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Comments on Gene-Enzyme Relationship[1]

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> "When we find, for example, that a certain gene difference results in the presence or absence of a particular enzyme, we have not proved that the gene directly produced the enzyme; it may merely have caused, through a series of intermediate processes, the production of an acid that inactivated or destroyed that enzyme, the acid having in turn been produced by another enzyme, and that activated by a co-enzyme, and that produced by a protein—when the latter was ionized by the gene! Who can tell, in this house that Jack built?" (Muller, 18).

To summarize some impressions from what I have learned today, may I just bring up the following points, one by one.

Dr. Monod asked whether the inducer carried the information needed for the specification of the enzyme. One permissible view holds that the enzyme, or its critical surface, is directly molded on the inducing substrate. The alternative, which I prefer, is that all the specifications are already inherent in the genetic constitution of the cell: the inducer signals a regulatory system to accelerate the synthesis of the corresponding enzyme protein. On this notion, substrate- induced or, better, substrate-regulated enzyme formation is an evolved adaptation to relieve the organism from always having to produce a full quota of its genetic potential of enzymes regardless of their immediate utility. My reasons for preferring the second formulation are: its consistency with other adaptive responses, as to oxygen or pH (6); the fact that enzymes of indistinguishable specificity are provoked by different inducers; and the occurrence of substrates which do not induce, and inducers which are not substrates. In addition, sensitive assay methods have generally shown that uninduced cells (grown in standard media) contain a basal level

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of the enzyme which may be about 0.1 to 1.0% of the fully induced level. Furthermore, the basal level is under genetic control, as is shown by so-called "constitutive" mutants and strains. (In looking for residual basal enzyme, it is important to avoid substrates which actively inhibit enzymic induction, as glucose often does.) The incongruent specificities of enzymic induction and action are readily understood: they have been evolved to overlap necessarily only for the principal natural substrate.

The immune response has provoked a similar discussion. Ehrlich had proposed that specific antibodies were normal products, subject to quantitative variation under the influence of the antigen. Pauling and others believe that the antigen plays a direct role in molding the antibody protein. Enzymes are generally less specific than antibodies in their range of complex formation, but more so in their catalytic action. Furthermore, antibodies are constructed from a common gamma globulin, whereas enzymatic specificity can call on a more fundamental variety in structure (27). We need not assume, therefore, that both syntheses follow the same plan.

Dr. Ephrussi has given us a disarmingly lucid presentation of the genetic problem of differentiation. We distinguish *development,* which is the realization of cellular potentialities, from *differentiation,* which is their irreversible restriction. So much emphasis has been put on the latter, perhaps because it is such a poser for geneticists, that I hope development will not be forgotten. It is not clear how far development depends on differentiation, and it may not at all in plants, but the irreversibility of specialization is an empirical generalization both in phylogeny and ontogeny.

Dr. Ephrussi agrees that embryologists have to study embryos, whatever hints the geneticist may be able to furnish from model microbial systems. Since the elegant experiments of Briggs and King on nuclear transplantation, I would add that the geneticists should study the embryologists, for they have introduced a methodology for the genetics of tissue cells. Perhaps it is not too much to hope (14) that these methods may be refined, and others borrowed from microbiology, to allow a really detailed analysis in conventional genetic terms of all that does go on in differentiation and its aberrations. Mutation, in the sense of random interruptions of the genetic information of the chromosomes, has been discounted as a likely factor in normal development (5). However, the work on nuclear transplantations re-emphasizes the possible role of other alterations of genetic quality, e.g., active and inactive states of specific genes, or local regulation of genic function by chromosomal activators (15, 16, 20).

Among Dr. Spiegelman's remarks, I was impressed by a technical advance he mentioned only casually, the isolation of bacterial nuclei from cytolysed protoplasts. This unique accomplishment should give access to new dimensions in the biochemical delineation of genetic and somatic functions in bacteria and help to clear up confusion and fruitless controversy in bacterial cytology.

This audience, is however, unlikely to adopt without exception Dr. Spiegelman's reasoning that intermediate polymers are lacking in the biosynthesis of specific proteins, simply because he could not find them. Intermediates are, of course, definable as compounds which do not accumulate except under exceptional circumstances that may not yet have been devised. Of course his conclusion may have stronger support on other grounds.

In the experimental account, he stated that RNA was required for enzyme synthesis, but DNA was not. Did the removal of DNA affect the synthesis of RNA, as might be expected if RNA is a direct copy of nuclear specificity?

Dr. Velick and Dr. Cohn debated dynamic turnover and the apparent discrepancy between the experiments on animals and on bacteria. But these have involved different physiological circumstances as well as different organisms. Bacterial enzyme synthesis is commonly studied in rapidly growing populations in which protein is being formed at a maximal rate from external nutrients. This type of unlimited protoplasmic increase is unparalleled in the metazoan except for the earliest stages of development, and metabolic turnover has necessarily been followed in organs and tissues which are preoccupied with their own maintenance as well as increase. We can hardly doubt that some part of a metazoan cell may wear out and need to be replaced. And I venture to predict that the same will be discovered for bacteria when they are studied under comparable conditions of nutritional restriction, where the reuse of pre-existing protein is obligatory for the maintenance of the cell. This may already have been discovered in the so-called "preferential synthesis" of lactase in nongrowing *E. coli,* for which a strict adherence to the denial of metabolic turnover would lead to the strained conclusion that the biosyntheses of these cells are confined to lactase (22).

It is well known that bacteria vary greatly in size during the culture cycle. I am not aware of any systematic studies on whether large cells can become smaller except by fission (but I believe I have seen this happen incidentally to other observations). If such observations can be coupled with analyses for percentage composition and for cellular viability, these cyclic changes may be useful to test whether individual,

viable cells can reuse their own substance for maintenance. Further attention should also be given to the enzymatic inductions of *Pseudomonas,* which are accomplished so quickly and completely in cells suspended in buffer (24). Of course, until the free amino acid pool of these cells is measured, this cannot be excluded as the nutrient for the rapid adaptation.

Dr. Cohn has also given us a provocative account of a regenerative feedback system which is maintained for many generations in bacteria held in threshold concentrations of an inducer-inhibitor mixture. There have been many speculations of such steady states—cf. the alkaligenic virus of Chiari and Löffler (12)—but few which can be validated in simple physiological terms. I hope the technique of maintaining the alternative states can be perfected to the point where they can be readily diagnosed for the progeny of single cells. This would permit a formal genetic analysis, the better to relate this system to traditional examples of cytoplasmic heredity, as well as to verify that the locus of the effect really is in the cytoplasm, or wherever it proves to be.

Dr. Gale's bold chemical attack on the functions of RNA is, of course, the starting point of many of our discussions and represents (in my opinion) the second important milestone of recent years in the reduction of genetics to biochemistry. I hope that his example and success will inspire many more enzymologists to tackle the complexities of genetics with the concrete methods as well as the abstract methodology of chemistry and physics. I also hope that they will stop to consider how complex these problems are if this does not deter the attack. Dr. Rotman has mentioned a detail which might be clarified. If the lactase of staphylococci is inseparable from large fragments, can one rely on increase in apparent activity as a measure of further synthesis of the enzyme? Or might part of the activity be released from bound particles? The cell-bound galactosidase of *E. coli* shows such a large increase of activity when the cells are disrupted that we have learned to be cautious about equating activity with amount (9, 23).

Dr. Hershey, as usual, has carefully phrased the questions that are brought up by his study. Since protein synthesis is not required for the synthesis of specific phage DNA beyond the first 10 minutes after infection, what is its function during that early interval? Is it merely to organize the accessory enzymes that may be needed for the energetics and precursors of phage replication, or does protein play a more direct intermediary role in the genetic continuity of the phage (25)? Dr. Levinthal has been doing some experiments in the salt mines near Detroit, to minimize cosmic ray interference, that have an important

bearing on the material continuity of phage DNA—are these ready to be brought to the surface?

Dr. Hotchkiss has given a methodical account of the evidence that the transformation of the pneumococcus consists in the transfer of hereditary fragments, embodied in DNA, from one cell to another. Since Griffith's discovery of the transformation of capsular types in 1928, the phenomenon has been interpreted in a variety of ways, including this, the *transduction* hypothesis. Though this term was coined to correlate the basic genetic findings on *Salmonella* (12, 29) with these data on the pneumococcus, the hypothesis was anticipated earlier, for example by Muller (19), notwithstanding persistent confusion (7, 8). The accounts by Hotchkiss and Demerec are a striking illustration of the basic unity of the modes of transduction, via DNA in the pneumococcus, via phage in *Salmonella.*

I am less optimistic, however, that current pedigree studies can decide the ultimate details of the mechanism by which fragments exchange with the recipient's chromosomes. The main question is whether the fragment is actually incorporated in an existing chromosome, which would require breakage at two points and the expulsion of the homologue, or whether its specificity is coded into a new copy of the chromosome as an incident of the next replication. The breakage hypothesis is so unappetizing that it has led to the most dubious alternative proposals for the concept of transduction itself (7), although a similar notion is generally taught for ordinary crossing-over. The second idea, of copy-choice or partial replication, which is a renewal of some of Belling's older ideas, seems to me a more plausible approach to the problems of both crossing-over and transduction. Unfortunately, the fact of segregation in transformed clones is not decisive, though it has been verified in direct single cell studies in *Salmonella* (13). One difficulty already mentioned is that pneumococci are two-celled, and *Salmonellae* are two- and four-nucleated bacteria, and the patterns of nuclear assortment at cell division may be imperfectly predictable. In addition, we do not know exactly when the fragment exchanges and whether it replicates by itself meanwhile. Persistent replication of a transduced fragment does occur in an *E. coli* system (17) where it leads to a more or less permanent "heterogenote" clone, whose cells are heterozygous for the one or few genes included in the fragment. In this system, exchange is delayed and we can thus make certain that a given fragment can exchange different elements. It is still uncertain, however, whether the initially transduced fragments are all exactly alike.

Transduction by phage, as seen in *Salmonella,* involves fragments

which may also consist of DNA, but as they are associated with the phage particle we have no direct evidence of this. Dr. Demerec has shown how this system can be applied to the most exacting genetic analyses, the "fine structure" of the linkage map. His conclusion that mutants for different steps of a biosynthesis occur in linked clusters is less startling only than the inference that their linkage order corresponds to the chemical sequence. Until the detailed evidence in support of both sequences has been published, I have no basis for a critical opinion and the interval may give the time needed to assimilate the findings to a consistent conceptual scheme. Meanwhile, I would ask whether every auxotrophic mutation for, say, histidine, has been tested and found to be linked in the same cluster. It would be surprising if Dr. Demerec's group has been spared distraction by secondary effects which students of biosynthesis have usually run into. Our own incidental experience with *E. coli* does not concur with this generalization, but it has not been purposefully oriented on Dr. Demerec's hypothesis, and the exceptions involve different markers. The lactase-deficient mutants of *E. coli* are, for example, located at various points. Lac_1 *and* Lac_4 are very closely linked, but these and Lac_2, Lac_3, and Lac_5 are not. Of these mutants, to which Dr. Monod has also alluded briefly, Lac_2 and Lac_4 are absolute negatives, and the others retain the capacity to produce lactase under special conditions (10, 11). A discouraging feature of generalizations is that they must fearfully await the first exception, as happened for example to the somewhat analogous theory of step-allelism in *Drosophila.* In any event, these observations reopen the question whether a linkage map of the genes makes any sense at all, which can be hoped for only when a given segment is completely charted.

Accepting the correspondence of sequences, we are bound to look for a concordant organization of the enzymes, an assembly line (21). Dr. Demerec suggests that this may be in the nucleus, that the genes themselves are the enzymes. Alternatively, we may interpolate a step and postulate a cytoplasmic structure, perhaps a mitochondrium, patches of which correspond to the map sequences. Indeed the seriated mutants may reflect defects in the pattern of integration of the enzymes, the points at which they hook on to work together, rather than the seat of specificity for the synthesis of the individual enzymes. A direct biochemical approach should save us from a protracted hypothetical discussion, viz. by isolation of the integrated enzyme complexes, or a direct evaluation of the activity and nuclear and extranuclear fractions.

Dr. Horowitz and Dr. Yanofsky have brought up the subtlest of physiological genetic controversies, the "one gene, one enzyme" theory.

I am told that the possibility that several genes may participate in the formation of one enzyme is no longer in dispute (2, 11, 28). Dr. Horowitz is principally concerned with the problem of pleiotropy, whether several enzymes or other primary effects can be related to a single gene as a lead to the fundamental question of how the genes work. There is no debate at all that genetic functions are ultimately mediated by enzymes; we are discussing only the organizational details.

Many of the objections to the one-to-one theory are "philosophical," but so is its strongest support. Without doubt, the only effective working hypothesis to help unravel the physiology of any mutant is to assume a single primary disturbance from which all else follows. However, I do not want to be too quick to assume that this primary effect is always the immediate production of the workaday enzymes of the finished cell. The hypothesis which obviously underlies the one-to-one theory is that a gene works as a unique template for "stamping the specificity" on an enzyme. My philosophical reservation is against the *implication* that "specificity" (or "information," as it is called nowadays) is something apart from structure.

Whatever controversy persists on the one-to-one theory is a corollary of the limitations of genetic experiment, as implied by the leading quotation from Muller. The function of a gene cannot be tested in isolation; at best we can compare genotypes, i.e., cells, which differ in respect of a single gene. (For the moment, let us take this concept for granted.) If these genotypes differ in the formation of one or more enzymes, are we entitled to say "the gene makes the enzyme"? In fact, until recently, we could only say that the cell has made the enzyme, but the experimental approaches which Gale has inspired may lead to more specific answers. To refer to mutant genes as making "mutant enzymes" still begs the question whether a given gene is the primary seat of specificity of an enzyme, or whether it has an indirect influence on the metabolic output of the rest of the cell, e.g., to specify which of several latent potentialities will be realized. Unfortunately, we have no way of obliging a cell to tell us everything it knows how to do: we can only read what it chooses to show us in a given context.

The main difficulty with the one-to-one theory is that it is experimentally indefensible, that there is no experimental test that can exclude it short of realized knowledge of how the genes work. Many examples of pleiotropic effects are known: one of the most spectacular is a generalized suppressor gene which can compensate for a number of mutant genes in *Drosophila* (4), an observation which tells us that many mutations are not the losses of information that we might have sup-

posed. In fact, although the one-to-one theory has been discussed as based on the properties of *Neurospora* mutants, the recent work discussed today has been almost the first explicit test of it, and Dr. Yanofsky's work has already overreached the simplest anticipations. From my own experience with *E. coli*, I could quote a mutation (Lac_3) which influences at least three enzymes involved in the fermentation of lactose, maltose, and glucose, respectively, but I would be the first to admit that these apparently pleiotropic effects stem from an unknown primary disturbance. But then how would we ever know whether a genetic effect is direct, or a house that Jack built? Another example from immunogenetics is better analyzed (26). The flagella of *Salmonella* consist of sero-specific proteins, of which two types are usually recognizable, each related to at least one specific gene (H_1, H_2). But whether flagella will be formed at all depends on the cooperation of several other genes (Fla_1, Fla_2, etc.) If we did not know the morphology of these proteins and, as we ordinarily must, had to be content with knowing whether or not they were produced by the cell, we would conclude that each of the *Fla* genes governs the synthesis of at least two proteins, as indeed they do in the long run. And in man, genetic defects in the synthesis of adult hemoglobin perturb his metabolic development and provoke the retention of another protein, hemoglobin F(1). Should we refer to the "thalassemia gene" as a determinant of hemoglobin F, or to its normal allele as a determinant of adult hemoglobin?

I would conclude that the hypothesis that each gene has a single primary function is the most effective axiom for experimental analysis, but that it would be premature to insist that genetic evidence shows this function to be the synthesis of a particular enzyme protein. In due course, this question can be settled by the methods of biochemistry rather than pure genetics. Meanwhile, genetic advances may apotheosize the hypothesis to a definition beyond the reach of criticism.

The traditional concepts of genes and loci have been built up primarily on the recombination test, which tells whether two mutants have corresponding loci on a linear chromosome. A gene can be defined as a unit of recombination on the implicit assumption that crossing-over can occur only between genes, not within them. But more refined tests have pushed this argument to its logical conclusion, that the units of recombination are smaller than the units of function and even of mutation, that they may even correspond to one or a few nucleotides in the DNA fiber, and that these are assuredly not units of the autonomous "self-reproduction" usually attributed to the gene (3). We are therefore obliged to retrace our steps and look at larger chunks of the chromosome to see

whether unit functions are compactly localized. We once thought that to locate a mutation was to locate a functional gene, but the acknowledged existence of position effects, i.e., of interactions along the length of the chromosome, raise unsuppressable questions as to the rigor of this technique (7). As they are pursued to their logical conclusion, the abstract formulations of genetics leave us less and less tangible knowledge of how the genes work. We can only hope that genetics has asked the right questions, which are now ready for the frontal attacks of biochemistry.

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General Discussion

STUART MUDD (University of Pennsylvania): I should like to inquire about what seems to me to be the most glaring missing link in the chain of evidence reported today. We have heard convincing evidence from Dr. Spiegelman and Dr. Gale that the ribonucleic acids are "personally concerned" in quite a specific way with the synthesis of proteins. Of course we are all familiar with the evidence that the specific genetic information is conveyed in the DNA molecule. The missing link would seem to be how the information, specifically conveyed from generation to generation by the DNA, is communicated to the RNA, which is personally responsible for the protein.

SOL SPIEGELMAN (University of Illinois): It is simply answered in words. The implication that I think most of us are laboring under is that the DNA acts as a vehicle of the genetic information in its passage from one generation to another. It is like a master plan which is kept in a locked file. When actual fabrication begins, i.e., when building of the machinery starts, this information is transferred to working plans which we call the RNA. It is the latter that actually does the job. The proof of this, of course, remains to be provided.

While I am on my feet I should like to take care of my part of Dr. Lederberg's summary. With respect to the question of the precursors and the certainty with which one can draw conclusions, of course we have been well aware in our laboratory of the fact that it is quite conceivable that there are intermediates at such low levels and of such evanescent stability that we just didn't find them. I find myself in exactly the same impossible position in which any empiricist finds himself in trying to prove a universal negative. In order to avoid experimental paralysis and frustrating futility, one has to decide how long one should continue to look for a thing which one can't find even by methods which one believes might well prove adequate. Well, we made that decision about a year and a half ago—to quit.

RUTH SAGER (Columbia University): I would like to ask Dr. Horowitz about the tyrosinase system that he described. Were any experiments carried out in an attempt to alter the ratio of heat-stable to heat-labile enzymes in the heterocaryons, independently of changes in the nuclear ratio, by some very drastic environmental treatment? The hypothesis behind this question, is an alternative to the one-to-one hypothesis: namely, that enzyme specificity, or some aspect of it, is determined not by a gene locus but by an enzyme-forming system inherited directly through the cytoplasm. Then, the two types of tyrosinase enzymes

might be carried on different cytoplasmic particles, and it might be possible environmentally to alter the ratio of these particles.

NORMAN H. HOROWITZ: The answer to the question is "No, the experiment has not been done." But cytoplasmic inheritance of the thermostability difference is ruled out by the fact that the difference is inherited in a strictly Mendelian way.

EDWARD L. TATUM (Chairman): While you are on your feet, Dr. Horowitz, may I ask another question: What would you predict would be the effect on the enzymes if you had both alleles in the same nucleus, as you might theoretically?

NORMAN H. HOROWITZ: I think you would probably get the same effect as Pauling found in the case of sickle cell hemoglobin. You get both proteins formed. In the heterozygote for sickle cell anemia both normal and abnormal hemoglobins are formed.

ROBERT J. RUTMAN (University of Pennsylvania): This may appear to be a pointless theoretical question: How is one to reconcile the one enzyme-one gene formulation with the fact that the genetic component must not only form or induce the particular enzyme required in a metabolic step but must also cause the appearance of enzymatic component(s) capable of its own reproduction?

NORMAN H. HOROWITZ: We don't know that the reproduction of the gene requires an enzyme. We don't know how the gene is reproduced. There is no reason to think it is enzymatic.

ROBERT J. RUTMAN: Presumably, when the transforming factors are introduced into cells, the subsequent "transformed" cell generations have complements of the specific deoxyribonucleic acid. All evidence indicates that this is a protein enzymatic function, i.e., that each generation also forms the enzymes needed for the new production of the specific transforming factor.

NORMAN H. HOROWITZ: The syntheses of the bases is enzymatic, but the putting together of the DNA molecule is not necessarily an enzymatic process. Dr. Hershey pointed out that phage protein may not be necessary for the duplication of phage DNA.

HARRY EAGLE (National Institutes of Health): Just a comment. There has been a good deal said this afternoon about protein turnover in mammalian cells. We have preliminary evidence which suggests that this does in fact occur in cells grown in tissue culture. When cells which had incorporated labeled amino acid were placed in a "cold" medium and kept in the logarithmic phase of growth, there was a rapid loss of the labeled amino acid from the cell protein into the medium.

CYRUS LEVINTHAL (University of Michigan): I should like to mention very briefly some experiments I have been doing in connection with the maintenance of the integrity of the DNA molecule during growth.

A technique has been developed for the measurement of the radioactivity of single molecules using a nuclear emulsion in which each β-particle disintegration leaves a recognizable track. In this way we can measure the activity of single radioactive molecules before and after growth has been allowed in a nonradioactive medium.

The general conclusions for the results so far obtained are that if we start out with phage particles, each of which apparently contains one very large piece of DNA, of molecular weight of some 35 to 40 million, and if we allow these phage particles to grow through one bacterial cycle which means a multiplication of roughly 50- to 100-fold, we find in the progeny approximately the original number of "hot" molecules. These few molecules have half the activity of the original "hot" molecule.

If we allow these phage particles to grow through a second generation of bacterial growth, that is, a total multiplication of, roughly, a factor of 3000, we still find phage particles with about half of the activity of the original large molecule of DNA. These results are in agreement with the predictions of the Watson-Crick model for DNA.

The question of whether or not this rules out classical crossing-over as a mechanism for the production of recombinants (we know there has been a good deal of mating in this system, and crossing-over would produce dilution of the P^{32}) is not quite settled, since we still must perform a genetic cross between a radioactive and a nonradioactive phage to determine whether the progeny particles with the high concentration of P^{32} have the genotype of the radioactive parent.

N. O. KAPLAN (Johns Hopkins University): I should like to make a brief comment about some work which Dr. Morton Swartz has been doing in our laboratory. This work touches on some of the remarks made by various speakers this afternoon.

Dr. Swartz has been working on a phenomenon which we call "activation of enzymes by boiling." This paradoxical phenomenon can be resolved into the fact that in crude extracts of *Proteus vulgaris* there is no nucleotide pyrophosphatase activity. However, on boiling this enzyme appears.

The phenomenon is due to a heat-stable pyrophosphatase associated with a specific heat-labile protein inhibitor. This type of protein inhibitor can be assayed very nicely when you have a heat-stable enzyme. Dr. Swartz and Dr. Milton Kern have found protein inhibitors not only for

nucleotide of pyrophosphatases but for other enzymes and in other microorganisms.

What I think is important about this work is that under changing nutritional conditions the concentration of enzyme does not change, but the concentration of inhibitor does change. I think the protein inhibitor enzyme complex may be related to what Dr. Yanofsky and others have been talking about today and may be quite significant, particularly when one wants to assay enzymes quantitatively. The hexokinase story with respect to insulin and pituitary hormone may be another example of this type of inhibitor enzyme complex.

The temperature mutants, described by Dr. Yanofsky, which grow only at higher temperatures, at 32° and 25°, may also be related to an inhibitor of this type. The work of Wagner and others also indicates the possibility that protein inhibitors may be factors not only in regulation of metabolism but also perhaps in production of mutants and in adaptation.

JACQUES MONOD (Institut Pasteur, Paris): I should not like to prolong the discussion, but the problem of protein renewal has come up repeatedly in the discussion. There is evidently a great deal of misunderstanding as to exactly what the issue is, what the experiments mean, what the interpretations are, and what experiments would prove that there is renewal of "finished" protein in intact cells.

May I be permitted to recall that the conclusion we arrived at two years ago was based on a simple and straightforward experiment which showed that there was no detectable, no physiologically significant, renewal of β-galactosidase sulfur in intact growing *E. coli* cells. In other words, the protein inside the intact growing cell was not measurably "dynamic." We further pointed out that protein turnover, as measured in animal tissues, evidently corresponds to the sum of several different phenomena; that the fraction of such turnover which is due to true intracellular "dynamicity" is undetermined; and that, for all one knows, this fraction might be negligible in most cases.

We never said, and never suggested, that all proteins had to be stable, in all cells, at all times. We were, in fact, explicitly careful to reject such an absurd inference. I do feel, however, that the widely accepted concept of an inherent "dynamicity" associated with the "biological state" of proteins in living cells has no adequate experimental basis, besides being clearly disproved in at least one case.

EDWARD L. TATUM (Chairman): Perhaps as Chairman I will be forgiven if I extend my prerogatives to include a few final thoughts. It is

perhaps not overly optimistic to predict that within not too long a period, when techniques become available for the needed structural information, the various aspects of enzyme synthesis, activity, and genic control, outlined during the first day's discussions, will be clearly interpretable in terms of the specific structural relationships of genes, nucleic acids, and proteins.

This goal, ambitious though it may seem at present, would appear to be overshadowed in importance by the even broader goal of understanding in precise terms the basic nature and biological integration of the synthesis, specificity, and functioning of the genes and enzymes required by an intact, living, flexible, adaptable, and efficiently functioning cell or organism.

Whether we shall ever be able to picture this integration or control in terms of the spatial relationships of genes and enzymes within the cell, of energetics, reaction equilibria, inhibitors, and so on, is perhaps as problematical as the success of the blind men in the fable in reconstructing the elephant. However, in view of our successes in the preliminary phases, I cannot help being optimistic about eventual success.