

### 3. Unification and Coherence as Methodological Objectives in the Biological Sciences<sup>1</sup>

The biochemist cannot understand what goes on chemically in the organism without considering genes any more than a geneticist can fully appreciate the gene without taking into account what it is and what it does. It is a most unfortunate consequence of human limitations and the inflexible organization of our institutions of higher learning that investigators tend to be forced into laboratories with such labels as “biochemistry” or “genetics.” The gene does not recognize the distinction - we should at least minimize it. (Beadle 1945b, p. 193).

In this chapter I respond to Wim van der Steen’s arguments (van der Steen 1993) against the supposed current overemphasis on norms of *coherence* and *interdisciplinary integration* in biology. On the normative level, I argue that these are *middle-range norms* that, although they may be misapplied in short-term attempts to solve (temporarily?) intractable problems, play a guiding role in the longer-term treatment of biological problems. This stance is supported by a case study of a partial success story, the development of the one gene - one enzyme hypothesis. As that case shows, the goal of coherent interdisciplinary integration not only provides guidance for research, but also provides the standard for recognizing failed integrations of the sort that van der Steen criticizes.

#### Introduction

This chapter is a defense against the challenge of Wim van der Steen (van der Steen 1993) to the view that the norm of unification of knowledge across (biological) disciplines serves, and *should* serve, as a major vehicle for improving the content of (biological) knowledge. I also deal briefly with the views of Bill Bechtel (Bechtel 1993) and Ken Schaffner (Schaffner 1993a) in my discussion of van der Steen’s position.

Van der Steen (van der Steen 1990, 1993, see also van der Steen and Sloep 1988, van der Steen and Thung 1988) argues forcefully against premature and misguided attempts to unify biological disciplines or theories. His argument is

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<sup>1</sup> The text is the submission version of chapter 3 (pp. 29-49) of my book, *The Epistemology of Development, Evolution, and Genetics* (Cambridge University Press, 2005). It is a light revision of the paper’s original publication in *Biology and Philosophy*, **8** (1993): 301-318. © 1993 Kluwer Academic Publishers. It was published as part of a symposium on integration in biology (Ruse and Burian 1993) and is reprinted by kind permission of Kluwer Academic Publishers. Work on the original paper was supported by a generous grant from the National Endowment for the Humanities. The paper has been improved by criticisms from the other symposiasts and numerous colleagues, by discussion at the International Society for the History, Philosophy, and Social Studies of Biology, and by some improvements in my treatment of the case study suggested by Norman Horowitz. I am grateful to all concerned for their support and assistance.

directed partly against misuse of methodologies that emphasize coherence between theories or require concordance in the descriptive and theoretical terminology employed by different disciplines. It is also directed generally against the role that such methodologies play in contemporary biology.

There is much of merit in van der Steen's treatment of particular cases. However, I shall argue that his normative stance - to wit, that the ideal of unification is often inappropriate and damaging even in cases where different disciplines address the same domain of problems or the same range of cases - is fundamentally mistaken. The issue between us turns, in part on two delicate questions; (1) what should count as the same domain of problems?, and (2) what is the proper scale on which to judge and to employ the norms relevant to coherence and unification in science? My position is that the overlap of problem domains must be locally resolved (i.e., by analyzing the specific content of the theories or disciplines at issue and, perhaps, by performing appropriate experiments) and that coherence and unification are norms of the middle range. Thus understood, I shall argue, those norms are crucial for the development of biological knowledge.

The central issues in the papers presented in the original symposium from which this chapter derives (Bechtel 1993, Schaffner 1993a, van der Steen 1993) concern normative methodology, not the description of actual reasoning patterns or the particular reasons for success and failure in particular cases. Unless I am mistaken, the four of us are generally (though not universally) in accord regarding the analysts of those case studies about which our knowledge overlaps. Yet, although we support our normative claims by reference to just such case studies, we reach divergent conclusions. Perhaps we suffer from sample bias, i.e., perhaps our choice of cases may have contaminated our intuitions. Perhaps our disagreements about normative methodology arise because we are asking different questions or because of unexplored normative differences of general philosophical interest. Let the reader beware!

#### A Framework for Discussion

Let us start from simple intuitions. Different schemes of classification and description are employed for different purposes. We are often, but by no means always and never entirely, free to use arbitrary concepts and notions designed to suit the purposes in hand. The value of a particular scheme depends *both* on the purpose(s) in hand and on available knowledge and techniques. Many of the purposes common in biology (for example, description of a physiological mechanism, establishment of a phylogeny, or application of evidence from different sources to evaluate competing theoretical accounts of a common problem) place specific constraints on the procedures and, ultimately, the concepts that may properly be employed. The constraints dealt with in this paper

are long-range, but local in ways emphasized by Bechtel (Bechtel 1993);<sup>2</sup> they ought not to be taken too seriously in the short term.

Biological purposes like those just mentioned require that we ultimately (though by no means immediately):

- (1) achieve coherence between different scientific descriptions of the phenomena of concern and also between those descriptions and any theoretical explanations of those phenomena, or
- (2) transform the problem of concern so as to remove the obligation to take into account one or more of the competing descriptions or theories.

In the context of van der Steen's concerns about interdisciplinary integration, it is worth pointing out that (1) applies to both intra- and interdisciplinary situations. The ideal of unification requires (at least) that discordant descriptions of the same phenomena, whether stemming from different disciplines or not, be brought into line with one another. Bechtel (Bechtel 1993) provides a nice interdisciplinary example: once major respiratory functions had been localized in mitochondria, it was necessary to achieve concordance between structural descriptions of mitochondria and descriptions of the behavior of the relevant respiratory enzymes. The most useful extended case study of the techniques of theory integration in biology known to me is Lindley Darden's book on the interactions between cytology and Mendelian genetics (Darden 1991). Her work reinforces the position I advocate here: scientists should attempt to make differing theoretical accounts of a domain of phenomena cohere with one another and with well supported descriptions of those phenomena whether the theories stem from a single discipline or from multiple disciplines.

Sometimes an important part of the process of reconciliation involves ascertaining that what seem, *prima facie*, to be different descriptions of the same phenomenon are descriptions of distinct phenomena. One way of transforming a problem is by dividing it into strongly separated problems. For example, the rejection of Haeckel's biogenetic law facilitated just such a separation between the problem of determining the causes of evolution and the problem of establishing phylogenies. Alternatively, problem transformation may call for a radical reconception of the problem that greatly alters its relation to 'neighboring' problems. This happened to the problem of differentiation when it was recognized that determination and differentiation are often independent steps that frequently take place at widely separated stages of the life cycle of an organism or in the history of a cell lineage.

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<sup>2</sup> All first order constraints are relative to the knowledge context. (For the term 'local constraints' in another context, cf. Maynard Smith, et al. 1985.) Those who are uncomfortable with this contextual aspect of knowledge claims and methodologies should remember that it is impossible to detach scientists (or any other knowing beings) from the world within which they live, operate, and evaluate their beliefs and theories.

One cannot expect to solve difficult problems quickly. Nonetheless, there is such a thing as failure. If, after a suitable period (where suitability depends on available technique, effort expended, and many aspects of the knowledge context) the relevant scientific communities fail to accomplish (1) or (2) they should, *in the end*,

(3) confess failure.

I do not think that one can escape the dilemmas implicit in this stance. Failure to reconcile the claims at stake in a dispute concerning a particular subject matter means either that the appearance of a single subject matter is false or that the disputing parties have failed to reach agreement about their common subject. If the dispute falls in the category of disputes about what is the case, these choices are both exclusive and exhaustive.

These considerations lead rather immediately to *qualified* and *contingent* norms and methodological prescriptions. These norms are long-term rather than immediate in a variety of ways. For example, they say nothing about the relative methodological priority of the conflicting protocols or the likelihood of truth of the conflicting theoretical assumptions of different disciplines, nor about the grounds for preferring one terminology or mode of description to another.<sup>3</sup> Again, it is a matter for judgment based on the local knowledge context whether the available means for resolving the issue have yet been adequately deployed. In this sense, the norms that I shall describe are very weak - and are often legitimately perceived to be weak by bench scientists and students of laboratory life. Nonetheless, (except by simply abandoning a seemingly pressing problem, they are very hard to remove; *on an appropriate scale*, precisely because they yield continuing constraints they do and *ought to do* a great deal to shape the direction and outcome of research in the middle term.<sup>4</sup> An analogy demonstrates the power of weak forces to dominate strong ones in appropriate circumstances: the gravitational force is twenty-three orders of magnitude weaker than the next weakest of the known fundamental forces in physics, yet gravity is the main gestalting agent of the universe on an astronomical scale. Whether norms of the middle range have shaping power in science cannot be settled by short-term studies.

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<sup>3</sup> There *are* things to say about such priorities and about how to estimate the likelihood of one theory being nearer to the truth than another. But the dependence of those things on the specific knowledge context ensures the local character of the norms governing sound methodology. In this respect, the more formal and abstract the statement of a norm, the more that norm functions like a meta-level constraint on more immediate norms.

<sup>4</sup> By the middle term, I mean to exclude a scale of days, weeks, or months, and also most interactions within a single laboratory, but to include the interactions between laboratories and disciplines on a scale of months, years, and perhaps, in extreme cases, decades.

### A Brief Case Study

To keep this rather abstract discussion attached to real biology - as we must if we are to make headway with the main issues at stake in these papers - one should work through a number of case studies. Alas, given space limitations, I can deal only with a single case, treated in telegraphic style. That case, however, will help considerably in mobilizing support for the norms of the middle range defended below - and it yields some suggestions about ways in which to meet van der Steen's strictures about biased choice of case studies.

Let me address those strictures briefly. Van der Steen is right, of course, that it is misleading to pay attention primarily to successful cases of interdisciplinary integration. Surely the vast majority of attempts to achieve integration fail. Nonetheless, we shall see that 'successful' integration involves many sidetracks and missteps. Careful examination of such cases shows how use of the *ideal* of integration provides important tools for correcting mistaken beliefs and for replacing less informative with more informative practices, protocols, and theories. In short, *in the face of uncertainty about whether an attempt at integration will succeed, one can obtain guidance about how to proceed by examining the means by which mid-course corrections have been made in instance in which successful integrations were achieved.*

Enough preliminaries! The case concerns the so-called one gene - one enzyme hypothesis. Most readers are familiar with the basic idea, but few know the early formulations of this hypothesis in the classical work of Beadle, Tatum, *et al.*, on *Neurospora*. This work broke new ground by establishing the first extensive correlations between defects in intermediary metabolism and gene mutations. Such correlations were crucial to the development of genetics because (with few partial exceptions) the complexity of genotype-phenotype interactions had hitherto prevented detailed analysis of the physiological steps affected or controlled by the actions of particular genes (on which, see the quotations in Box One).

In fact, as originally formulated, the one gene - one enzyme hypothesis was as wrong in its details as were Mendel's laws - for good and interesting reasons. Among these, we shall focus on two, concerning presuppositions about the nature of genes and the process of enzyme synthesis. There are two orthodoxies in the background, presupposed in many early (rather inarticulate) formulations of the one gene - one enzyme hypothesis. It is easy to show that both presuppositions were well supported at the time, i.e., in 1941-5, although the first was beginning to be seriously challenged by the end of this period.

Most geneticists believed that proteins had to be the key components of genes; genes were either proteins (perhaps, more specifically, enzymes) or nucleoproteins, but if the latter, the protein components had to provide genes with the specificity required to control the synthesis of different enzymes (see Kay 1992). Nucleic acid was a boring tetranucleotide which, at best, provided a structural framework helping space amino acids during protein synthesis, thus

allowing the protein component to assume and retain a stable configuration for it to serve as a template in the formation of enzymes with specific activity.<sup>5</sup>

#### Box One

##### *Prior Limitations on Knowledge of Gene-Enzyme Correlations*

From the standpoint of physiological genetics the development and functioning of an organism consist essentially of an integrated system of chemical reactions controlled in some manner by genes. It is entirely tenable to suppose that these genes[,] which are themselves a part of the system, control or regulate specific reactions in the system either by acting directly as enzymes or by determining the specificities of enzymes.... In investigating the roles of genes, the physiological geneticist usually attempts to determine the physiological and biochemical bases of already known hereditary traits.... There are, however, a number of limitations inherent in this approach. Perhaps the most serious of these is that the investigator must in general confine himself to a study of nonlethal heritable characters. Such characters are likely to involve more or less non-essential so-called "terminal" reactions. The selection of these for genetic study was perhaps responsible for the now rapidly disappearing belief that genes are concerned only with the control of "superficial" characters. A second difficulty, not unrelated to the first, is that the standard approach to the problem implies the use of characters with visible manifestations. Many such characters involve morphological variations, and these are likely to be based on systems of biochemical reactions so complex as to make analysis exceedingly difficult.

Considerations such as those just outlined have led us to investigate the general problem of the genetic control of developmental and metabolic reactions by reversing the ordinary procedure and, instead of attempting to work out the chemical bases of known genetic characters, to set out to determine if and how genes control known biochemical reactions (Beadle and Tatum 1941b, pp. 499-500, notes omitted).

Throughout the scheme [of control of pigment synthesis in *Drosophila* - the best case previously available in animals, RB] we have indicated genes acting through the intermediation of enzymes. In a sense this is a purely gratuitous assumption, for we have no direct knowledge of the enzyme systems involved. Since, however, we know that in any such system of biological reactions, enzymes must be concerned in the catalysis of the various steps, and since we are convinced by the accumulating evidence that the specificity of genes is of approximately the same order as that of enzymes, we are strongly biased in favor of this assumption (Beadle and Tatum 1941c).

This doctrine interlocked with a second - namely that a single precursor could yield many enzymes by altering its conformation in response to a template, sometimes involving the substrate, sometimes involving genes, sometimes both.<sup>6</sup>

<sup>5</sup> Cf. Astbury (e.g., Astbury 1938), whose advocacy of the role of nucleic acid as a structural frame is cited favorably by Wright (Wright 1945). The notion that genes serve as templates does not depend on Astbury's account of the role of nucleic acid, as is clear from the quotations from Gulick, Beadle, and Wright in Box Two.

<sup>6</sup> (Monod 1947) articulates this widely shared view. Spiegelman (Spiegelman 1950) reviews the extraordinary range of potential mechanisms of enzyme synthesis still open (including template-driven conformational changes). N. Horowitz cautions (pers. commun. 28 Jan., 1992) that the template theory was "equally consistent [with] the idea that many different polypeptides were available in the cell, and that the gene selected the

There were strong experimental arguments against supposing that enzymes are synthesized *de novo*, so a template mechanism was considered the most likely mode of gene action. This position was reinforced by the idea that a template mechanism would explain the connection between the autocatalytic function of genes (their ability to make copies of themselves) and their heterocatalytic functions (their ability to make enzymes and other proteins). Box Two illustrates these two stances in contemporary texts.

Box Two

*Grounds for Supposing that Genes are Proteins and that Enzyme Synthesis Involves Conformal Change of Precursors*

... either the gene molecules are basic proteins held in the chromonema by longitudinal nucleic acid molecules or they are nucleoproteins some of whose nucleic acid straddle from gene to gene, or they are nucleoproteins alternating with a basic protein filling substances, to which they are bound on both sides by their nucleic acid valencies (Gulick 1938, p. 163).

Nucleic acid is itself too simple a material and too uniform in nature to be responsible for the specificity of the genes. Similar statements have been made with respect to the protamines and histones extracted from sperms. The possibilities of diversity among protein molecules through the different possible arrangements of the amino acids and through attachment of prosthetic groups is, however, so nearly infinite that there seems to be no theoretical difficulty in connection with gene specificity, even if only a minute portion of the visible chromosome is genic (Wright 1941, pp. 492-493).

This control [of specific biochemical reactions] can be most simply explained by supposing that genes act directly by determining the specificities of enzymes which in turn control the specific biochemical reactions involved [p. 27]... If each biosynthesis involves, as seems likely, a series of reactions, a number of genes should be concerned with each synthesis, and it should be possible to block a given process in any one of a number of different places. In several instances we have obtained strains of independent origins in which a given synthesis is defective. In some cases these are genetically and physiologically identical, but in others the two mutations are different genetically and grow normally as heterocaryons [i.e., when multiple nuclei are present within one cell, each bearing one of the mutations - RB]. Presumably in these the synthesis is blocked at different steps in the two mutants.... If all the genes concerned in a given synthesis are mutable we should then also be able to estimate the number of steps involved. It should then also be possible to determine the course of the biosynthesis and the type of reaction controlled by each gene by the isolation of intermediate products (Tatum and Beadle 1942, p. 33).

One gland tissue produces one enzyme, another gland produces some other. Is this because in the different tissues different genes are permitted to "do their trick", or is it that different cytoplasm induce the same gene to yield a slightly different product? One is tempted to suppose that each gene produces just one active principle [ref. to Tatum and Beadle 1942], and that the differing outcome in the diverse tissues of the body

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one, or ones, that it could interact with and produce an enzyme." He suggests that this option was favored by Beadle and Wright.

is because this first active product induces more or less different results when it works on different cytoplasmic substrates. This a priori assumption may, or may not, be true. It is conceivable even if not too plausible, that feeding a different substrate to the gene may induce it to alter the nature of its own primary product...

The gene's primary products are unknown to us. For the most part, the multitudinous enzymes we find abundantly present in tissues and organs are doubtless not the ones that were produced by genes. The list of enzymes found thus far in the nucleus is not impressive, and except for the nuclear phosphates they are in rather scant concentration. Seemingly what the genes produce are formative enzymes, doubtless largely of the sort involved in the synthesis of protein molecules, not much known to science, representing early links in the chains of causation that lead up to the later synthesis in the cytoplasm of our more familiar cytoplasmic enzymes (Gulick 1944, p. 19). Assuming that it is true that every biochemical reaction has a specific gene directing its course, how is this control achieved?...

Genes are thought from various lines of evidence to be composed of nucleoproteins or at least to contain nucleoproteins as essential components. They have the ability to duplicate themselves which of course they do once every cell division. The manner in which this self-duplication is brought about is one of biology's unsolved problems, but it is thought to involve a kind of model-copy mechanism by which the gene directs the putting together of the component parts of daughter genes. If this is the mechanism and genes contain protein components, gene reproduction is a special case of protein synthesis. Since many cases are known in which the specificities of antigens and enzymes appear to bear a direct relation to gene specificities, it seems reasonable to suppose that the gene's primary and possibly sole function is in directing the final configurations of protein molecules.

Assuming that each specific protein of the organism has its unique configuration copied from that of a gene, it should follow that every enzyme whose specificity depends on a protein should be subject to modification or inactivation through gene mutation. This would, of course, mean that the reaction normally catalyzed by the enzyme in question would either have its rate, or products modified or be blocked entirely (Beadle 1945c, p. 660) (refs. omitted).

To suppose that a highly specific giant nucleo-protein molecule is formed from nutrients by such a step-by-step process [as is typical of biochemical transformations] seems intolerably complex, even making due allowance for repetitions and for the possibility of catalytic combinations of successively larger blocks. I think that most geneticists have long agreed that there must be short cut. The gene must somehow act as a model on which a daughter gene is formed as a whole (Wright 1945, p. 293). [On p. 295 the parallel claim is made, without explicit argument, for the mechanism of protein synthesis.]

The hypothesis of a single precursor for multiple enzymes reinforced the idea that genes should be composed of proteins for two reasons: (1) proteins were the only biological substances known to be able to assume the great variety of structures and configurations that would be required for them to serve as templates, and (2) if genes, as proteins, acted by producing conformational changes in other proteins (which Horowitz believes was not Beadle's favored hypothesis, see

n. 6), the processes of autocatalysis and heterocatalysis would be closely related instances of template action, thus removing the seeming paradox that the major functions of genes required incompatible mechanisms of gene action (see para. 2 of Beadle 1945a, in Box Two). I should add that the early challenges to the protein orthodoxy were taken more seriously than some historians recognize. For example Beadle (Beadle 1945a) and Wright (Wright 1945) both recognized the importance of the Avery group's findings about transformation of pneumococcus (Avery, MacLeod and McCarty 1944) as suggesting that in some cases nucleic acid might be the crucial component of genes. Beadle's handles this point cautiously at (Beadle 1945a, pp. 71, 75-76, and 86). For all of these reasons, the one gene - one enzyme hypothesis, as first proposed, was conceptually committed to important claims, soon proved to be false, about the nature of gene action, the character of the relevant biochemical interactions, the kinetics of cellular responses to novel carbon sources or antigens, etc. This is not surprising, for all the details of gene action were, inevitably, still obscure. To that extent, so were the early formulations of the one gene - one enzyme hypothesis (see Box Three).

#### Box Three

##### *Early Formulations of the One Gene - One Enzyme Hypothesis*

...[A variety of investigations have] established that many biochemical reactions are in fact controlled in specific ways by specific genes. Furthermore, investigations of this type tend to support the assumption that gene and enzyme specification are of the same order [pp.499-500]... The preliminary results [concerning *Neurospora*] summarized above appear to us to indicate that the approach outlined may offer considerable promise as a method of learning more about how genes regulate development and function. For example, it should be possible, by finding a number of mutants unable to carry out a particular step in a given synthesis, to determine whether only one gene is ordinarily concerned with the immediate regulation of a given specific chemical reaction (Beadle and Tatum 1941a, p. 505).

Such a view does not mean that genes directly "make" proteins. Regardless of precisely how proteins are synthesized, and from what component parts, these parts must themselves be synthesized by reactions which are enzymatically catalyzed and which in turn depend on the functioning of many genes. Thus to the synthesis of a single protein molecule, probably at least several hundred different genes contribute. But the final molecule corresponds to only one of them and this is the gene we visualize as being in primary control (Beadle 1945c, p. 660) (refs. omitted). [See also (Beadle 1945a, pp. 18-19, 60, 63, 82, and 86-87, 1945b, pp. 190-192).]

In conclusion, the results so far obtained with *Neurospora* support the synthesis that genes concerned in biosyntheses, and probably all genes, act in a primary way by determining the specificity of, or in controlling the production of enzymes. The results also support the view that a one-to-one relation exists between gene and enzyme. At present it seems likely that any apparently multiple gene effects in *Neurospora*, when completely analyzed biochemically and genetically, will be found to be due to common primary reactions, or to secondary interactions not directly related to the action of the mutant gene under consideration (Tatum and Beadle 1945, p. 129).

Still, these false commitments were part and parcel of the very formulation of the hypothesis. To a large extent, the ability to overcome these ‘mistakes’ depended on the search for integration among biochemical, cytological, and genetic knowledge; it was this search that guided the major steps from this point forward. The struggle to reconcile biochemists’ and geneticists’ accounts of the mechanisms of enzyme synthesis and the controls that governed them yielded much of the evidence on which doctrines concerning the mechanisms of gene action eventually came to rest. It is necessary to understand this struggle (and much more) in detail if one is to understand the paths by which it came to be recognized that nucleotide sequence determines amino acid sequence in the formation of proteins.

#### A Preliminary Model

It *is* fair to accuse me of bias in choosing my case. If ever a problem called for integrating hitherto separate disciplinary treatments of a common subject, it was Beadle and Tatum’s problem - genetic control of enzyme production in *Neurospora*. Still, the case is typical of a rather large class of cases. First, it starts from poorly dovetailed descriptions of ongoing processes in particular organisms - in this instance, *Neurospora*, which produce spores that do or do not grow in precisely identifiable circumstances. Second, an account of the details involved in the focal problem must employ descriptors from different disciplines. Here the descriptors are genetic, cytological, and biochemical – genetic to identify the strains and the genes whose action is to be discovered, cytological to describe the characteristics of the cells and colonies produced, and biochemical to describe the media on which growth is achieved or blocked and the products that accumulate in nutritionally deficient *Neurospora*. Third, as Beadle and Tatum explicitly recognized, *intradisciplinary* approaches to the basic problem could not get around the technical and conceptual difficulties inherent in the separate practices of the three disciplines most centrally involved.

But it is not obvious how seriously this choice of example affects the normative issues. Indeed, Beadle and Tatum’s strategy (described in the second paragraph of Box One) is basically derived from that employed in Beadle and Ephrussi’s earlier work, which Ephrussi, at least, considered a *failed* attempt to integrate *embryology* and genetics.<sup>7</sup> Ephrussi’s aim in that work was to perform genetic analysis on characters at the end of the developmental chain instead of starting from genes and analyzing whatever characters those genes were found to determine. The reasons for Beadle and Ephrussi’s failure to achieve the integration they sought (which is *not* the same thing as failure of their research!)

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<sup>7</sup> Compare the account of that strategy offered in (Ephrussi and Beadle 1935, p. 98). See (Burian, Gayon and Zallen 1988, pp. 389-400) for a discussion of that work, esp. pp. 393-395 and 397-398, for an account of the earlier strategy. Horowitz argues (pers. commun. 28 Jan., 1992) that the account presented here overstates the difference of goals between Beadle and Ephrussi and Beadle and Tatum. From the side of Ephrussi, at least, I disagree. See (Burian, Gayon and Zallen 1988, 1991) for further details.

are precisely those described in the first paragraph of Box One. Their inability to overcome the complexities of the developmental pathways of *Drosophila* should not be considered a serious argument against the soundness of the underlying strategy that they employed. Rather, it shows that successful problem solving requires sufficiency of the available means.

In both cases, the need to bring multiple modes of description to bear on the problem of concern (genetic control of enzyme synthesis for Beadle and Tatum, genetic and developmental control of pigment synthesis in a higher organism for Beadle and Ephrussi) forced the program of research to assume an interdisciplinary character. And the internal dynamic of the disciplines in question produced some seemingly paradoxical results (e.g., for Beadle and Tatum, regarding the kinetics of enzyme synthesis and the relations among the components of nucleoproteins). In both cases it became imperative to seek a coherent account of the competing descriptions provided by the disciplines involved, laden with discipline-specific presuppositions and theoretical commitments.

Such seeming paradoxes are at least as likely to arise in cases that do not yield successful integrations as in those that do. Indeed, a central reason for considering the one gene - one enzyme hypothesis to be successful is that the positions taken initially by the principals and by the vast number of research scientists who came to employ the hypothesis were transformed by the demand for coherence and the insistent and continued operation of the norm of integration. The resultant transformations in beliefs and practices contributed to a reconciliation of many of the conflicting claims propounded by biochemists, cytologists, and geneticists regarding the distribution and function of materials in the cell, the sequence of events in enzyme synthesis, the relationships among nuclear and cytoplasmic factors in determining specificity, and the means by which to evaluate differences regarding such issues. But these transformations also complicated the knowledge of gene action to the point that, by the end of the fifties, the original hypothesis no longer was considered literally true and no longer played a central role in organizing the strategy of research.

All of this suggests a preliminary moral: *once scientists recognize that their claims about a common subject matter conflict, they face a higher order norm according to which they ought to (attempt to) reconcile their differences*. It is worth noting that the conflicting claims can be at any level. The arguments between Darwinians and the followers of Kelvin regarding the age of the earth demonstrate that the issue can be over a 'simple matter of fact' as easily as it can be over the theoretical or conceptual commitments employed in describing or explaining a range of phenomena.

The means for resolving the conflict may not be at hand; resolution may have to await the invention of new techniques or the adaptation of techniques borrowed from elsewhere. In retrospect (especially in light of Beadle and Tatum's success), it is clear that Beadle and Ephrussi did not have the tools they needed to succeed in their attempt to integrate embryology and genetics or to provide a

genetic account of developmental pathways. Nonetheless, the need for reconciliation remains obvious in such cases - and it brings with it the obligation to develop the tools required for resolution. Such situations suggest many difficult questions about the matching of tools, organisms, institutions, and conceptual frameworks required to solve major problems. These are among the questions which, I believe, will play a central role in the next decade of work in history, philosophy, and (yes!) sociology of biology.

We have here a small beginning of an account of when one ought to seek integration and of when it might count against one's work that the quest for integration had failed. It is an account that depends, critically, on the central role of the norm of a certain sort of disciplinary integration as an objective of science.

#### Normative Methodology

The *standard of progress* implicit here is reasonably clear: it is the achievement of concordance among discrepant discipline-based accounts of pertinent phenomena. This standard rests on the desirability of integration; it assumes, in turn, that (for properly formulated questions) there is but one (multiply describable) truth. But this standard of progress, by itself, tells us nothing about the circumstances in which integration is *feasible*, nor about the form it should take. The difficulty of determining feasibility provides ample grounds for skepticism regarding the value of insistence on integration in the short term, thus reinforcing some of van der Steen's concerns.

However, the openness of the *form* of integration raises a difficulty for one of van der Steen's principal criticisms of integration as a norm. It also poses problems for Schaffner's General Reduction-Replacement Model (GRR) insofar as the latter aims to provide significant methodological guidance to scientists.

Let us take these difficulties one at a time. Van der Steen (van der Steen 1993) argues that the combinatorics of integrating all pairs of disciplines are prohibitive. But this combinatorial argument has a dubious premise - to wit, that successful integration proceeds pairwise between arbitrary disciplines rather than between each of many 'peripheral' disciplines and one 'central' discipline. One virtue of old fashioned reductionism was that it favored the integration of *many* theories or disciplines by means of a single grounding theory or under the umbrella of an overarching discipline. Van der Steen's combinatorial argument is irrelevant where such a thing is possible. Even if one is pessimistic about anything resembling full-fledged reduction, one need not envisage separate integration, between every pair of disciplines.

Indeed, such a picture is absurd. Consider the sequel to the work on the one gene - one enzyme hypothesis. That work, plus much related work, belongs near the center of a set of problems, techniques, and results that ultimately provided the basis for a new discipline - molecular genetics. Over the course of about thirty years, the development of that new discipline reformed a massive region of the disciplinary and intellectual landscape in biology in such a way that genetics became inescapably relevant to problems that had, until recently, been

impervious to genetic considerations. Molecular genetics gradually came to provide the techniques of choice for dealing with hitherto intractable problems. Genetic knowledge and techniques came to be applied to an evolving and expanding domain of problems, but there was nothing like the spawning of two hundred new disciplines. With time, genetic techniques became the primary tools, and knowledge of the mechanics of gene action and gene regulation provided the primary insights, for a large number of basic problems. “Borrowings” became ever more frequent. This, rather than pairwise formation of hybrid disciplines, was the primary mode of unification.

Turning to Schaffner’s GRR (Schaffner 1993a, see also Schaffner 1993b), the difficulty is this: Suppose one can find reduction or replacement connections satisfying the GRR model *after* a successful integration. Unless one has independent grounds for specifying in advance both the *form* (reduction or replacement?) and the *direction* in which to go, the model can provide only *ex post facto* justification of a scientist’s research strategy. More to the point, it can justify incompatible strategies equally well, depending on which discipline one takes as one’s starting point.

Beyond this general criticism of the specificity of the GRR model, I have substantive concerns about its adequacy. Unlike Schaffner, I hold that the most fruitful reconstruction of molecular biology does not focus on a central theory in the classical philosopher’s sense of a body of laws from which, by use of initial or boundary conditions, one derives an account of what to expect in particular cases. Molecular biology is more like a (theoretical!) auto mechanics than it is like Newtonian mechanics; it is best understood as detailed knowledge of, and a body of techniques for studying, a congeries of molecular mechanisms whose operation depends only on *general* physicochemical laws. It is by means of these mechanisms that information is processed and transmitted, that substances in physiological contexts enter into chain reactions to yield particular products and alter morphology etc. (Burian 1996) offers an argument in favor of such an account.

This criticism illustrates the limited resources available to normative methodology. A rational reconstruction along the lines of GRR is very useful for analyzing theory relations after the fact, but it does not usefully discriminate among alternative strategies for those who actively seek to forge relations between theories or disciplines in conflict. For this purpose, the best that we can offer is less formal *higher order norms*, operating at a meta level or functioning as rules of thumb. Such norms say something about *what is yet to be done*, but very little about *how to do it*.

One reason that we cannot do better is that the professionalization of scientists within different disciplines equips them with distinctive practices, standards for evaluating knowledge claims, and disciplinary norms for generating and evaluating knowledge, with no generally satisfactory means of resolving the

conflicts that occasionally result.<sup>8</sup> Scientists cannot escape the necessity of working with ‘local’ standards in this sense. This is nicely illustrated by Bechtel’s analysis (Bechtel 1993) of the formation of the discipline of cell biology, with its own ethnocentrism. This *inevitable ethnocentrism* means that progress should be measured as much in terms of the changing interrelations of disciplines as in terms of the particular advances made by particular scientists within a discipline or a ‘cross-disciplinary research cluster’.

Van der Steen is thus right to insist that there are many competing norms in science and that one of the difficulties the scientist faces is how seriously to take which norms in which circumstances. In a genuinely pluralistic enterprise, no substantive norm or group of norms can characterize all of the work that is undertaken at a single time. In this respect, the norms of the separate disciplines - and their terminologies, presuppositions, weightings of evidence, and so on - should be allowed to operate with considerable autonomy and without much mutual interference *in the short term*. But when work in different disciplines bears on a given problem, their practices, terminologies, and standards for evaluation of experimental evidence must be brought into accord with respect to the matter at hand for it to count as satisfactorily solved.

Thus, *the solution of a major problem requires some form of coherence or unification*. In terms of the case study undertaken above, the claim that genes determine the specificity of enzymes cannot stand alone; sooner or later it must be integrated with other biochemical findings or it will be infirmed by its failure to apply to the chemical reactions that actually take place in real organisms. Similarly, if the study of the detailed structure, behavior, and internal mechanisms of cells is to provide an adequate description of the mechanisms underlying cellular behavior and morphology, it should yield a coherent body of descriptions (whether or not they are unified by a theory in any classical sense).

What do such examples mean for our normative questions? Not that the norms governing genetic, biochemical, cytological, physiological, neurobiological, or evolutionary investigations should be sacrificed to some overarching requirement of unification. Rather, *after investigations in separate disciplines have gone their own way, where those investigations produce conflicting or poorly matching claims about particular cases, about the mechanisms or processes underlying those cases, or about the expectable patterns or laws, the matter cannot be taken as settled. In consequence, scientists must resolve the discrepancies between the claims of different disciplines before the problems on which they focus can count as solved*. In cases of conflict, unification remains a central higher level norm that, even if it does not enter the everyday life of particular scientists or laboratories, must be satisfied for there to be a

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<sup>8</sup> It should be remarked that the practices, standards, and norms are open ended and not wholly rigid, but subject to revision. And the interplay of factual knowledge with disciplinary norms allows results obtained by work in other disciplines eventually to penetrate and alter the practices and standards of a given discipline.

convincing resolution of the issues at hand. The norm of unification requires that such long-range problems not be dropped unless they are satisfactorily eliminated by problem reformulation or transformation.

It is important for the health of science that the work of, and standards employed in, different disciplines be made mutually coherent. Attempts to achieve coherence often result in what Schaffner focuses on in his case study – to wit, the analysis of causal sequences across levels of aggregation (e.g., biochemical causes of cellular behavior). But such local instances need not, and I predict often will not, write up into globally unified causal mechanisms or theories. What must be made to cohere are the *general causal analyses* of the different disciplines and their interpretations of the results of applying various experimental techniques to particular cases.

When things are well behaved, integration may yield a neat reductionist story; planets behave very nearly like Newtonian mass points acting under gravitational attraction and many gases behave in good accord with Maxwellian thermodynamics. But in cases more typical of the biological sciences, in which the behavior of higher-level entities is effectively supervenient on that of lower-level entities, no broad unification along the lines of an extended theoretical reduction ought to be expected. Even where there are “mechanisms all the way down,” our higher-level descriptions may not (and, I think, often will not) map neatly on mechanistic descriptions of the phenomena at lower levels of aggregation. Unification does not require reduction of the sort I am here rejecting, not even as a norm. This is the moral I would draw, in contrast to Schaffner, from his studies of “theories of the middle range.”

What weight should be given to unification as a methodological objective? The answer is highly variable and must be justified locally. The justification must pertain to the particular domains and problems in question and must be conducted in light of what is known about the relevant objects and processes and about the techniques used to investigate them. It is a matter of judgment when to take the norm of unification seriously. Van der Steen is right: premature unification of concepts is harmful. But this in no way undercuts the legitimacy of unification as a generally applicable higher-level norm.

It is not obvious that a properly developed account of premature unification will turn (as van der Steen expects) on conceptual as opposed to factual considerations. Our case study helps make this point. In retrospect, the fusion that Beadle sought to achieve between biochemical and genetic concepts could not have worked along the lines that he pursued *not* because there was a conceptual error in attempting to analyze the gene as a (nucleo)protein or as a heterocatalytic template, but because as a *matter of fact* genes are not entities of this sort and do not behave in the manner thus predicted. Furthermore, to detect the misbehavior of particular genetically characterized strains (given the techniques available at the time) one had to appeal to biochemical and cytological findings. This meant that one had to employ biochemical standards to characterize *genetic* lesions – enforcing a change in practice that eventually had fundamental

consequences for genetics. But if the findings of genetics, cytology, and biochemistry had to be correlated to establish what was, and what was not, under genetic control, then the factual (and resultant conceptual) errors in Beadle's (partially premature) attempt at unification could best be detected by pursuit of unification as a goal - by attempting to unify the descriptions provided by each of the three disciplines at stake of the behavior of *Neurospora* and other organisms.

On what should the weighting of methodological norms depend? The quickest answer is not very satisfactory: on many things, varying widely from case to case. To make the point in a quick and dirty way, the feasibility of unification depends *inter alia* on the limitations of available techniques. Until one could reliably separate cytoplasmically controlled phenomena from those controlled by nuclear genes in *Neurospora*, experiments on this organism would not yield unification of genetic and biochemical concepts. Until one could reliably bring about genetic exchange between strains of bacteria, limitations of technique severely restricted the degree of unification that could be expected between bacterial physiology and the extensions of Mendelian genetics.

These are, of course, not the only pathways by means of which conceptual links could be forged between studies of microorganisms and the pre-existing work in genetics, *but without some sort of technological advances beyond what was available in the late thirties, such links could not have been successfully forged.* And this is a factual, not a philosophical claim.

Typically, as new techniques and ways of exploiting the properties of particular organisms or groups of organisms are found, a series of questions are opened up about the connections with other information about those organisms and the various theoretical descriptions employed in accounting for the behaviors in question. Armed with the right questions, new techniques open up the opportunity to seek unification where it has not been available. And armed with new concepts, sometimes inspired by empirical findings and sometimes not, scientists revise the list of available and technically tractable questions, thereby altering the rankings of plausibility among theories and hypotheses. Thus, *retaining unification as a long-term objective is the key to exploiting many technical advances so as to resolve hitherto intractable problems.* To argue, with van der Steen, that the higher order aim of integration of knowledge is often damaging is to miss its importance as a guiding ideal *even if one cannot expect a full-scale integrated theory in biology.*

### Conclusion

The consequence of these considerations is this: A methodologically central higher-order goal of the biological sciences is unification of theories and descriptions across disciplinary boundaries so as to achieve coherence of descriptions and explanation in application to particular cases. That goal can be mobilized, at best, only where specific considerations suggest that different terminologies that do not map easily onto one another or that yield contradictions when forcibly combined nonetheless overlap in their reference to entities,

processes, or mechanisms. Attempts at unification fail more often than not, for the implicit methodology of unification is weak in the short term. Still, it is powerful in the middle or the long term. That methodology consists in the attempt to find explicit linkages of a great variety of types between the entities, properties, behaviors, and processes described in one discourse and those described in another - linkages that will allow the separate modes of discourse to mesh together without necessarily becoming intertranslatable - cf. recent work on supervenience.

To the extent that this account is sound, it is incumbent upon us to investigate the factors that support or infirm the judgment that neighboring disciplines are not sufficiently coherent in their descriptions of common problems or in their findings about, or explanations of, phenomena that fall in both of their respective domains of knowledge. It is also incumbent on us to find ways of estimating the relative importance of bringing neighboring disciplines into line with one another in a given instance as opposed to elaborating the programs of each in independence of the other. This paper will have accomplished its purpose if it has presented a persuasive case to the effect that one ought to be able to articulate an account of the sorts of considerations that enforce a high priority on local (or, better, regional) unification and that the resultant methodology is not wedded to a grand scheme of the unity of science or the traditional pictures of theoretical unification or theory reduction.

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