.

Experiential Responses

Occasionally during the course of a neurosurgical operation under local anesthesia, gentle electrical stimulation in this temporal area, right or left, has caused the conscious patient to be aware

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