

How the Choice of Experimental Organism Matters: Epistemological Reflections on an Aspect of Biological Practice

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Unless we recognize our innate biases in animal model choice, we limit our potential as experimenters. Two biases seem common from my observations. First is the anthropomorphism that we all seem to get from the monkeys in zoos and circuses, coming as it does long before we aspire to be scientists. Second is for the animal or animals with which we worked during our early days in our fields. Both of these are easy to understand and forgivable. What has neither of these saving attributes is an unwillingness to consider the entire biologic kingdom as a source of possible models of one or another human functions, normal or diseased.¹

The value of an organism² as an experimental tool, or in field studies, depends not only on various features of the organism,³

1. R. W. Prichard, "Animal Models in Human Medicine," in *Animal Models of Thrombosis and Hemorrhagic Disease*, NIH Publication No. 76-982 (Washington, D.C.: U.S. Department of Health, Education and Welfare, 1976), p. 172; used as a chapter epigraph at p. 24 of *Models for Biomedical Research: A New Perspective*, a report of the Committee on Models for Biomedical Research (Washington, D.C.: National Academy Press, 1985).

2. I shall take "organism" in a very broad sense here, including such artificial "organisms" as somatic cell lineages in tissue culture. Such biological "material" plays much the same role as an organism for the purposes of this paper.

3. This seemingly essentialist *façon de parler* ("the organism") is for convenience only. One of the most important features of "an" organism (i.e., conspecifics, or organisms belonging to a particular strain, perhaps an especially prepared laboratory strain) may be the variability "it" exhibits. Nor is variability *always* undesirable. Consider, for example, genetic studies of the norm of variation (i.e., the range of phenotypes produced by a given genotype under various circumstances). As this illustration shows, the use or construction of a specially prepared laboratory strain aims to limit variation *primarily in those respects that need to be controlled for the purposes of the experiment.*

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but also on the problems to be addressed and the available experimental and field techniques. Indeed, even when some organism is “the” right one for a theoretical job, its rightness is temporary and more or less local or regional.⁴ It depends not only on the job, but also on the techniques employed and the social or institutional support system for doing that job.

Most biologists realize that the choice of organism can greatly affect the outcome of well-defined experiments and can thus have a major impact on the valuation of biological theories. Anyone who does not appreciate the point need only think of well-known cases in which the choice of organism led investigators down a garden path. Consider three familiar instances: First, recall the difficulties Gregor Mendel faced when he tried to satisfy Carl von Nägeli that his “law for *Pisum*” was generally valid by attempting to apply it to *Hieracium*.⁵ Second, consider the strong experimental support for Hugo de Vries’s mistaken, but not in the least misguided, mutationism obtained from the study of *Oenothera* in the first decade of this century.⁶ Third, to cite an animal example, remember the behavior of the chromosomes of the parasitic nematode *Ascaris*. Theodor Boveri discovered “chromosome diminution” in *Parascaris aequorum* (formerly *Ascaris megalcephala*): the chromosomes remain intact in germ-line cells, but shatter and are parceled

4. This point follows easily from Zallen’s correct conclusion that a wise choice of organism depends on “the best match of the properties of the organism with the experimental equipment being used” (D. T. Zallen, “The ‘Light’ Organism for the Job: Green Algae and Photosynthesis Research,” *J. Hist. Biol.*, this issue, p. 278). Changing techniques, changing background knowledge, the domestication of an alternative organism – these are but some of the changes in the context of knowledge and practice that can alter the “rightness” of an organism for a particular job.

5. Translations of the original documents into English are collected in Curt Stern and Eva Sherwood, eds., *The Origin of Genetics: A Mendel Sourcebook* (San Francisco: W. H. Freeman, 1966). The “misleading” behavior of *Hieracium* is often mentioned, though not analyzed in detail, in the secondary literature. The failure of *Hieracium* to behave like *Pisum* surely reduced the likelihood that Mendel’s work would receive immediate wide attention.

6. A. H. Sturtevant, “On the Choice of Material for Genetic Studies,” *Stadler Genet. Symp.*, 1 (1971), 51–57 (cited by Zallen, this issue), gives a brief account of the unlucky character of de Vries’s choice of *Oenothera*. It took extremely painstaking cytological work to learn that plants in this genus have ring chromosomes containing balanced lethal mutations and other aberrations that interfered with “normal” Mendelian behavior. For more technical treatments of these problems, see, e.g., S. Emerson and A. H. Sturtevant, “Genetical and Cytological Studies on *Oenothera*. III. The Translocation Interpretation,” *Z. indukt. Abstamm. Vererb.*, 59 (1931), 395–419; or R. E. Cleland, “Some Aspects of the Cytogenetics of *Oenothera*,” *Bot. Rev.*, 2 (1936), 316–348.

out differently in different somatic cell lineages. This discovery, made fairly early in the attempt to connect chromosomal behavior to heredity, lent powerful, albeit temporary, support to August Weismann's theory of inheritance.⁷

There must be a huge number of cases like those involving *Hieracium*, *Oenothera* and *Ascaris*, in which an unlucky choice of organism led investigators astray. Such cases are not widely studied because of scientists' and historians' understandable tendency to dwell on success stories.⁸ The papers in this section of the *Journal of the History of Biology* exhibit this tendency – that is, they focus on influential choices that did not lead into blind alleys. To understand what goes into such “successful” choices, one should study some contrasting cases – that is, cases in which the choice, alteration, or construction (see the paper by Robert Kohler in this issue) of organisms to facilitate experimental work failed to have a major impact on the directions in which biological knowledge developed. This important but difficult task is, alas, beyond the grasp of this paper.

Instead, I will explore some generalizations about successful choices and raise some related epistemological questions about the consequences of choice of organism. Since alternative choices of experimental organism can lead in significantly different directions, the epistemological questions are obviously important. They have the potential to alter the evaluation of biological knowledge claims significantly by revealing some of the limitations and qualifications that actual choices place on that knowledge. Our understanding of these limitations will almost certainly be improved when we can compare some significant “failures” in choosing organisms with the better-known “successes.”

FRAMEWORK

This paper will be organized around the following three claims.

7. The phenomenon is briefly described in S. Gilbert, *Development Biology*, 2nd ed. (Sunderland, Mass.: Sinauer, 1988), pp. 266–267. Cf. T. Boveri: “Die Bildung der Richtungskörper bei *Ascaris megalocephala* und *Ascaris lumbricoides*,” *Jenaische Z. Naturwiss.*, 21 (1887), 423–515; “Die Befruchtung und Teilung des Eies von *Ascaris*,” *ibid.*, 22 (1902), 685–882; and “Über die Teilung centrifugierter Eier von *Ascaris megalocephala*,” *Wilh. Roux Arch. Entwicklunsmech*, 30 (1910), 101–125.

8. A valuable exception is G. Mitman and A. Fausto-Sterling, “Whatever Happened to *Planaria*? C. M. Child and the Physiology of Inheritance,” in *The Right Tools for the Job*, ed. A. E. Clarke and J. H. Fujimura (Princeton: Princeton University Press, 1992), pp. 172–197.

I shall draw extensively on the case studies published in this issue, plus some others presented very briefly here, in order to motivate and support these contentions.

(1) Various peculiarities of an organism, some known and some unknown at the beginning of an investigation, significantly affect its suitability for that investigation. It may require a considerable amount of work over a long time to ascertain which of the organism's characters aid and which impede a particular investigation (see 1A and 1B below). Because evolution is a branching process with many irregular steps, the extent to which crucial characters occur in other organisms is a question of "evolutionary contingency." Thus, even though on the available evidence some choices are wise and others unwise, scientists cannot be sure in advance that the organisms they have chosen are suitable as a means of investigating their questions, especially if those questions are general ones. This point is related to, but distinct from, the point (touched on in 1C, below) that it takes a great deal of work to "standardize" or "domesticate" organisms and protocols so that results in different laboratories or field studies can be reliably compared. Reliable results about chromosome distribution in *Ascaris* and about the distribution of phenotypes in F_2 progeny of intraspecific crosses of *Hieracium* or *Oenothera* do not remove the rare features of the physiology of inheritance in each of these organisms.

(2) Various attributes of organisms (including mating systems, ecological roles, infections carried, etc.) can transform the investigators' job, forcing them to revise the presuppositions with which they began their investigation and to turn toward domains and findings rather distant from those for which the organism was originally to be employed.

(3) The epistemological evaluation of the support for (general) theoretical hypothesis in biology is thoroughly comparative. The use of fieldwork or experimentation with an organism or group of organisms to support theoretical hypotheses requires detailed and substantive knowledge of the special features of the organism(s) and the experimental techniques in question. But such knowledge is not sufficient to justify theoretical hypotheses, because what is known about the experimental organism(s) must also be set into a wider context of knowledge about other organisms and the relevant evolutionary and phylogenetic relationships. Thus, the evaluation of theoretical knowledge in biology is deeply dependent on a broad base of knowledge about the particularities of different organisms and their alternative biochemical mechanisms, life cycles, means of survival, strategies of reproduction, et cetera. This is an

important consequence of the contingency of evolution and of the fact that organisms and lineages, unlike the fundamental particles of physics, always differ from each other in significant ways.

1. THE SUITABILITY OF ORGANISMS

A. *Traits and Suitability*

The epigraph of this article suggests that biologists can draw model organisms from the entire biologic kingdom. Perhaps so. But one should always ask whether the model is faithful in the relevant ways to that for which it is supposed to serve as a model, and whether it allows a useful analytical approach to the problem at hand. The answers to such questions depend on which aspects of which phenomena are being studied. Some organisms are more adaptable than others, but there are always jobs for which a given organism is unsuited. Often alternative organisms satisfy the relevant criteria for doing particular jobs at least as well as the one that is chosen. But the problems involved in tooling up with a new organism, the advantages of working with one already familiar or used on a large scale, the importance of reliable data on the behavior of the organism and of the availability of reliably characterized strains suited to particular purposes – all of these considerations bias the evaluation of “suitability” away from an abstract deliberation based merely on the criteria ideally set by the questions to be investigated and the known properties of the relevant organisms. As Frederic L. Holmes’s paper makes clear, there are cases in which it is probably not possible to answer the question whether frogs were the most suitable organisms for certain investigations or simply the most easily available and familiar among reasonably well-suited organisms. Similarly for rats and *Drosophila*, as Bonnie Clause and Kohler point out.

In many important cases phylogenetic proximity is not an appropriate measure of the suitability of a model for a given process. For example, as Doris Zallen’s paper shows, the choice of a suitable organism for studying photosynthesis turned, in the first instance, on solving such physical problems as preventing obstructing layers from interfering with access of light or with diffusion of the gases produced in photosynthesis. Or, to cite a new example, many questions about mammalian ontogeny are difficult to study because of interactions between mother and fetus across the placenta and because of the inaccessibility of the fetus. In at least some instances, birds are better “model organisms” than mammals for studying certain medically relevant aspects of early

mammalian or human developmental processes. Bird embryos, after all, experience no direct maternal input once the egg is complete and, thus, no subsequent maternal influence on biochemical processes in the embryo. Biochemically, as it happens, some endocrinological processes in development are virtually identical in certain birds and mammals. And bird embryos can be studied without the disruptive procedures required for studying mammalian embryos in utero.⁹ Yet, investigators' familiarity with the ubiquitous rat and discomfort with the relative phylogenetic distance of birds as compared to rats have helped make it difficult for avian models to be taken seriously.

On the other hand, even in biochemistry and molecular biology there are cases in which phylogeny reflects, at least in part, critical differences that have arisen in the course of evolution. Thus, to take an extreme example, the structural differences between the genetic material of procaryotes and of eucaryotes are sufficiently great that procaryotes make poor models for many issues concerning gene regulation and gene structure in eucaryotes.¹⁰ This fact frustrated the early optimism of molecular geneticists after the development of the operon model of gene regulation (cf. Jacques Monod's oft-cited quip, "what's true for *E. coli* is true for the elephant"); procaryotes simply are not an adequate model for the regulatory apparatus affecting gene expression in eucaryotes.

The differences among the cases to which I have alluded in the last three paragraphs illustrate both the range and the specificity of the considerations that go into the evaluation of a particular organism for a particular job. In the face of the incompleteness

9. I should reveal my bias. This claim rests partly on my wife's use of avian models to study the role of thyroid hormones in ontogeny. She argues in detail for the preferability of avian models to rats (or sheep, whose ontogeny is in relevant respects closer to humans' than is that of rats) as tools for understanding the ways in which thyroid hormones regulate certain aspects of early development, including some that are medically relevant to humans. See, e.g., F. M. A. McNabb, "Development and Aging of the Thyroid in Homeotherms," in *Development, Maturation, and Senescence of Neuroendocrine Systems: A Comparative Approach*, ed. M. P. Schreibman and C. G. Scanes (New York: Academic Press, 1989), pp. 333–351; F. M. A. McNabb and D. B. King, "Thyroid Hormones in Growth, Metabolism and Development," in *The Endocrinology of Growth, Development and Metabolism in Vertebrates*, ed. P. K. T. Pang and M. P. Schreibman (New York: Academic Press, 1993), pp. 393–417.

10. A useful exposition of some of the peculiarities of gene structure and organization in eucaryotes may be found in T. Hunkapillar, H. Huang, L. Hood, and J. H. Campbell, "The Impact of Modern Genetics on Evolutionary Theory," in *Perspectives on Evolution*, ed. R. Milkman (Sunderland, Mass.: Sinauer, 1982), pp. 164–189.

of our knowledge of even the best-known organisms, the degree to which particular processes in one can serve as a model of, or surrogate for, particular processes in another is usually open to question. This is part of the dialectic, noted by Hans Krebs and emphasized in Holmes's paper, between working with organisms that offer special advantages and attempting to gain unobscured access to "basic principles" pertaining, ideally, to large classes of organisms or to organisms in general. Given what we know of the opportunism and tinkering that characterize evolutionary change, we must always be aware of the risk that a series of experiments based on a particular organism deals with a special case. It requires *particular* knowledge of a wide range of relevant cases to evaluate this risk.

B. *The Complexity of Suitability*

Even when experimental work aims to answer a well-defined question with well-defined materials, it is subject to unexpected contingencies. In biology, the features of the organisms under investigation are a source of some of the most important contingencies involved. (Kohler's account of the *Drosophila* work in T. H. Morgan's laboratory is particularly striking in this regard.) Because of these contingencies, when different organisms are used to investigate the very same question, they may yield systematically different results. Or one organism may yield clear-cut results while another yields no useful results. Thus, some embryologists sought to answer the fundamental question whether a differentiated somatic cell nucleus from an adult is totipotent (i.e., able to generate all cell types) by transplanting such nuclei into enucleated eggs. When this was done in several species of sea urchins, no result was obtained because the eggs rejected the foreign nuclei; a few years later, precisely parallel experiments succeeded with frogs.¹¹ Similarly, seemingly small details of experimental technique, or small changes in experimental protocols or reagent concentrations or purity, can make a major difference in the clarity, or even the character, of experimental results. Among other

11. This project was attempted, e.g., by P. P. Slonimski as a thesis project ca. 1947–48. According to Slonimski, the problem of rejection of nuclei by sea urchin eggs was not solved until the 1980s. As is familiar, a similar project was carried out successfully by Briggs and King in frogs in the early 1950s; see, e.g., R. Briggs and T. J. King, "Transplantation of Living Nuclei from Blastula Cells into Enucleated Frogs' Eggs," *Proc. Nat. Acad. Sci. U.S.A.*, 38 (1952), 455–463. I am grateful to Dr. Slonimski for describing his project in an interview and for his encouragement of my research.

consequences of this familiar fact, one is important for our purposes: small differences in technique can significantly alter the value or the evidential importance of work with a particular experimental organism. What is involved is an interaction among (at least) the questions about investigation, the features of the organisms employed, the skill of the investigators, the experimental tools and techniques available at the time, and a vast panoply of social and institutional factors (which latter are underemphasized in this paper).

No abstract formulation can capture the wealth of relevant details that play a role here – or the different *sorts* of details that must be taken into account in different cases. Some suggestive examples from the papers in this issue help to make the point. William Summers's paper, for example, implicitly asks why Félix d'Hérelle's arguments that phage should be classed as obligate intracellular parasites met such limited acceptance in the mid-twenties and thirties. One contributing factor among very many, suggested in my interviews with André Lwoff and Élie Wollman,¹² was the tendency of many bacteriologists and most students of phage from the twenties through the forties to think of bacterial cultures as uniform wholes. One consequence of this predilection was that a conceptually clear key experiment was not performed for a long time after it was technically possible – namely, starting bacterial cultures from single bacterial cells of so-called lysogenic strains (i.e., strains containing latent phage). The point was to determine whether *a single bacterium*, itself uncontaminated by free phage, could initiate a lysogenic culture – a culture with no free phage, which nonetheless could produce active phage – and, if so, whether the kinetics of the phenomenon fit better with d'Hérelle's or Jules Bordet's theory (described by Summers).¹³

Kohler argues that the scale on which an experiment or a series of experiments is carried out can sometimes be crucial, as it was in the search for mutations in *Drosophila* stocks in Morgan's laboratory. When this is so, secondary factors or secondary uses of the organism can play an important role in determining whether

12. These interviews were held in 1988 and 1984, respectively.

13. Lwoff performed an important series of such experiments starting in 1949, leading to the definition of conditions in which phage production could be brought about ("induced") in some strains of lysogenic bacteria. The first report is A. Lwoff and A. Guttman, "Les problèmes de la production du bactériophage par les souches lysogènes. La lyse spontanée du *Bacillus megatherium*, *Comp. Rend. Acad. Sci. Paris*, 229 (1949), 605–607; the first full account of the series of experiments is A. Lwoff and A. Guttman, "Recherches sur un *Bacillus megatherium* lysogène," *Ann. Inst. Pasteur*, 78 (1950), 711–739.

it is employed long enough or on a large enough scale to do the job (here, of finding mutations – but note that “the” job may not be one the investigator had in mind). Beyond the obvious tissues of cost, convenience, length of time required for the protocol, and so forth, the organisms’ other uses *are* important. As Kohler shows, the usefulness of *Drosophila* for studies on experimental evolution, for teaching, as a screen for mutations, and so on played an important role in bringing it to the point where the mutation studies overtook the rest. A similar point, though vastly different in detail, derives from Clause’s account of the multiple uses of the Wistar rat. Again, the economic importance of organisms (see the paper by Muriel Lederman and Sue Tolin), or their importance as disease vectors (see Summers), can lead biologists to do a sufficient amount of work with them that they learn of their special virtues for purposes unrelated to those for which they were originally employed.

C. Conservative vs. Risky Strategies in Choosing Organisms

Holmes, Clause, Kohler, and Zallen all emphasize the immense amount of work required to construct and obtain reliably reproducible results from an experimental organism. (Fieldwork also may require similarly heavy investment to establish identification procedures and protocols that allow different investigators to generate reliably reproducible results.)¹⁴ A major part of the effort may go into fine-tuning and standardizing the organism (see Clause and Kohler), matching the strain or organism to the experimental protocols, or revising those protocols so that the experiments yield clear results or bear directly on the question in hand. Not only must the strains be defined, but the nature of the variation from organism to organism must be understood and counteracted where it interferes with the experimental protocol (which it does not always do!). Furthermore, both protocols and organisms must be adjusted to one

14. A moderately familiar example helps make the point: In the 1930s, the difficulties in determining the population structure of *Drosophila pseudoobscura*, which seemed to have intersterile races, were ultimately resolved by the identification of a sibling species, *Drosophila persimilis*. The problem of whether the “races” in question were good species was so great – and so theoretically consequential – that the issue played a role in the estrangement between Theodosius Dobzhansky and Alfred Sturtevant. The complex issues involved are well described in W. Provine, “Origins of the Genetics of Natural Populations Series,” in *Dobzhansky’s Genetics of Natural Populations I–XLIII*, ed. R. C. Lewontin, J. A. Moore, W. B. Provine, and B. Wallace (New York: Columbia University Press, 1981), pp. 1–83.

another in the service of the aim of the experiment. H. J. Muller's efforts to construct ever more refined laboratory strains of *Drosophila* in the period after he received the Nobel Prize provide an extreme example of this sort. During this period, a considerable part of the effort in Muller's laboratory was devoted to constructing esoteric special-purpose strains of *Drosophila* to allow the experimental resolution of extremely specific questions regarding chromosomal mechanics, gene locations, modifier genes, gene regulation, et cetera.¹⁵

Given the heavy investment involved in constructing or gaining control of a laboratory organism¹⁶ (see Clause and Kohler), it is typically quite costly to change organisms, particularly in those instances in which a new organism must be domesticated or adapted to a new purpose. This is not merely a matter of familiarity and comfort; the difficulties encountered are often a function of significant differences in physiology, biochemistry, morphology, genetic content, controls of gene regulation, and so on *ad indefinitum*. Furthermore, when a "large body of experimental information has accumulated" about a particular organism,¹⁷ that information itself constitutes a resource enabling experimenters to develop protocols and to interpret experimental results in terms of standardized knowledge of the organism. Since, in the end, the behavior of a new organism might prove hard to interpret and the organism might prove unsuitable for the task at hand, the resistance of some experimental biologists to changing organisms is understandable. In general, it is both easier and safer to stick with a "familiar" organism and exploit it to the full rather than to start working with a less familiar or less fully developed alternative, even when that alternative is potentially well suited to a particular task. For such reasons as these, biologists often hesitate for an extended period before deciding which new organism, if any, to invest in.

15. I examined the contrast between this work and that of Milislav Demerec during the same period in a talk, "Model Organisms and Research Strategies in Mendelian Genetics," available on request, delivered at the 17th International Congress of the History of Science, Berkeley, Calif., 1985. The central point of the contrast concerned Demerec's readiness to switch organisms in hope of finding the "right" organism for pursuing particular problems, vs. Muller's attempt to adapt "his" organism to the question at hand.

16. Including such "organisms" as somatic cell lineages. D. T. Zallen and R. M. Burian, "On the Beginnings of Somatic Cell Hybridization: Boris Ephrussi and Chromosome Transplantation," *Genetics*, 132 (1992), 1-7 (esp. pp. 3-5, and references therein), provide a minimal sense of the immense investment required to gain control of such systems and the length of time it takes to learn whether there will be a significant payoff.

17. Zallen, "'Light' Organism," p. 274 (above, n. 4).

After all, working with a new organism constitutes a major investment, one that usually requires some years before it becomes clear whether it will pay off as promised or lead into a blind alley.

To some extent, questions of style and personality enter into the decision whether to stick with an organism or switch to another in pursuing a particular problem. Some investigators are so attached to a particular organism or so confident that they can adapt it to almost any task that, like Muller, they do not seriously consider switching to alternative organisms. Others, motivated by a particular problem, are happy to switch to a more promising organism even at the cost of a few years' labor.¹⁸ Still others, perhaps more adventuresome or more easily bored, fear going stale or missing something because of their commitment to a particular organism or problem. Such individuals are more likely to make a major switch of problems and/or organism every decade or so.¹⁹ It is worth observing that there are almost always serious candidate organisms available, organisms that meet some but not all of the desiderata relevant to the task at hand.²⁰ Because this is so, and because blind alleys are so common, it is desirable that there be considerable variance among investigators in the degree of inertia (or conservatism) and, conversely, in the willingness to take a chance on tooling up for a different attack on a problem – or for an attack on a new problem.

2. TRANSFORMING THE JOB

All of the articles in this group, but especially Kohler's, suggest that the interaction between the protocols employed by an investigator and the features of an experimental organism can transform

18. As a referee pointed out, investigators may have different underlying assumptions about whether most organisms, or only a few very special ones, are suitable for investigating a particular problem. Additionally, some problems simply require working with many organisms or a variety of organisms. This is perhaps more common in fieldwork than in experimental work.

19. To avoid misunderstanding, I should stress that good experimentalists constantly seek to improve their protocols and the match between organism and protocol. The claim in the text concerns major reorientations in an experimental program. I discuss the matter of style briefly at pp. 160 ff. of a predecessor to this article: R. M. Burian, "How the Choice of Experimental Organism Matters: Biological Practices and Discipline Boundaries," *Synthese*, 92 (1992), 151–166.

20. The features that an organism should possess in order to be suitable for a given job are determined in good part by the problem at issue and by the available techniques. In their papers in this issue, Holmes and Zallen provide exemplary lists of desiderata appropriate in different cases and circumstances. See also the next section.

the job undertaken by the investigator. I shall briefly deploy two examples here to indicate how both the organism and the available techniques can alter the tasks for which a given organism is employed. As the second example shows, it is sometimes possible to remove limitations pertaining to the use of an organism by a change of technique.

(1) In the mid-1930s, Philippe L'Héritier and Georges Teissier performed the first population cage experiments with *Drosophila*. They showed, among other things, that unfavorable mutations (such as *bar*) could be maintained in a population in a stable balanced polymorphism in spite of the deleterious effects of the mutation on the flies that carried it.²¹ Such experiments required a rapid way of counting thousands of flies without disrupting the population or altering its numbers. For this purpose, a useful device was to anesthetize the flies briefly with CO₂, spread them on a photographic plate, and count images rather than flies. As it turned out, in some populations a substantial proportion of the flies were killed by this procedure. Given their plan, the experimenters had to gain control of their counting technique. L'Héritier made a special study of this phenomenon. The sensitivity to CO₂ proved not only to be heritable *but to be maternally inherited* – that is, to be produced by some genetic factor other than a chromosomal gene, most likely contained in the cytoplasm deposited into the egg by the mother. Eventually, the need to understand and gain control of this CO₂ sensitivity came to play a central role in L'Héritier's research; after twenty years or so (interrupted by World War II), he established that it was due to a maternally transmitted viroid, since labeled *sigma*, pandemic in most *Drosophila* populations.²² The behavior of the fly, altered by an infection, had displaced L'Héritier from population genetics to a study of cytoplasmic inheritance.

(2) Staying with *Drosophila*, one aspect of the well-known gulf between embryology and genetics from the 1920s through the 1960s²³ concerned the requirements placed on experimental

21. See, e.g., P. L'Héritier and G. Teissier, "Une expérience de sélection naturelle. Courbe d'élimination du gène 'bar' dans une population de *Drosophiles* en équilibre," *Comp. Rend. Soc. Biol.*, 117 (1934), 1049–51; P. L'Héritier and G. Teissier, "L'élimination des formes mutantes dans les populations de *Drosophiles*. Cas des *Drosophiles* 'ebony'," *Comp. Rend. Soc. Biol.*, 124 (1937), 1099–1101.

22. See P. L'Héritier, "The CO₂ Sensitivity Problem in *Drosophila*," *Cold Spr. Harbor Symp. Quant. Biol.*, 15 (1951), 99–112; idem, "*Drosophila* Viruses and Their Role as Evolutionary Factors," *Evol. Biol.*, 4 (1970), 185–209.

23. There is, by now, a large literature on this topic. For examples, see Mitman and Fausto-Sterling, "*Planaria*: (n. 8, above); G. Allen, "T. H. Morgan and the Split between Embryology and Genetics," in *A History of Embryology*, ed. T. J. Horder,

organisms by the research agendas of these two disciplines in light of their respective classical techniques. To study early ontogeny, embryologists needed large, transparent, manipulable eggs that formed a series of visibly distinct cells and easily marked cell lineages. Given these and other favorable conditions, embryologists could follow the pathways by means of which various tissues and organs arose, and could study the effects on ontogeny of various manipulations, transplantations, and chemical insults. Although maize meets most of these conditions, virtually no animal then employed in, or known to be suited to, classical genetic experimentation does. An ideal genetic organism would be easily raised in the laboratory, allow controlled matings to yield multigeneration pedigrees, have a relatively short generation time, be able to tolerate both inbreeding and outbreeding, have a good supply of well-known and easily scored mutations, and, by the 1920s, have a small number of visible and easily distinguished chromosomes. Take *Drosophila*, the classical genetic organism, as an example. It is badly suited to classical embryology: the egg is small, difficult to manipulate, and encased in a tough opaque coating; and the first hundred or so nuclei, identical in appearance, form a syncytium (i.e., a single cell with multiple cell nuclei) before cell walls are formed. That dramatic change proceeds in parallel throughout the embryo over a brief period and is very hard to follow; even then, most of the resultant cells are not well marked. There are further disadvantages as well, but this is enough to make it clear that *Drosophila* is very poor material for classical embryology.²⁴

J. A. Witkowski, and C. C. Wylie (Cambridge: Cambridge University Press, 1986), pp. 113–146; A. Clarke, “Embryology and the Rise of American Reproductive Sciences, circa 1910–1940,” in *The American Expansion of Biology*, ed. K. Benson, J. Maienschein, and R. Rainger (New Brunswick, N. J.: Rutgers University Press, 1991), pp. 323–350; S. F. Gilbert, “The Embryological Origins of the Gene Theory,” *J. Hist. Biol.*, 11 (1978), 307–351; idem, “Cellular Politics: Just, Goldschmidt, Waddington, and the Attempt to Reconcile Embryology and Genetics,” in *The American Development of Biology*, ed. R. Rainger, K. Benson, and J. Maienschein (Philadelphia: University of Pennsylvania Press, 1988), pp. 311–346; J. Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics* (New York: Oxford University Press, 1987); and numerous writings of J. Maienschein.

24. A significant number of biologists in the twenties and thirties sought organisms suited to both embryological and genetic work, or to employ a “genetic” organism in embryological studies or vice versa. For studies of one biologist who attempted to bridge this gap using *Drosophila* inter alia, see R. M. Burian, J. Gayon, and D. Zallen, “The Singular Fate of Genetics in the History of French Biology, 1900–1940,” *J. Hist. Biol.*, 21 (1988), 357–402, esp. pp. 389–407, and “Boris Ephrussi and the Synthesis of Genetics and Embryology,” in *A Conceptual History*

In recent years, however, this situation has changed dramatically. A wealth of new molecular techniques (e.g. *in situ* hybridization and immunofluorescence) allow students of development to mark rare molecules and follow their distribution over short periods of time during ontogeny. In addition, there are powerful new techniques for altering and inactivating the genes that produce those molecules. Together, these techniques have allowed step-by-step visualization and dissection of the earliest signals that lay down heretofore invisible boundaries within *Drosophila* eggs and early larvae. Recently, there has been enormous progress in analyzing the controls by means of which these boundaries affect the ontogeny of the organism. In effect, the conditions described above are now being met – it is now possible to visualize occurrences behind the integument of the egg, to manipulate and perturb the egg from its normal state in very specific ways, and to mark and follow cell lineages. Joining the new techniques to the immensely powerful preexisting genetic practice and information available for *Drosophila* has made this organism into a preferred organism for the study of development. Thus, in this instance, an organism that used to be wholly unsuited for a major task (the study of early development) has become particularly suited for that job, bringing with it a major new set of evolving experimental practices.²⁵ This illustrates how new techniques can bring about remarkable changes in the jobs that can be performed with an organism. It also illustrates the value of an enormous data base and of well-developed experimental practices with a given organism. Finally, it shows how great a length of time (here at least thirty years!) may be involved in adapting an organism and experimental techniques to a task for which the organism was not initially suited. No wonder many experimentalists find it more productive to continue working with, and adapting, their favorite organism incrementally to new jobs.

of Modern Embryology, ed. S. Gilbert (New York: Plenum, 1991), pp. 207–277. A number of the other studies in the latter volume bear on this topic.

25. For those unfamiliar with these developments, a useful book, summarizing recent work, is P. Lawrence, *The Making of a Fly* (Oxford: Blackwell Scientific Publications, 1992). The organization of topics in this volume indicates the extent to which classical embryological questions are yielding to the new techniques: the first seven chapter headings are “The Mother and the Egg” (including gastrulation and segmentation), “The First Coordinates,” “Patterning the Embryo,” “Cell Lineage and Cell Allocation,” “Positional Information and Polarity,” and “Spacing Patterns.”

3. THE BREADTH OF THE BIOLOGICAL KNOWLEDGE CONTEXT

Evolution is a branching process in which each organism (each lineage, each species) has distinct characters, differing in some ways at least from the organisms (lineages, species) from which it stemmed. This means that each organism provides an imperfect window on the properties of other organisms. Even with contemporary techniques of cloning, which, for relatively simple organisms, can come extremely close to producing organisms with identical properties,²⁶ mutation and epigenetic differences produce divergence within lineages. This truism proves to be of great importance. At (virtually?) all levels of the biological world – including the biochemical – it is an open question how general the findings produced by the use of a particular organism are. Consider a few illustrative examples of the “depth” of this point. The genetic code is not universal – some ciliated protozoa and mitochondria translate certain codons differently than in the “universal” code.²⁷ (The differences in translation depend on the population of transfer RNAs in the surrounding medium.) Some organisms (or “organisms” – to wit, viruses) have no metabolism of their own. There are organisms (viruses) whose genetic material is not DNA. There may be organisms (“prions”) whose genetic material, if any, is not composed of nucleic acid. A given strand of DNA, even when it is transcribed to RNA, may yield different information according to the biochemical context – e.g., because of “overlapping reading frames,” because the “readout” of DNA sometimes stops at one point and sometimes another, or because a given pre-messenger RNA is spliced in alternative ways before being translated.²⁸

At every level of biological organization, there are innumerable results like these. This makes epistemological evaluation of experimental work in biology especially difficult. To what extent are the results obtained with an organism (or a group of organisms) general, and to what extent can they be reliably extrapolated?

26. In (most?) mammals, the ontogeny of the immune system guarantees that even identical twins will have genetically distinct somatic cells and immune responses. This illustrates the difficulty of obtaining full reproducibility in biological systems.

27. J. Darnell, H. Lodish, and D. Baltimore, *Molecular Cell Biology*, rev. ed. (New York: Scientific American Books, 1986), pp. 108, 929.

28. Except for the claim about prions, all of these claims are uncontroversial and can be documented adequately in virtually any good current textbook of molecular biology or molecular genetics.

This is an especially acute version of the traditional philosophical problem of induction. In light of considerations like those just supplied, we know we are dealing with a congeries of contingently different systems whose regularities, even if they trace back to fundamental (e.g., biochemical) laws, depend at least as strongly on the contingent, evolutionarily derived configurations of the components of the system as they do on those laws. In this respect, the epistemological situation of biology is different from that of any form of mechanics, including quantum mechanics, for *biological knowledge is knowledge of large numbers of particular systems that cannot be identically prepared*. As such it cannot, in principle, be derived from a body of laws plus initial or boundary conditions. Substantive knowledge of evolutionary history, of alternative biological mechanisms, of phylogenies, and so on, is needed to evaluate the power of a given result.

Like Stuart Kauffman and many others, one can attempt a statistical mechanics of complex systems of a general class within which organisms fall.²⁹ *For specific biological knowledge, however, one needs, in addition, knowledge of the historical (i.e. evolutionary) processes that change, or can change, the properties underlying the statistics*. At every level, the contingency of evolutionary processes must be taken into account. It follows that, in the end, proper evaluation of the knowledge gained by working with a given organism or group of organisms requires that knowledge to be set into a comparative and evolutionary framework. This is part of what I mean by the breadth of the knowledge context in biology. If my account is correct, detailed knowledge of (historical) biological contingencies constrains – and ought to constrain – the evaluation of experimental work in biology and the knowledge claims based on that work.

This stance is reinforced by considerations regarding the interaction between choice of organism and choice of experimental technique or tools. The practices, problems, and epistemological prospects of a discipline can be altered as radically by a change of experimental tools as by a change of organism. Consider the suggestion in the previous section that the epistemological situation of embryology (significantly relabeled “developmental biology”) has been improved by the introduction of contemporary molec-

29. S. Kauffman, *The Origins of Order: Self Organization and Selection in Evolution* (New York: Oxford University Press, 1992). See also R. M. Burian and R. C. Richardson, “Form and Order in Evolutionary Biology: Stuart Kauffmann’s Transformation of Theoretical Biology,” in *PSA 1990*, vol. I, ed. A. Fine, M. Forbes, and L. Wessels (East Lansing, Mich.: Philosophy of Science Association, 1992), pp. 267–287.

ular techniques. The improved prospects are not unconnected with the fact that molecular techniques have allowed many embryologically intractable organisms such as *Drosophila* to do work in developmental biology. Similar points can be made about population genetics. The transformation of that discipline's treatment of genetic variation when it was invaded by the technique of gel electrophoresis (originally a tool of protein biochemistry) is relatively familiar. The more recent switch from tools for analyzing proteins to tools for analyzing DNA has brought about an equally dramatic transformation. Thanks to the new techniques, many formerly unresolvable questions about variation (e.g., about the extent of neutral variation, and the extent to which selection has eliminated variants) have become much more tractable.³⁰ For our purposes, the moral is straightforward: it is not possible to carry out a reliable epistemological evaluation of work of this sort without deep and detailed knowledge of the methodologies employed, of the features of the organisms studied, and of the matchup (or interaction) between the two. It is not a matter of principle, but of biology, that there is more information about the history and the variation of organisms contained in DNA than in proteins. Such biological knowledge is an inescapable component of the sound evaluation of biological knowledge claims. Epistemological evaluation of biological knowledge claims must employ some sort of bootstrapping technique, for it must rest, in part, on biological knowledge.

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30. R. C. Lewontin, *The Genetic Basis of Evolutionary Change* (New York: Columbia University Press, 1974), provides an epistemologically sophisticated account of the problems that were supposed to be solved by the use of gel electrophoresis, and the then-apparent limitations of the technique for this purpose. Lewontin has recently argued that work at the DNA level can resolve many of the problems that could not be settled by electrophoresis. The principal reason is not limitations of the technique as such (though they are important), but the much greater information about variation contained in DNA molecules as compared with protein molecules.