8. Technique, Task Definition, and the Transition from Genetics to Molecular Genetics: Aspects of the Work on Protein Synthesis in the Laboratories of J. Monod and P. Zamecnik[1]

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> In biology proteins are uniquely important. They are not to be classed with polysaccharides, for example, which by comparison play a very minor role. Their nearest rivals are the nucleic acids… *The main function of proteins is to act as enzymes.*
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> …In the protein molecule Nature has devised a unique instrument in which an underlying simplicity is used to express great subtlety and versatility; it is impossible to see molecular biology in proper perspective until this peculiar combination of virtues has been clearly grasped (Crick 1958).

Introduction

This epigraph, from Francis Crick's seminal article "On Protein Synthesis," can serve as a reminder that it is important to distinguish between molecular genetics and molecular biology. Scientists have often used the terms "molecular biology" and "molecular genetics" interchangeably, thus confounding the two. As Doris Zallen has pointed out, however, this usage has always been problematic (Zallen 1996). I maintain that the failure to distinguish between molecular genetics and molecular biology bears on an important historiographic issue - the nature of scientific disciplines. On the account I will advocate, it is important to counteract the confusion between the two because molecular genetics is clearly a discipline, while molecular biology is not.

On my rather traditional account, disciplines are organized and institutionalized bodies of research focused around a core group of questions. Molecular biology, taken widely, is extremely well organized and institutionalized; nonetheless, on my account it is not a discipline, because it does not center on a focal group of questions. Molecular biology, after all, studies, among many other things, the structure and behavior of proteins, but also of polysaccharides, lipids, lysosomes, ribosomes, membranes, muscle fibrils, etc., etc. Molecular biology is thus a technique-based field that impinges on, or includes, a number of disciplines, many interdisciplinary investigations, and many investigations whose disciplinary location, if any, is uncertain. Molecular genetics, in

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contrast, is not only an organized and institutionalized domain of scientific research; it is also centered around a reasonably compact set of well-circumscribed focal questions.

This point is not merely terminological. Whatever words we employ, it is important to distinguish between scientific research based on question-centered "disciplines" and research not so based (see also Burian 1992 and, for some hints on institutionalization, chaps. 2 and 5, above). Disciplines in this sense are obviously and importantly connected with favored, though changing, bodies of technique and practice, and are marked by a variety of sociological indicators - journals, departments, communication networks, pedagogical tools, Kuhnian exemplars, patronage, and so on. But the sociological indicators are not enough: if one does not take the central questions of a discipline into account, one's understanding of the dynamics of disciplinary and scientific change will be defective. Again, this point is not terminological. If we fix the use of the term "discipline" as I have suggested, skeptics may still challenge the usefulness of the category *discipline*, thus understood, for describing the organization of scientific work and practices.

Prima facie, molecular genetics is a discipline in the sense just adumbrated. It is built around a small body of central questions: What is the genetic material? How is that material organized? How does gene structure relate to gene expression and gene function? By what mechanisms are genes (or is genetic information) transmitted from one generation to the next? How does the genetic material eventually affect particular traits of organisms? For example, given all the right cellular machinery, how do genetic differences (interacting with other contributing causes) bring about sexual differentiation or determine whether or not a cell is able to respire? Because these questions have been pushed to the molecular level, almost all detailed issues in molecular genetics are finer-grained than these exemplary questions suggest, but most the work in that discipline can be easily located with respect, just such questions.

These exemplary questions are not written in stone, for they are transformed by changing practices, techniques, beliefs, and knowledge. This is readily seen by comparing the technical instantiations of the central questions of genetics at different times and places. Compare, for example, early twentieth-century Mendelian formulations regarding transmission of unit characters with those of the 1930s and 1940s regarding autocatalysis and heterocatalysis, or those of the 1960s and 1970s regarding DNA replication and transcription, gene expression, and post-transcriptional processing. Or again, compare the emphasis in France just after mid-century on genetic regulation of cellular states with the contemporaneous emphasis in the United States on the structure of the genetic material. Still, the core issues that run through all of these alternative formulations have been near the center of the discipline of genetics for most of the century. They concern the materials of which genes (or units of genetic function) are made, their physical structure and organization, how they are transmitted, how they function, and how their functions are controlled.

This chapter focuses particularly on one way in which questions are transformed. Questions are refracted and altered by the interaction between what a number of us have called "local traditions" or "local cultures" (see, e.g., Gaudillière 1992, Gaudillière 1993). I shall amplify on some of the ways in which these local traditions interact below. But first, let us complete the contrast between molecular biology and molecular genetics as just characterized.

Not all biological work is organized in question-centered disciplines like genetics. Thus, taxonomic branches of biology - from botany and zoology to algology, ornithology, and protozoology – are not organized around focal questions like those of genetics. Molecular biology - by which I understand the study of organisms and of biological processes at the molecular level - is more like molecular botany or molecular zoology than it is like molecular genetics, more like a molecular auto mechanics than it is like molecular mechanics. To be sure, molecular biology mainly studies molecular mechanisms (Burian 1996). But consider the variety of mechanisms at stake: protein folding, protein action and interaction, muscle and nerve action, fluid transport in phloem and xylem, metabolite action, kinetosome (re?)production, the molecular basis of immune reactions, the interactions among receptors, hormones, and hormone analogs, and many aspects of photosynthesis (Zallen 1996), of bioenergetics, and of biochemistry, etc.

The above list is somewhat random; molecular biology deals with an immense diversity of issues. In consequence, there are important questions about the glue that holds this so-called discipline together. My own view is that the best way to understand the interactions across the different problems, disciplines, and traditions that are subsumed under molecular biology is in terms of the overlapping techniques that allow many questions, posed by different disciplines and by investigators in different contexts, to be approached by common tools and with a variety of experimental systems.

These ideas about the nature of molecular biology raise important issues about the ways in which techniques are passed from group to group, from discipline to discipline - and the ways in which they are transformed in the process. The central theme of this paper is that disciplinary dynamics are greatly affected by the importation of novel experimental systems, techniques, and questions from "outside" - i.e., from other disciplines and groups - into working groups and local traditions. My thesis is that *the technical instantiations of the central questions of a discipline are often transformed by the attempts of working groups to domesticate novel techniques, perspectives, and experimental systems in the attempt to address those central questions, as yet unresolved within the preexisting "local" knowledge context.* This thesis has consequences regarding the proper mix of sociological and "object-level" (experimental or theoretical) analyses needed to understand disciplinary dynamics. That mix will be the focus of a subsequent study. The present paper outlines paired case studies that support the thesis and illustrate its application.

For this purpose I shall examine certain aspects of the work on protein synthesis in the laboratories of Jacques Monod and Paul Zamecnik. One aim in so doing is to stimulate others to develop a better account than I can provide of the modes of interchange and influence between experimental and theoretical workers, between those who have command of a technique and those who have a problem to which to apply it, between workers in different disciplines. One of the important tasks for the history of science during the next decade is to clarify the structure, substance, and effects of such interchanges.[2]

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[2] In a number of recent lectures, Peter Galison has discussed this issue in terms of a "trading zone" between experimental and theoretical workers. I believe a more general approach and terminology are needed, since the interchange takes place between working groups of many stripes and is not restricted to any particular location or "zone." The present study illustrates these

Differentiation: Protein Synthesis in Procaryotes as a Model

Some of the founding figures of molecular genetics became interested in the problems surrounding genetic control of cell differentiation and organismic development around the time of World War II. During the 1950s and 1960s, many of them treated differentiation in terms of the regulation of protein synthesis. The underlying hypothesis was that differentiation is an irreversible commitment of a cell lineage to the manufacture of a coordinated set of "luxury" proteins - i.e., specialized proteins not needed to maintain the life of the cell. Thus, the primary differences among nerve, kidney, skin, and blood cells were thought to depend on the specialized sets of proteins that they make, which, in turn, affect their morphologies, interactions with other cells, and responses to biological signals and stimuli.

On this approach, the problems of control of gene expression and of protein synthesis were substituted for the hitherto intractable problem of differentiation. For reasons of technical ease, many founders of molecular genetics came to study protein synthesis and its regulation mainly in microorganisms, especially bacteria (procaryotes), yeasts, and single-celled fungi (eucaryotes) rather than in multicellular eucaryotes. I cannot go into great detail here, but even a minimal sketch of some aspects of this substitution of the difficult, but relatively more tractable, problem of control of protein synthesis in microorganisms for the problem of differentiation in multi-cellular eucaryotes proves illuminating.

To capture the spirit of this substitution, I quote from Jacques Monod's first major English-language paper, a review of work on enzymatic adaptation. Enzymatic adaptation concerns the ability of starved bacteria to switch from a depleted carbon source to an entirely different carbon source; it was renamed "enzyme induction" in the mid-1950s, after it had been established that bacteria make a new battery of enzymes in order to digest a new carbon and that they possess, but do not express, the genetic information for making those enzymes before switching.[3] In 1947 Monod justified attention to this then-esoteric topic by arguing for its larger biological significance. He wrote: "The widest gap, still to be filled, between two fields of research in biology, is probably the one between genetics and embryology. It is the repeatedly stated - and thus far unsolved - problem of understanding how cells with identical genomes may become differentiated, that of acquiring the property of manufacturing molecules with new, or at least, different specific patterns or configurations."[4]

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points. An example, not discussed below, may reinforce this point: it is the importation of gel electrophoresis into population genetics from protein biochemistry (Hubby and Lewontin 1966, Lewontin and Hubby 1966). The practice of the former discipline was thoroughly transformed in the process, but it is highly strained to treat the adoption of a thoroughly routinized practice from another context in terms of interactions in a "trading zone."

[3] It is particularly interesting to compare Spiegelman and Monod in this connection, as is done by Gaudillière, (Gaudillière 1992) and by S. Gilbert, (Gilbert 1996). Cf. also (Monod, et al. 1953).

[4] (Monod 1947, p. 224). The persistence of this theme in Monod's work is obvious from the conclusion of his and Jacob's review of work on the operon and protein synthesis (Jacob and Monod 1961).

> The conclusions apply strictly to the bacterial systems from which they were derived; but the fact that adaptive enzyme systems of both types (inducible and repressible) and phage systems appear to obey the same fundamental mechanisms of control, involving the same

In the 1960s, Monod made the notorious remark that what is true for *E. coli* is true for the elephant. In dealing with this claim, it helps to recall how central the problem of differentiation had been in his thinking. *Monod substituted a technically well-articulated problem for a prior, ill-defined general problem:* overstating, but not by much, he substituted the problem of enzyme induction (or, more generally, control of protein synthesis) in the bacterium *E. coli* for that of differentiation in the elephant and all multicellular organisms.

In making this substitution, Monod's group was bringing distinct disciplines and local traditions together. The problem of differentiation had belonged to embryology and physiological genetics, that of enzymatic adaptation to bacterial physiology and biochemistry. Furthermore, since enzymatic adaptation does not result in overt differentiation, but only in a controlled shift in the enzymes manufactured by bacterial cells, the substitution of the problem of enzymatic adaptation, then enzyme induction, then protein synthesis, for that of differentiation in the cells of higher organisms was quite adventuresome.

Such substitutions often stem from interactions between local traditions in which competing groups articulate their questions and develop their techniques so as to make their work more effective than their competitors'. The immediate traditions within which Monod began his work were those of microbiology in the Pasteur Institute, as instantiated in André Lwoff's nutritional biochemistry, and of Boris Ephrussi's program to reconcile embryology with genetics.[5] The interactions with these traditions (which were by no

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> essential elements, argues strongly for the generality of what may be called "repressive genetic regulation" of protein synthesis…
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> The occurrence of inductive and repressive effects in tissues of higher organisms has been observed in many instances, although it has not proved possible so far to analyze any of these systems in detail… It has repeatedly been pointed out that enzymatic adaptation, as studied in micro-organisms, offers a valuable model for the interpretation of biochemical co-ordination within tissues and between organs in higher organisms. The demonstration that adaptive effects in micro-organisms are primarily negative (repressive), that they are controlled by functionally specialized genes and operate at the generic level, would seem greatly to widen the possibilities of interpretation. The fundamental problem of chemical physiology and of embryology is to understand why tissue cells do not all express, all the time, all the potentialities inherent their genome. The survival of the organism requires that many, and, in some tissues most, of these potentialities must be unexpressed, that is to say *repressed*. Malignancy is adequately described as a breakdown of one or several growth controlling systems, and the genetic origin of this breakdown can hardly be doubted.
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> According to the strictly structural concept, the genome is considered as a mosaic of independent molecular blueprints for the building of individual cellular constituents. In the execution of these plans, however, co-ordination is evidently of absolute survival value. The discovery of regulator and operator genes, and of repressive regulation of the activity of structural genes, reveals that the genome contains not only a series of blueprints, but a co-ordinated program of protein synthesis and the means of controlling its execution (p 354).

[5] These claims are controversial. Jean Gayon, Doris Zallen, and I have examined these traditions and provided some evidence of Monod's allegiance to them. (Burian 1990, Burian and Gayon 1991, Burian, Gayon and Zallen 1988, 1991). J. P. Gaudillière's dissertation (Gaudillière 1991), which pays much greater attention than we have to the institutional and biochemical settings

means the only ones that Monod exploited) transformed both of them in important ways, and were resisted by both Ephrussi and Lwoff. Ephrussi resisted the assimilation of differentiation to gene regulation in procaryotic cells, for he was convinced that cytoplasmic heredity in different cell lineages caused differentiation in eucaryotes,[6] while, well into the 1950s, Lwoff maintained that *cellular* regulation involved elements "endowed with genetic continuity" located throughout the cell, and that it was quite distinct from genetic regulation, especially the regulation of protein synthesis (Lwoff 1949; see also Burian and Gayon 1991).

Monod and his co-workers employed the techniques of chemical kinetics; these techniques set their work off from that of those who worked mainly with cell structure, with end products, or with biochemical equilibria. The combination of his commitments regarding technique and his views about differentiation helps explain important aspects of his experimental program. Although he learned to do genetic experiments in the late 1930s at Caltech and although he often argued, from the mid-1940s on, that genetics is crucial to understanding the control of protein synthesis, he did almost no genetic experiments until 1958,[7] finally employing techniques brought into his group by Arthur Pardee and François Jacob (Pardee, Jacob and Monod 1958, 1959). The reason is straightforward: classical genetics provided no approach to fundamental questions about differentiation and development and no easy way to do kinetic experiments. When he adopted (and adapted) the genetic tool, it was in kinetic experiments, possible only in microorganisms, utilized to analyze the timing of gene expression via the production of proteins under the control of a newly introduced gene. It is only at this point that Monod's personal research can be said to have begun dealing directly with traditional genetic questions.

It is too large a job to explore here the extent to which molecular geneticists substituted the study of protein synthesis and its control for the study of differentiation during the fifties and sixties. However, an impressionistic survey of a number of key

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relevant to Monod's work, has reinforced our view on this issue. Gaudillière now rightly emphasizes the importance of a third tradition, that of Pasteurian immunochemistry, in Monod's work (Gaudillière 1993).

[6] Ephrussi argued, cautiously, that one could not extrapolate safely from procaryotes to eucaryotes, but he did not insist that the mechanisms he favored would be found. Well before he started working in somatic cell genetics, however, he insisted on the need to study differentiation in multicellular eucaryotes. For arguments that differentiation may be caused in the cytoplasm, see, e.g., (Ephrussi 1953, esp. pp. 4-6 and 99-109). Later, in (Ephrussi 1956), Ephrussi combated the orthodoxy of the day by insisting that differentiation should be treated nearly independently of microbiological findings because the most striking phenomena of differentiation occur in metazoa - and that (following Lederberg), "embryology will ultimately have to be studied in embryos." Cf. also (Ephrussi 1958, Lederberg 1958, esp. pp. 384-388, Lederberg and Lederberg 1956, esp. pp. 113-115). For an account of Ephrussi's views on this topic as he turned to work on somatic cell genetics, see (Zallen and Burian 1992).

[7] There is room to argue about which experiments to count as genetic. An important borderline case, perhaps the only exception, is (Monod 1950), which shows that genes and enzymes are distinct entities since the presence of a gene allowing facultative production of an enzyme is independent of the actual *production* of the enzyme. But the focus of Monod's concern even here is not centrally genetic: it is the role of the substrate in determining the "specific structure" of adaptive enzymes "in the production the specific molecule" (p. 58).

papers during this period shows that an important group of leaders in the molecularization of genetics thought that differentiation could be fully explained in terms of gene expression as analyzed in studies of protein synthesis.[8] After all, most of them were committed to the view that all information relevant to development is encoded in chromosomal DNA (perhaps allowing minor exceptions for organelles like chloroplasts and, later, mitochondria). There were no good tools with which to look at post-transcriptional processing of mRNAs until well into the 1970s - and even if there had been, the predominant ethos among geneticists (as opposed to biochemists or embryologists) would have treated post-transcriptional processing as part of the genetically controlled apparatus for regulating gene expression.

Given the tools available in the 1950s, microorganisms offered great technical advantages for the study of protein synthesis and its genetic control. It is not surprising that the first steps toward many of the breakthroughs alluded to above were made by the use of microorganisms. Among the favored organisms, procaryotes like *E. coli* K-12 and single-celled eucaryotes like *Neurospora* and yeast each offered specific advantages after extensive domestication. This is not the place to discuss the advantages and liabilities of particular experimental systems, but each of them contributed significantly and distinctively to the reformulation of questions about the control of protein synthesis and to the development of new experimental tools.[9]

Genetics, Biochemistry, and Protein Synthesis: *E. coli* vs. Tissue Slices and Cell-Free Systems[10]

Monod was far from alone in substituting the analysis of protein synthesis plus control of gene expression for an analysis of differentiation. Yet it is important to recognize that some workers took on protein synthesis as such, while others (like Monod) took it on both in its own right and as part of a further set of problems involving gene expression and differentiation. I shall now illustrate some differences in problem articulation, technique, and choice of experimental system that arose between those concerned with gene expression and some of the biochemists working on protein synthesis. This discussion will illustrate the roles of local tradition, technique, and experimental system in shaping problems and altering questions.

In the 1950, biochemists studying protein synthesis in liver tissue slices developed a cell-free system in which to study protein synthesis. The very fact that creating a cell-free system was a primary objective reveals a central difference with Monod: Such a system served Monod as a useful incidental tool, but it could not solve his main problems concerning cellular mechanism, regulation and control of protein synthesis.

The biochemical work just alluded to made fundamental contributions to our understanding of protein synthesis. We shall consider here important work carried out in

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[8] A single emblematic reference illustrates this theme: (Markert 1964).

[9] A useful account of the particular advantages offered by *Neurospora* is presented by (Perkins 1992). It is to be hoped that more studies (especially comparative ones) of the advantages - and consequences - of domesticating particular organisms will be carried out to the near future.

[10] See (Rheinberger 1992a, 1992b, 1993, 1995) for close studies of the research covered in this section. See also (Hoagland 1990, esp. chaps. 4-6) for a useful retrospective account of the same work.

the mid-1950s in Paul Zamecnik's laboratory, one of the John Collins Warren laboratories of the Collis P. Huntington Memorial Hospital of Harvard University.

The Huntington's laboratories were directed by Joseph Aub from 1936 to 1956, in which role Aub was succeeded in 1956 by Zamecnik. Aub, who had a formative influence on Zamecnik's career, believed that cancer is a form of unregulated or improperly regulated growth; thus, he established a local tradition of basic research on cancer in the context of studies of (normal) growth. Accordingly, he encouraged Zamecnik to pursue work on the mechanisms of protein synthesis independent of any particular focus on cancer as such.[11] In the work at issue here, Zamecnik's group established the existence and importance RNAs initially classified operationally as "soluble" RNA (sRNA), now called transfer RNA (tRNA): sRNA was the RNA still in solution in the supernatant at pH 5 after "microsomes" - ribosomes, fragments of endoplasmic reticulum, and related material - were spun out at 100,000 g in an ultracentrifuge. A cell-free system had to include sRNA in order to make new protein. Zamecnik's group showed by biochemical techniques that this RNA was involved in the "activation" of amino acids (a step previously identified as necessary before amino acids could be incorporated into proteins), and in transport of the activated amino acids to the ribosomes, where they were incorporated into proteins.

By 1958 Zamecnik's laboratory had demonstrated that there are many different soluble RNAs, all relatively small (about 70 or 80 nucleotides), and that some, probably all, of them combine enzymatically with a single activated amino acid. In brief, these RNAs were the "adaptors" of Crick's "adaptor hypothesis,"[12] the vehicles by which single amino acids were brought to the ribosome to be added to the growing string of amino acids synthesized there.[13] They soon knew, furthermore, that the sRNAs, each small and bound to a single amino acid, could not determine the sequence of the amino acids synthesized by the cell.

Work with the cell-free system, and many others, demonstrated that the RNA in ribosomes is tightly bound to protein and turns over slowly. By about 1960, in light of various kinetic analyses plus work on Crick's sequence hypothesis, it became unlikely that the signal containing the information for building a new protein is in the RNA of the ribosomes.[14] Some other signal had to travel from the DNA to the ribosomes in order for

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[11] For background, see (Hoagland 1990, Rheinberger 1992a, 1992b, 1993).

[12] See (Judson 1979, pp. 268-270, 287-295, 313-328, et passim). See also (Hoagland 1960) and the portion of F. H C. Crick's originally unpublished "On Degenerate Templates and the Adaptor Hypothesis," printed at pp. 290-291 of (Judson 1979). For retrospective accounts, see (Crick 1988, Hoagland 1990).

[13] (Hoagland, Zamecnik and Stephenson 1959, Zamecnik 1960, 1969). It is worth adding that Crick thought that the adaptors would have to be considerably smaller than 70-80 bases long; much work was needed to establish that biochemically identified sRNAs served as Crick's postulated adaptors.

[14] It should be emphasized that a great many pathways led to this result. This stands out in (Chantrenne 1961, esp. pp. 63 ff.). Here are two examples: (McQuillen, Roberts and Britten 1959), which shows that the turnover of RNA in ribosomes is much slower than that of the signal controlling the production of specific proteins: (Brenner 1961), which shows that phage use preexisting bacterial ribosomes to manufacture phage protein. The experimental arguments to this effect depended less on the specifics of any single set of experiments than on the accumulation of a great variety of information about gene action, rapidity of signal generation, speed of

the DNA to determine the order of the amino acids in the proteins. This signal, found and analyzed in considerable detail in the first half of the 1960s, came to be called messenger RNA (mRNA). It was found by a kind of triangulation involving the work of many groups working with different tools and in different traditions.[15]

One reason for putting the matter this way is to counteract the heroic version, common to Crick, Horace Judson, and many others, according to which the key insight belonged to a small group of insiders from Cambridge, the Institut Pasteur, and the phage group.[16] On the contrary, it was the interactions within a much wider network that made the existence of mRNA seem plausible, even necessary. Let me reinforce this point.

There is considerable pre-1960 evidence, supported by Zamecnik's spontaneous recollections in 1979 and Mahlon Hoagland's retrospective account,[17] to show that the early work on sRNA was wholly independent of Crick's theorizing. Until 1957, the Zamecnik group's development of the liver slice and cell-free systems had no connection at all with Crick's adaptor or sequence hypotheses, which were first stated publicly after those systems had been applied to the problems of amino acid activation and transport to the ribosome. This independence of investigative pathways is in keeping with Watson and Crick's early avoidance of biochemistry and the firmly biochemical orientation of Zamecnik's work.[18] Indeed, it is a familiar point, one that I will soon reinforce, that the breaking of the genetic code was in the end largely a *biochemical* achievement,

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processing, speed turnover, interchangeability of tRNAs across systems, similarities among ribosomes, etc, For this reason, though the PaJaMo experiment (Pardee, Jacob and Monod 1959) was crucial in calling forth the hypothesis of mRNA, it was but one of very many pathways toward recognition of the need for a new class of RNAs.

[15] There are literally thousands of relevant references, including (Gros, et al. 1961, Hershey 1953, Hoagland, et al. 1958, Lamborg and Zamecnik 1960, Nirenberg and Matthei 1961, Nomura, Hall and Spiegelman 1960, Rich 1960, Volkin and Astrachan 1956). Cf. J. D. Watson's Nobel Lecture, (Watson 1963) for a good contemporary review and (Siekevitz and Zamecnik 1981) for a biochemical retrospective, oriented mainly toward work on ribosomes and the role of tRNAs.

[16] See, e.g., (Judson 1979, pp. 427 ff.). Many variant of this account have been published: e.g., (Crick 1988, chap. 11).

[17] See Zamecnik's response to R. Olby in (Zamecnik 1979, pp. 299-300). On the independence of the work in Zamecnik's lab from that of Crick's adaptor hypothesis as of 1957, see (Hoagland 1990, 93 ff., Hoagland, Zamecnik and Stephenson 1959, esp. pp. 112-113, Zamecnik, 1969). This impression is strengthened by reference to the bibliographies of Zamecnik's pre-1960 papers. (Judson 1979, pp. 326-327) provides more evidence that Zamecnik and Hoagland had completed their 1956 experiments yielding attachment of activated hot leucine to sRNA, followed by its incorporation into a protein, before they learned of the adaptor hypothesis.

[18] Thus, (Zamecnik 1960) treats protein synthesis in terms of the biochemistry of "the pathway from free amino acid to biologically active protein" (p. 256). His concern is mechanisms of synthesis: the analysis of protein synthesis might yield understanding of the mechanisms of peptide bond synthesis; the reversed action of proteolytic enzymes cannot explain the precisely defined sequence of amino acid incorporation into protein. Soluble RNA supplies activated amino acids to the machinery that assembles proteins; rRNA is a constituent of that machinery. RNA also has something to do with condensing the amino acids in the correct order in a synthesized protein, but there is no evidence that Zamecnik's attack on this problem prior to 1960 depended significantly on recognition of the informational or genetic aspects of nucleic acids. He viewed the problem in terms of the biochemistry of nucleic acids and proteins.

accomplished primarily by biochemical and not molecular-biological techniques. Controversially, the same can be said for the run up to the discovery of mRNA.

A helpful way of understanding the contrast implied here between biochemical and molecular-biological traditions concerns the way the cell was analyzed into functional parts; for Zamecnik and the biochemists in his group, cells were analyzed into compartments in terms of the *operations* that separated bits of cellular machinery. Thus there was the mitochondrial compartment (defined in terms of the pellet that included mitochondria under low-speed centrifugation), ATP and the ATP production system (the biochemically isolated energy-production system), the microsomal compartment (which included the materials sedimented by high-speed centrifugation), and soluble RNA (plus whatever other substances were left after the purification procedures applied to the final supernatant after high-speed centrifugation).

In contrast, Monod's group, which was concerned with the regulation of cellular states and with the physiological controls that determine which enzymes are synthesized by a cell, divided cells up in terms of cellular geography (e.g., cytoplasm vs. chromosome), or functional geography, as measured by in vivo kinetics. Their compartmentalization did not match the one produced by Zamecnik's operations. They did not study the action of inducing agents on isolated ribosomes, and their use of cell-free extracts served largely to support the analyses produced by in vivo kinetics. Applied to enzyme induction, that tool was supposed to reveal where inducing agents acted and which mechanisms were activated to produce the substances whose synthesis was induced.

This contrast between Monod and Zamecnik's groups marks a series of technical commitments and differences in their central problems. The Zamecnik group, seeking to understand normal and abnormal growth in the tradition of Aub, was most concerned with the machinery by which the cell manufactures proteins. The Monod group was most concerned with the regulatory system by means of which cells managed to alter or switch the enzymes or proteins they manufactured, with the primary aim of solving the problems surrounding differentiation rather than those surrounding growth. If both groups could be said to be working on "the" problem of protein synthesis, that problem was importantly transformed by the local traditions through which it was viewed.

Theory, Experiment, and Exchange across Boundaries: Some Comments on Cracking the Genetic Code

The dead ends that Francis Crick encountered in his beautiful theoretical papers attempting to crack the genetic code are of particular interest for our purposes. Crick posed the variants of the coding problem so clearly that it is slightly less difficult than it might otherwise be in so complex a case to trace the tangled pathways by which the issues he raised were resolved. As is well known, those pathways were quite different from the ones that he first thought would bear fruit: They were far more biochemical and far less theory-driven than he anticipated.[19] A cursory examination of the differences

[19] The standard reference here is (Nirenberg and Matthei 1961). See also (Judson 1979). By 1963, Crick's judgment on "the place of theory" was rather tempered: Good theories, even if incorrect, "enable us to tighten up our logic and make us scrutinize the experimental evidence to some purpose... Whether theory can help by suggesting the general structure of the code remains to be seen. If the code does have a logical structure there is little doubt that its discovery would greatly

between Crick's early expectations and the experimental pathways by means of which those questions were answered is revealing.

The main point to be gained from such considerations does not require much detail. It is that the mRNAs that determine the sequence of amino acids in proteins and the correlating code were far more likely to be discovered by means of a biochemical detour than by means of structural analyses like those attempted by Watson as extensions of Watson and Crick's analysis of DNA, e.g., (Tissiéres and Watson 1958, reviewed in Watson 1963), or by means of theoretical analyses of coding constraints like those attempted by Crick. Put strongly: Because of the nature of the coding apparatus, *which was, of course, unknown*, structural and in-principle theoretical solutions to the coding problem were beyond the available means - and remain so even now.

The fact that the code is in a strong sense arbitrary could only be found out experimentally. The fact that it is not based, e.g., on a spacing mechanism such that each amino acid fits into a unique pocket of information-bearing DNA or RNA means that Watson's structural approach had no point of purchase. Such theoretical approaches as those of Crick and George Gamow are unworkable because of the mechanics underlying the arbitrariness of the code. As Zamecnik's (and others') work showed by 1960, there are two sites on tRNAs that can vary independently of each other, one for the encoding sequence (soon shown to be, as Crick suggested, a triplet) and one for the attachment of a single amino acid.[20]

Furthermore, there is no constraint barring redundancy in the code. Taken together, these results have a consequence that could not have been known a priori: *no abstract treatment of the coding problem can produce a determinate solution.*

Furthermore, since proteins are not directly synthesized on a DNA template, to get at the code it is necessary to operate on the intermediate that carries sequence information. Since this intermediate, mRNA, is usually short-lived, unstable, relatively minor proportion of cellular RNA, in practice one had to develop mutually adapted experimental systems and biochemical protocols to do that job. The requirements for getting at the mechanisms of protein synthesis and information transfer by this route could not have been foreseen in advance.

This account suggests that, given the available techniques, the unanticipated biochemical detour was unavoidable in practice. There is a general lesson here for students of creative science: Most interesting problems in science are open ones, subject to reformulation. It is advisable (perhaps necessary) for work on such problems to take place via exchange across the boundaries of disciplines, groups, and local traditions. Opportunism is the rule in tackling open problems, for they are likely to require mobilization across interfaces - mobilization of techniques, traditions, disciplines, and, in the case of experimental biology, a variety of experimental systems.

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help the experimental work. Failing that, the main use of theory may be to suggest novel forms of evidence and to sharpen critical judgment. In the final analysis it is the quality of the experimental work that will be decisive" (Crick 1963, pp. 213-214).

[20] The unanticipated independence of these sites provides one reason that Crick underestimated the size of the adaptors. Evidence clinching their independence was provided by (Chapeville, et al. 1962), which showed that replacing the amino acid on a particular tRNA by a different amino acid, substitutes the new amino acid into proteins at the precise places where the original amino acid occurs when the unaltered tRNA is used.

Attempts to solve open problems must be disciplined by creating reliable practices potentially bearing on those problems. The development of such practices is typically the accomplishment of small groups of laboratory specialists working with some degree of institutional protection within a discipline or a local tradition. But reliable practices are not enough. Reliable practices, after all, may reliably produce artifacts. It is also necessary to show by triangulation that those practices answer the original problem or a well-established successor. *Creative science requires not only severe technical refinement of specialized tools and techniques within local traditions, but also leaky boundaries allowing exchange between groups and traditions, so that the competing problems, techniques, and questions can interpenetrate each other, so that triangulation is possible.*

More about Choice of Technique and Experimental System

In consequence of these considerations, the matching of experimental system to techniques is critical. In general one cannot know in advance what steps will yield a good match. For example, as could not then have been known, in the late 1950s a tissue culture of heart or muscle cells would not have yielded enough tRNAs or mRNAs to be detected by the techniques then in use, especially given the uncertainties about the details of protein synthesis. Again, the liver slice system and the cell-free culture system based on it contained so many proteases (enzymes that digest proteins) that, even though it was possible to chase activated amino acids, attached to tRNAs, as far as the ribosomes, it was extremely difficult to follow the incorporation of amino acids into synthesized protein.[21] Because the work was at the edge of available technique *and because it was unclear what was being sought*, many artifacts slowed the analysis of the details of protein synthesis and the recognition of messenger RNA.[22] Additionally, the kinetics of many experimental systems were not clean enough to make the clues they offered stand out. This was the case for Elliot Volkin and Lazarus Astrachan's new RNA fraction in *E. coli* after infection with phage T2 (Volkin and Astrachan 1956). Their RNA had a base-pair composition matching the phage's DNA, and it turned over quickly. In hindsight, they had found a fairly clean mRNA signal, but at the time it was not clear that it was

[21] The creation of an *E. coli*-derived cell-free system, sought earlier, but finally achieved in 1960 (Lamborg and Zamecnik 1960), provided a crucial tool used by Tissières, Watson, Matthei, Nirenberg, and many others during the period of most rapid progress in the early sixties. Further work is needed to assess the advantages of this system over its predecessors, but it clearly proved to be of major importance.

[22] It is unusual for scientists to acknowledge their near misses openly. Zamecnik offers a good example of such an admission: "*Description of a blind spot*. Let me mention one of our efforts to examine the polypeptide polymerization site by means of electron microscopy… In 1960 we began to prepare ribosomes from rabbit reticulocytes which [we] subjected to high resolution microscopy. We looked hard for our principal objective, the location of tRNA molecules on the ribosomes, but without success. Frequently there were to be seen strands of what appeared to be RNA unraveling from the ribosomes and running from one ribosome to another. . . I felt uneasy about this, considering it to be evidence of roughness in our preparative methods. A year or two later these electron micrographs might have served as textbook pictures of messenger RNA and polysomes. However, at the moment I was fixed on the importance of ribosomal RNA itself as the genetic message [as was nearly everyone in the field! –RB] and had no eyes for the messenger" (Zamecnik 1969, 9).

connected with protein synthesis. Volkin and Astrachan themselves suggested that they had found an intermediate in the manufacture of phage DNA, not of protein.

In the later 1950s, in virtue of the then-unknown details of protein synthesis, biochemical kinetics turned out to be one of the most useful of the available techniques for studying the intermediate steps between DNA and protein. Biochemical kinetics were not part of the armamentarium with which Crick or most members of the phage group initially approached the problem. There was nothing wrong with their choice to place their bets elsewhere – provided that, like Crick, they paid attention to developments that forced the problem onto new turf and, in the process, transformed it. What makes this result all the more revealing is that the new turf was already occupied by preexisting groups that had not yet recognized the aptness of their tools for a problem that they had not considered - especially not in Crick's style.

In circumstances like these, the interactions among groups with flourishing local traditions, groups flexible enough to allow their tools and problem formulations to be bent by those interactions, are crucial to the dynamics of disciplines and of scientific knowledge, and to the formation of new disciplines such as molecular genetics. When potentially influential groups working at interdisciplinary interfaces revise prior practices and problems, they create the opportunity to establish new traditions, perhaps even new disciplines. To use an analogy familiar from evolutionary biology, it is in such circumstances that founder effects occur. These play crucial role in the founding of major new traditions.

Task Definition

Choice of technique and experimental system are not enough. There is also the problem of task definition. The direction in which a line of work is taken is sensitive to the questions with which one starts, and to the connections of those questions with the central problems of the disciplines to which the relevant investigators are (or come to be) allied. There are powerful effects here, as can be seen by the contrast between Monod's and Zamecnik's groups, both of which employed chemical kinetics on similar systems. Someone centrally interested, like Monod, in *the regulation of protein synthesis* will make different choices than will someone investigating, like Zamecnik, *the mechanics of the assembly of the chain of amino acids*. These differences greatly affected the "investigative pathways," to use F. L. Holmes's phrase, of the Monod and Zamecnik groups.

Thus, although the choices of the groups overlapped, one's signal was, at least sometimes, the other's noise. The groups continued to employ different systems - the former aiming to understand the genetic and epigenetic *control* of protein synthesis, the latter to isolate and characterize the *machinery* that assembles proteins and the signals it employs. Their choices of experimental systems and of focal issues had major effects, as such choices often do, driving the groups in different directions. Thus, the "natural" job to do with an intact cell that manufactures different enzymes in precisely determined circumstances is to work out the ways in which those commitments are made or controlled, while the "natural" job to do with a cell-free system is to work out the details of the machinery assembling proteins. The differences in the jobs thus led to different understandings of common issues and to the elaboration of different tools, concepts, and issues (allostery vs. ribosome biochemistry, structure, and function). Such differences are

the stuff of which local traditions are made - and they make it necessary for creative scientists to reach out beyond their local traditions.

Conclusion

Our central case studies suggest that if one wishes to understand the approaches that laboratory groups take toward major problems such as protein synthesis or the regulation of gene expression, it is important to articulate the issues of concern in the local cultures within which those groups operate. They also suggest that to get at the dynamics of disciplinary change - indeed, of scientific change generally - it is equally necessary to understand the interactions *between* laboratory groups and between local scientific cultures. The ways in which major scientific problems are handled and evolve are, of course, affected by a great many factors. I have shown that these include at least the uses that laboratory groups make of each other's findings, the power and limitations of the techniques they employ, the idiosyncrasies of the various experimental systems they employ, and the transformations that all of these effect in the technical articulation of the central questions of the relevant discipline(s). It is to be hoped that the present paper will encourage others to take up the challenge of articulating the interactions among all these factors.

In closing, I would like to raise a larger historiographical issue that indicates how hard a job this may prove to be. This issue is the problem of the scale on which we work. One can examine individual careers, laboratory groups, local traditions, communication networks, institutions, disciplines, national traditions and cultures, and problems that are continued for long periods across boundaries of all these sorts. It is obviously important to engage in comparative studies at all of these levels, for each of them affects the dynamics of scientific institutions, disciplines, theories, and local practices. Yet there remains a nagging worry about how to integrate the findings of such diverse studies, for one of the most difficult problems facing students of scientific work and scientific processes is that of evaluating the interaction of factors across such levels. It seems to me that one of the most important tasks for historians working with case studies like those I have sketched here is to confront us with that problem and to force us to face it squarely.

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