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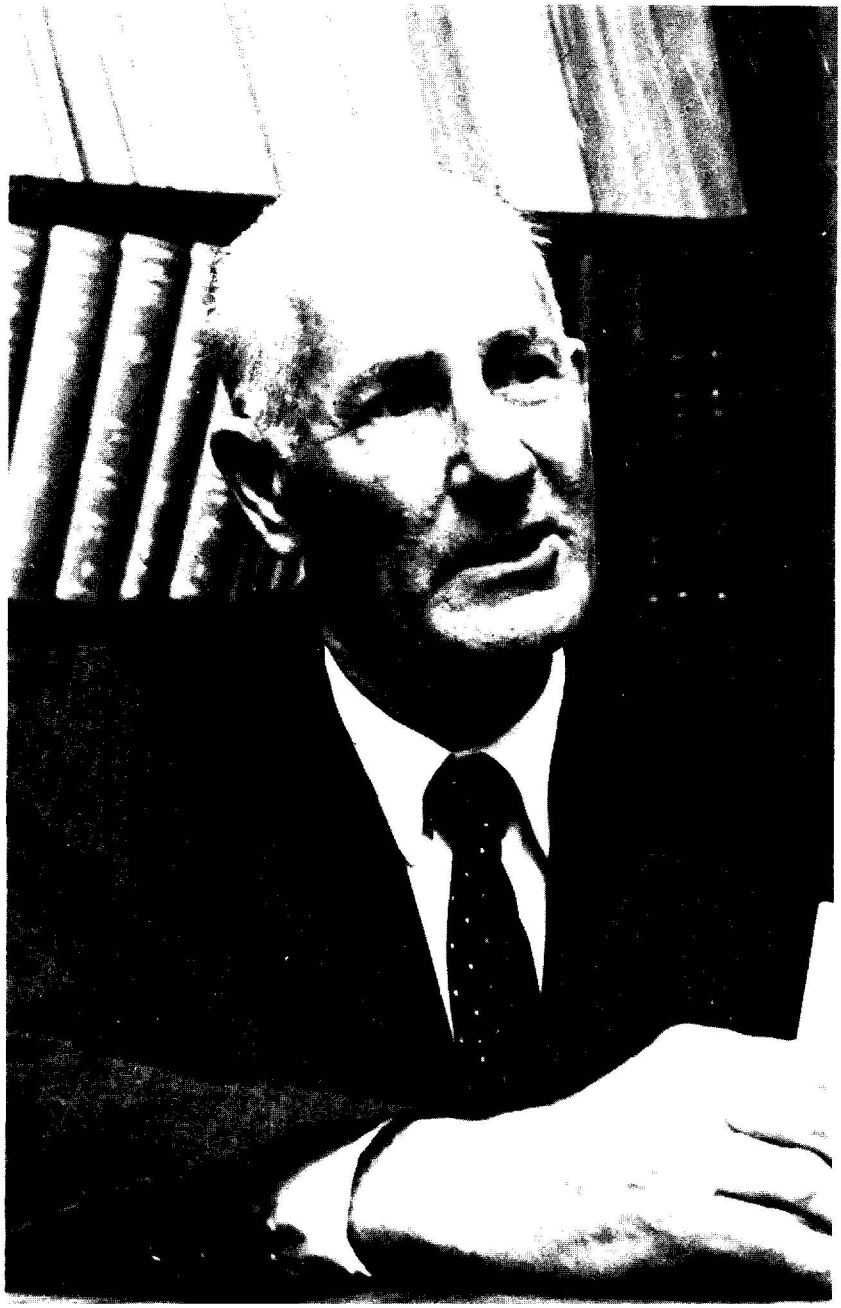

RECOLLECTIONS

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In these exciting times when elementary and high schools teach modern biology, including many of the intricacies of biochemical genetics, the long slow process by which our present knowledge in this area was gained is not often fully appreciated. A third of a century elapsed before Mendel's work was "rediscovered" and properly appreciated. Archibald E. Garrod's (1) prophetic appreciation of the relation of genetics and biochemistry, beginning soon after the so-called rediscovery of Mendel, lay fallow for more than forty years despite the fact that he published widely and relatively voluminously. As late as a quarter of a century after the Mendel work came to light, Harvard's distinguished professor of biology, William Morton Wheeler (2), ridiculed genetics as a small bud on the great tree of biology, a bud so constricted at the base as to suggest its eventual abortion. Wheeler's colleague in paleobotany, Jeffrey (3), also expressed his disbelief in the work of the then flourishing school of *Drosophila* genetics. Fortunately, neither succeeded in significantly retarding the rapid advances then being made, many of them by two Harvard contemporaries, Edward M. East and W. E. Castle. It is of interest to note that Thomas Hunt Morgan (4) remained a skeptic about Mendelian interpretations for the first ten years after the rediscovery, that is until he established the sex-linked nature of the white eye trait in *Drosophila.*

Now that genetics is widely accepted as one of the most basic aspects of all biology, it is perhaps of interest that some of us old enough to have participated in or otherwise to know something of the history of present day genetics now record our recollections. I attempt to do so in the limited area of biochemical genetics of which I have had a small part.

Of the myriads of environmental influences large and small that have to do with the course of one's life, few are likely to be long remembered with any degree of clarity or confidence. Yet behavioral scientists are increasingly aware that what happens early in life can be of the greatest significance in later years. Unfortunately when one attempts to recall such thoughts and events as have influenced later attitudes and behavior, the uncertainties are many. Thus it is with a good deal of doubt and temerity that I attempt to record events influential in that part of my life that has had to do with biochemical genetics.

I was born in 1903 of parents who owned and operated a 40-acre farm near the small town of Wahoo, Nebraska. Both had grown up in similarly small

communities: father in Kendallville, Indiana and mother in Galva, Illinois. Both were inherently intelligent but limited to high school in formal education.

Because of its small size our farm was highly diversified, with field crops such as alfalfa, potatoes, and corn; truck crops including asparagus and strawberries for market; plus cattle, horses, hogs, and chickens. All of these were supplemented by retail selling of produce, including out-of-state apples and potatoes purchased in carload lots. In this and other ways I was intimately involved in matters of biological significance. We kept rabbits, ferrets, bees, cats, dogs, and for a time, a pet coyote. Hunting, fishing, and trapping were enjoyable pastimes. With these plus routine chores and farm work, life was never dull.

Mother died when I was four and a half. My older brother, a younger sister, and I were in part raised by a series of housekeepers, some very good, some poor, and one or two terrible.

My earliest years of formal school were in a genuine little red, one-teacher, wooden schoolhouse in town, which was a mile and a half from home. During my twelve years in this and other local schools I was exposed to perhaps a dozen teachers. Like our housekeepers, they were a thoroughly mixed lot.

With the accidental death of my older brother it was tacitly assumed I would eventually take over the family farm, a prospect I looked forward to with a certain amount of confidence and pleasure. But neither father nor I had reckoned with a young high school teacher of physics and chemistry, Bess MacDonald. She did not pretend to be, nor was she, a profound authority in either of the subjects she taught. But she did have a remarkable knack of interesting us, for example, in chemistry by challenging us with unknowns to identify by classical qualitative methods. But more than that, she took a personal interest in our aspirations and hopes.

I spent many nonschool hours with her at her home, during which she convinced me I should go on to college, even though I might eventually return to the farm. My psychological insight is not sufficient to describe our rather unusual relationship. Perhaps for me she was a kind of mother-substitute.

Father was not keen on the college idea, being convinced that a farmer did not need all that education. But determination won and I enrolled at the University of Nebraska College of Agriculture, fully intending to return to the farm. Had it not been tuition-free with an opportunity to work for living expenses, I doubt if I could have managed.

Again my plans were modified by teachers. In my first year I was so impressed by a required course in English that I thought to follow it up. In fact I was offered part-time employment reading student papers during my second year. Fortunately for English, the professor went off to Palestine to study the literature of the Bible. His successor did not pick up the commitment.

In rapid succession thereafter I became enamored of entomology, ecology, and genetics. I was happy with general and organic chemistry and did well in both, but was not carried away to the point of proposing to major in that general area.

After my second year I was given a summer job classifying genetic traits in a wheat hybrid population, this for Professor Keim of the Agronomy Department. In my spare time I read about genetics and found my interest increasing markedly.

I was given other assignments including laboratory instruction in an agricultural high school program given by the College at that time. I read student papers and examinations in the elementary genetics course. I had charge of a laboratory supply department set up to provide samples of crop plants and other materials for instruction in high schools that gave courses in agriculture. During summer periods I grew various exotic crop plants for this purpose, collected and mounted representative weed seeds, made up orders, mailed them out, and kept records. In my senior year I worked on a special problem on root development and survival of fall-seeded grasses of economic importance. I also devised a key for the identification by vegetative characters of local native grasses.

Keim was a remarkable person in many ways. He did not profess to be a great scholar. But he had an uncanny ability to size students up and encourage them, which he did with a kind of understanding I have never been able fully to fathom. Some he sent back to the farm, some to be county agricultural agents, others to teach high school, and a few to go on to graduate school. I've known half a dozen or more of the latter and have never known one to be a misfit.

The nearest he ever came to an error of judgment that I know of was in getting me a teaching assistantship at Cornell and admission to graduate school to work on the ecology of the pasture grasses of New York State. It might not have been a mistake if I had seen eye-to-eye with the professor who was to sponsor my thesis research. But I did not, and soon resigned my teaching assistantship to work in genetics and cytology with Professor R. A. Emerson. That was 1926. Shortly thereafter he gave me a part-time research assistantship.

This surely was one of the best things that ever happened to me. Emerson was the perfect employer, graduate advisor, and friend. He turned problems over to me. One of my special assignments was to complete a summary of all genetic linkage studies in maize up to that time (5). I had half time for course work and for my own thesis research.

These were indeed exciting times for all of us working with Emerson. He was the outstanding plant geneticist of his time and was a tremendously stimulating person to work with and under, and his group of graduate students at the time were outstanding. They included George F. Sprague, Marcus Rhoades, Barbara McClintock, H. W. Li, and perhaps a half dozen others.

Emerson's contributions to genetics came at a time when support for the new science was minimal and the doubters many. He moved from the University of Nebraska College of Agriculture to Cornell University in 1914, in part because he felt his work was judged by the Nebraska authorities to be too theoretical ever to be useful agriculturally. Thus it is of considerable interest to note that in addition to his remarkable work in basic genetics, which of course indirectly but significantly furthered the art and science of plant breeding, Emerson conscientiously assumed direct responsibility for more than his fair share of plant breeding. By genetically transferring resistance to the disease anthracnose to commercially desirable dry beans, he saved the important bean industry of New York State from utter collapse. He also succeeded in transferring disease resistance to commercially grown cantaloupes.

Emerson was one of the first of the early American workers fully to appreciate the work of Mendel, this at a time when even T. H. Morgan was still a skeptic. As I pointed out in 1960 (6), Emerson never published until he had extracted the truth from his experimental material and verified it not once but many times in many ways. Predecessors had studied the inheritance of plant and aleurone colors in corn and had been distracted by incidental modifying factors and apparent inconsistencies with Mendelian principles to the point that some of them actually renounced those principles. It was Emerson's persistence, clear thinking, and hard-headed checking of facts that established the truth and showed beyond doubt that these apparently complex systems of inheritance in reality have an understandable genetic basis. His papers on kernel and plant color inheritance in maize are outstanding as solid experimental work, sound reasoning, and clear presentation. His early studies of quantitative characters, carried on in part through collaboration with E. M. East of Harvard, importantly influenced genetic thinking. His work on variegated pericarp led to the concept of unstable genes, another significant milestone in the history of genetics.

Important as were his own scientific contributions, in many ways it is Emerson the man most vividly remembered by those privileged to know him well. He was cordial in his relations with his friends and colleagues. The contagious enthusiasm and zest, so clearly displayed in his scientific work, were extended to other activities, bowling and hunting for example. During corn season he was first in the experimental garden and among the last to leave, an example that no doubt increased the productiveness of all who worked with him. Bag lunches eaten in the shade of the garden shed during these periods of intense field activity were of special interest to students and other associates. It was there that the unpublished lore of corn genetics and geneticists was most likely to be recalled. It was also a setting in which Emerson became best known to his students. It was also in such informal ways that he did much of his teaching. He was freely available to students but it was his policy that they come at their own instigation. At all times he was willing to be helpful but he did not direct student research in any formal manner.

Emerson's research materials were freely available, not only to his own colleagues and students but as well to investigators elsewhere. This generosity played an important part in making corn the best known of all higher plants from a genetic point of view and had the effect of interesting investigators throughout the world as well as significantly increasing general genetic understanding.

With the growth of the corn group the system of communicating unpublished information through conversation became inadequate. During 1932 at the International Genetics Congress at Ithaca a "corn meeting" was held where it was decided that a central clearinghouse of information and seed stocks would be established at Cornell. Out of this there evolved a series of mimeographed "corn news letter" edited by Marcus Rhoades and sent to all interested corn geneticists. Later this became the *Maize Genetics Cooperation News Letter,* a somewhat more formal organization for the dissemination of information not published in formal journals and for recording seed lines available for research.

One of the groups of mutant types being worked on from the earliest days of

Emerson's research were those affecting chlorophyll synthesis and function. I vividly recollect Emerson's attempts to interest plant physiologists and biochemists working on photosynthesis in making use of such mutants as tools in fathoming the physiology and biochemistry of chlorophyll structure and function. None responded, otherwise biochemical genetics might have moved forward more rapidly.

In my own attempts to improve my understanding of chemistry in relation to genetics, I audited courses in physical chemistry and biochemistry. The latter was given by James B. Sumner and it was during this period that he first crystallized the enzyme urease from the jack bean. Biochemists will recall the long lag between this accomplishment, and acceptance and confirmation of it as authentic and thus a significant forward step.

The time was clearly ripe for the new discipline of biochemical genetics. But few biochemists or geneticists were then intellectually or psychologically prepared, despite the fact that Archibald E. Garrod had a quarter of a century earlier clearly suggested a one-to-one relation between gene action and enzyme activity, and had published both repeatedly and voluminously (7).

My own graduate research in cytogenetics was both rewarding and significant. In part I worked on the genetic control of meiosis using corn lines in which chromosome behavior was markedly modified genetically. The asynaptic mutant was the first, polymitotic a second, and sticky chromosomes a third. I also worked closely with Emerson on the relation of corn to its nearest wild relative, a Mexican plant known as teosinte, this, incidentally, a relationship still not fully resolved and which I am now again actively investigating.

A significant turning point in my career came in 1931 with the completion of my graduate work. I had hoped to be awarded a National Research Council Fellowship to continue my corn cytogenetics work at Cornell, by far the best place to continue in terms of facilities and associates. But the wise chairman of the Fellowship Board, Charles E. Allen of the University of Wisconsin, intervened, pointing out that remaining for postdoctoral work in the same institution in which one took his PhD degree was in principle less desirable than moving to another institution where, other things being equal, new experiences and insights were more likely to be acquired. He said he would approve the award if I would accept my second choice as a place to continue. That was the California Institute of Technology where Thomas Hunt Morgan had recently moved from Columbia to establish a new Division of the Biological Sciences. Emerson approved and I concurred, little realizing at the time that this would be another best thing that ever happened to me.

Caltech biology was indeed tremendously stimulating. Among those who were there in genetics and related areas when I arrived as a research fellow were Morgan, Sturtevant, Bridges, Dobzhansky, Schultz, Anderson, Emerson (son of R. A. Emerson), Belar, and the Lindegrens. Darlington, Haldane, and Karpechenko spent time there as visiting scholars.

General enthusiasm was at a high level and persons in other fields were caught up in it. Linus Pauling took a personal interest in genetic crossing over. R. A. Millikan delighted in escorting visitors to Biology where he could give a masterly

account of *Drosophila* investigations. Charles Lauritsen and associates were building a million volt X-ray tube which became available for medical and biological use.

At first I concentrated on my corn cytogenetics program but soon became actively interested in *Drosophila,* then by far the most favorable organism for genetic study. I worked with Dobzhansky, Emerson, and Sturtevant at various times on genetic recombination in the hope that this would tell us significantly more about the nature of the gene. It didn't do as much as we had hoped, though decades later it became clear that if we had really learned enough about recombination a good deal more about the nature of the gene could have been revealed.

An additional and significant turning point in my career began with the arrival in 1933–1934 of Boris Ephrussi from Paris as a Rockefeller Foundation Fellow. He was actively interested in tissue culture and tissue transplantation as a means of learning more about gene action.

We spent long hours discussing the curious situation that the two great bodies of biological knowledge, genetics and embryology, which were obviously intimately interrelated in development, had never been brought together in any revealing way. An obvious difficulty was that the most favorable organisms for genetics, *Drosophila* as a prime example, were not well suited for embryological study, and the classical objects of embryological study, sea urchins and frogs as examples, were not easily investigated genetically.

What might we do about it? There were two obvious approaches: one to learn more about the genetics of an embryologically favorable organism, the other to better understand the development of *Drosophila.* We resolved to gamble up to a year of our lives on the latter approach, this in Ephrussi's laboratory in Paris which was admirably equipped for tissue culture, tissue or organ transplantation, and related techniques.

Morgan arranged to continue my Caltech salary, then $1500 annually, which was 33% less than the previous year because of the great depression. Only years later did I find that this stipend was almost surely provided by Morgan personally. Caltech was in dire financial straits at that time and though Morgan was extremely frugal with Institute funds, he remained always generous in personally supporting causes he thought worthy. Leaving a wife and small son in Pasadena where living costs were unbelievably low at that time, I went to Paris to work with Ephrussi. Fortunately living costs were also very modest there, provided one could do with bare necessities. My daily subsistence expenses, room and food, were approximately two dollars.

In Ephrussi's laboratory we tried tissue culture without remarkable success or promise. We switched to *Drosophila* larval embryonic bud transplantation which turned out to be successful despite assurances from the Sorbonne's great authority on the metamorphosis of the blow fly that we could not succeed.

We knew from Sturtevant's work on naturally occurring mosaic flies that the character vermilion eye (absence of brown component of the two normal eye pigments) was nonautonomous in the sense that if one eye and a small part of the adjacent tissue were vermilion and the remainder wild type, the genetically vermilion eye would produce both pigment components. Obviously an essential

part of the brown pigment system was produced outside the eye and could move to it during development. We confirmed this by transplanting genetically vermilion embryonic eye buds in the larval stage to wild-type host larvae. Although it was thought a priori by some to be extremely difficult if not impossible, a technique for doing this was devised. It involved two people working cooperatively through paired binocular dissecting microscopes focussed on one recipient larvae.

We confirmed the existence of a diffusable substance which we called vermilion-plus substance (8). A second mutant lacking brown eye pigment was found to behave similarly—the so-called cinnabar character. Reciprocal transplants between the two mutants lacking brown pigment showed that there were two substances involved, one a precursor of the second. We postulated that one gene was immediately concerned with the final chemical reaction in the formation of substance 1 and the second with its conversion to substance 2.

We investigated the twenty some other eye-color mutants then known in *Drosophila* and found just these two in direct control of the two postulated chemical reactions (9).

Since most biologically significant reactions are enzymatically catalyzed, we assumed the two eye-color genes, cinnabar and vermilion, directly controlled the two postulated enzymes. This was the origin in our minds of the one gene/one enzyme concept, although at that time we did not so designate it.

In formulating this interpretation we were much encouraged by the previous related work of Caspari and others (10) on related pigmentation in the meal moth *Ephestia* and also the work of Scott-Moncrieff (11) and earlier workers on the genetic control of anthocyanin pigments in higher plants.

It is of interest and I believe of some significance that Jacques Monod, then an instructor at the Sorbonne, took a keen interest in our work and spent a good share of his spare time in Ephrussi's laboratory following progress and discussing results with us. Later when Ephrussi returned to Caltech for a year where we continued our collaboration, Monod also came as a visiting investigator.

An obviously important next step was the identification of the two brown pigment precursors. Ephrussi and Khouvine worked on this aspect of the problem in Paris and I at Harvard with Kenneth Thimann and later at Stanford University with Tatum and Clarence Clancy. Tatum demonstrated a functional relation of one of the precursors to tryptophane and he and Haagen-Smit at Caltech came close to identifying it (12).

Butenandt, Weidel & Becker (13) in Germany took up the search and were able to identify the so-called vermilion-plus substance by trying then known relatives of tryptophane; it was kynurenine.

As an interesting sidelight, kynurenine had been isolated and identified years before by Clarence Berg of the University of Iowa, son of a Wahoo harness-maker who had lived only a few miles from the Beadle farm. Had we only known, we could have got kynurenine from him.

At about this stage in our work Tatum's father, then a pharmacologist at the University of Wisconsin, came to Stanford on a family visit. One day as he was visiting our laboratory he called me aside to tell me that he was concerned about

the professional future of his son. "Here you have him in a position in which he is neither a pure biochemist nor a bona fide geneticist. I'm very much afraid he will find no appropriate opportunity in either area." I recall my response very clearly: "Professor Tatum, do not worry, it is going to be all right."

I recall another episode illustrating the doubts held as to the future of the new hybrid approach. We had tried earlier to interest in joining our group a young biochemist at Columbia University who had been recommended by Professor Hans Clarke. He declined because the three part-time positions he then held were financially somewhat more rewarding than the one for which we were responsible. On again meeting him more than two decades later he told me he had many times regretted not seeing more clearly the opportunities in biochemical genetics.

At about this time, 1940–1941, Tatum gave a course at Stanford on comparative biochemistry. Auditing his lecture one day it suddenly occurred to me that there was a much easier approach than we had been following for identifying genes with known chemical reactions. If, as we believed, all enzymatically catalyzed reactions were gene controlled in a one-to-one relation, it would obviously be much less time consuming to discover additional such relations by finding mutant organisms which had lost the ability to carry out specific chemical reactions already known or postulated. For two reasons the obvious organism to use for such an approach was the red bread mold *Neurospora*. First, its cytogenetics had already been worked out by the mycologist B. O. Dodge (14), whom I had earlier met at Cornell University, and the Carl Lindegrens whom I knew from my early years at Caltech. Second, we knew from the work of Nils Fries (15) in Sweden that many filamentous fungi not too distantly related to *Neurospora* could grow on chemically defined media containing a proper balance of inorganic salts, a source of carbon and energy such as a sugar, plus one or more known vitamins.

So why not determine the minimal nutritional requirements of *Neurospora*, produce mutant types by X or ultraviolet irradiation and then test these for loss of ability to synthesize one or more components of the ~~minimal~~ supplemented medium? We soon found the minimal medium to consist of simple inorganic compounds, a suitable carbon and energy source such as sucrose, plus the one vitamin biotin. That was 1941 and fortunately biotin had just become commercially available as a concentrate sufficiently free of amino acids and other vitamins to serve our purpose.

The 299th culture from a single ascospore, whose parent culture had been X rayed, proved not to grow on minimal medium but did so with added Vitamin B_6. It was then a simple matter to determine that a genetic unit, presumably a single gene, had been mutated by crossing the mutant strain grown on a supplemented culture medium with the original strain of the appropriate mating type and then testing cultures from the eight single spores derived from a single meiotic event. Our test showed that four such cultures required Vitamin B_6 while four did not, indicating change in a single genetic unit (16).

Could we produce more such mutant types with other requirements? The answer was yes, for other vitamins and for various essential amino acids. In sequences of biosynthetic reactions leading to a given endproduct we could identify genes for individual steps, in general one gene and one only for a specific biosynthetic step.

In addition to biochemical mutants, which for the most part are normal morphologically when grown on properly supplemented media, a variety of morphologically altered types were found, some quite bizarre in appearance. During the time we were accumulating these along with scores of nutritionally altered mutants Doctor Charles Thom, a widely recognized authority on fungi, especially of the genus *Penicillium* and related genera, paid us a visit. As we toured the laboratories he was obviously keenly interested but made few comments. After we had demonstrated a fair sample of the work under way and a number of morphologically diverse mutant types, Doctor Thom called me aside and said "You know what you need here?"

"What," I asked.

"A good mycologist," was the answer. "Those cultures you call mutants are not mutants at all. They are contaminants."

To the question of how, when crossed with the original type, they could segregate according to established Mendelian principles he had no answer. I'm sure he left convinced we were the most inept mycologists he had ever seen. He had never been an ardent admirer of genetics and we obviously failed to influence him in that regard.

At this stage of our investigations it was obvious that we could increase our rate of progress significantly by supplementing our research personnel. We were fortunate in obtaining the additional financial help needed for this from the Rockefeller Foundation which, through grants to the Stanford Biology group, had made the initial work possible. Herschel K. Mitchell, Norman H. Horowitz, David M. Bonner, Francis Ryan, Mary Houlahan, and others joined the team. Through C. Glen King of the Nutrition Foundation we received support for graduate students including Adrian M. Srb, August Doermann, David Regnery, Frank C. Hungate, Taine T. Bell, and Verna Coonradt.

Although the Research Corporation did not support our work financially, its officers gave us much appreciated encouragement in the following way: The Rockefeller Foundation had earlier made a $200,000 grant to the C. V. Taylor group of biologists at Stanford, of which Tatum and I were members. Knowing Taylor's persistence, persuasiveness, and ambition for his group, the officers of the Foundation had placed a condition on the grant, namely that he not apply for additional funds from the Rockefeller Foundation during a following ten year period. I of course knew of this, and thus inquired of Frank Blair Hanson of the Rockefeller Foundation if there was any objection to our applying to the Research Corporation for supplemental support of our special project. There was not, so on that same day I approached the Research Corporation and was told they would provide the needed $10,000. Just as the details of how formally to apply were being discussed a telephone call came to me from Hanson of the Rockefeller Foundation, saying that they had reconsidered our special situation and felt that since they had provided initial support they thought it appropriate to provide the requested supplement. On reporting this to the Research Corporation officers, I was immediately told it was right and proper that the Rockefeller Foundation should continue the support, but that if we would send them a carbon copy of our formal

request they would agree to provide the $10,000 if the Rockefeller Foundation for any reason did not do so. That is the kind of confidence that really inspires a research team. The Rockefeller Foundation did make the grant, but it was only years later that I learned it had been Warren Weaver who had recommended that the exception be made. His record of judging projects that paid off, scientifically speaking, was one of remarkable success and I have always been grateful that we did it no serious damage.

During this visit to the Research Corporation R. E. Waterman, who had worked earlier with R. R. Williams in isolating and characterizing thiamine, pointed out to me that G. W. Kidder of Amherst was working with a protozoan and had obtained results very much like ours. He added that Doctor Williams knew the details, and that I would have a good chance of seeing him if I were to hurry over to the 42nd Street Airlines Terminal where he was waiting for an airport limousine. I did find him and was led to believe Kidder indeed had results very much like ours in *Neurospora*. We were of course anxious to learn more about it. On doing so we found that the work that had so understandably impressed Williams had to do with special cultural conditions under which *Tetrahymena vorax* could synthesize thiamin (17) and was not at all designed to answer the types of questions we were asking.

By 1942 we had gone a fair way in the process of identifying genes with specific chemical reactions. Then the classical work of Garrod (7) was rediscovered, or perhaps more correctly, properly appreciated, by J. B. S. Haldane and Sewall Wright (18, 19). Back in the early part of the century, very soon after the rediscovery of Mendel's paper and the confirmation of his principles, Garrod had demonstrated that the human disease alcaptonuria was a simple Mendelian recessive trait characterized by an inability to further degrade 2,5-dihydroxyphenyl acetic acid (alcapton or homogentisic acid), a metabolic derivative of phenylalanine. Unlike their normal counterparts who further degrade alcapton, alcaptonurics excrete it in the urine where, upon exposure to air, it oxidizes to a blackish compound. Not only did Garrod correctly deduce the relation of gene to enzyme and to chemical reaction, he also used alcaptonurics to identify intermediate compounds in the sequence of reactions between phenylalanine and alcapton. In a like manner he characterized several other genetically controlled metabolic reactions in man.

On learning of this long-neglected work it was immediately clear to us that in principle we had merely rediscovered what Garrod had so clearly shown forty years before. There were three differences of significance: First, we could produce many examples. Second, our experimental organism was far better suited to both chemical and genetic investigation. Third, ours was a time far more favorable for acceptance of the obvious conclusions.

Like Mendel, Garrod was far ahead of his time, but unlike Mendel, his work was not buried in a relatively obscure journal: Garrod published in standard journals and wrote a widely distributed book, *Inborn Errors of Metabolism*, first published in 1909 with a second edition in 1923 (7). His work was well known to Bateson, the early British enthusiastic advocate of Mendelism. Bateson and his associate Punnett advised Garrod on the genetic aspects of his studies of biochemical defects

in man, and Bateson's classical 1909 book, *Mendel's Principles of Heredity* (20), referred to it in some detail. For reasons most difficult to understand it then dropped out of the genetic literature until revived in 1942.

In giving a seminar on biochemical genetics at the University of California at Berkeley, in the late 1940s I pointed out that among others, Goldschmidt's 1938 book *Physiological Genetics* (21) failed to mention Garrod's contribution. Professor Goldschmidt, who was in the audience, came up after the seminar and explained that he had known of Garrod's work and could not understand how he had omitted mention of it. Clearly, like many others, he failed to appreciate its full significance, else he could not have forgotten it.

In retrospect one wonders how such important findings could be so thoroughly unappreciated and disregarded for so many years. Obviously the time was not ready for their proper appreciation. Even in 1941 when Tatum and I first reported our induced genetic-biochemical lesions in *Neurospora* few people were ready to accept what seemed to us to be a compelling conclusion, namely that in general one gene specifies the sequence of one enzyme (or polypeptide chain). In 1945 I gave a series of some two dozen Sigma Xi lectures in as many colleges and universities of the country. The skeptics were many, the converts few. Even at the time of 1951 Cold Spring Harbor Symposium on Quantitative Biology the skeptics were still many. In fact the believers I knew at the time could be counted on the fingers of one hand, despite the eloquent and persuasive additional evidence presented at that meeting by Horowitz & Leupold (22).

In speculating on the long-continued reluctance of geneticists and others to accept the simple gene/enzyme concept so clearly implied in Garrod's early work, the anthocyanin studies, and the more recent microorganism studies, Horowitz (personal communication) tells me A. H. Sturtevant had once pointed out to him that this was because of a widespread belief in the so-called pleiotropic (many effects) action of genes. In the sense that the terminal results of a single gene mutation may appear multiple, this can be said to be correct. But in terms of the primary effect of such a mutation in replacing a single amino acid in a polypeptide chain for example, it is clearly not.

With the working out of the Watson-Crick double helix structure of DNA, its method of replication, and its role in protein synthesis, the difficulty in accepting the concept of one gene/one enzyme largely disappears, for it can now be stated as one functional DNA sequence/one primary polypeptide chain.

The work I have discussed was but a small part of a prelude to the magnificent new era of biology ushered in through the elucidation of the structure of DNA two decades ago. Our knowledge of living things at the molecular level has continued to increase exponentially. In a real sense genetics has come to be recognized as an integral and basic part of all biology, of biochemistry, biophysics, immunology, virology, physiology, the behavioral sciences, plant and animal breeding, and all the rest.

Largely as a result of its advances, the opportunities and challenges have never been greater in the areas of biology. Nor have the intellectual rewards to those adequately prepared and sufficiently motivated.

In my own situation, I tried a quarter of a century ago what I thought of as an experiment in combining research in biochemical genetics with a substantial commitment to academic administration. I soon found that, unlike a number of my more versatile colleagues, I could not do justice to both. Finding it increasingly difficult to reverse the decision I had made, I saw the commitment to administration through as best I could, often wondering if I could have come near keeping up with the ever increasing demands of research had I taken the other route. My doubts increased with time.

As one bit of evidence that occasional satisfactions do accrue to academic administrators, I cite an example involving James D. Watson. On his return from the Cambridge Medical Research Council Unit shortly after he and Francis Crick had worked out the double helix structure of DNA, Watson continued research as a Senior Research Fellow at the California Institute of Technology, Division of Biology. His draft board address, however, remained Chicago, and at this time the board members concluded his deferment from military service had been sufficiently long and thereupon reclassified him 1A.

Being convinced his potential contributions to science would far outweigh anything he might do to promote the mission of the military, we set out to convince the authorities that his deferment should be continued. Successive appeals to higher and higher levels were consistently denied and the Watson file grew correspondingly thicker. Finally, through the help of the National Research Council, the appeal was carried to the highest level, the Presidential Review Board. At this level previous decisions were reversed and Watson assigned to what in Washington was facetiously referred to as "the rare bird category," a designation that seemed especially appropriate to Watson, a dedicated bird watcher.

Those of us involved were of course much pleased that our efforts had been successful. Personally I was never quite able to decide the appropriate sentiment to express to the military, condolences or congratulations.

Now, on retirement from administrative duties, I have returned to a relatively simple research project of four decades ago with Emerson, namely the origin of *Zea mays,* Indian corn. It involves a combination of genetics, ecology, archeology, biochemistry, and other related disciplines in ways I am glad to say I find intellectually and emotionally satisfying.

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