6

Model Organisms: Of Flies and Elephants

Most of the spectacular advances in experimental biology made in the last 100 years came from research on a remarkably small number of organisms. Here are some examples: During the second decade of the twentieth century, Thomas Hunt Morgan and his students laid the foundations of modern genetics by experimenting with just a single species, the fruit fly *Drosophila melanogaster* (see Section 3.2). The advent of molecular biology, which began in the 1940s, came mainly from research on the bacterium *Escherichia coli* and its bacteriophages (viruses that infect bacteria). Neurophysiologists unraveled the mechanisms of neurotransmission (see Section 2.1) using the giant nerve cells of squid. The rat and its liver played a central role in elucidating the major metabolic pathways such as the urea cycle and oxidative phosphorylation (see Section 3.3 and Chapter 4). The mouse was and still is the favorite lab animal of immunologists, giving rise to a major increase in biomedical scientists' understanding of the mammalian body's defense mechanisms. Baker's yeast, *Saccharomyces cerevisiae*, proved to be a powerful tool for studying the biology of eukaryotic cells, for example, the biogenesis of mitochondria or the regulation of the cell cycle. The nematode worm *Caenorhabditis elegans* was one of the first organisms that allowed biologists to study behavior, embryonic development, and other biological processes at the molecular level (see Section 2.5). In the 1970s, *Drosophila* made a spectacular comeback as a main experimental organism for developmental biology. More recently, it was joined by the see-through zebrafish *Danio rerio*. Most of what is known on the molecular biology of plants came from studies on the mustard weed *Arabidopsis thaliana*. For most of these organisms, the full genomic DNA sequence has now been determined by various sequencing consortia, and this is widely seen as an important complement to the human genome sequence (Kornberg and Krasnow 2000; International Human Genome Sequencing Consortium 2001).

Thus, twentieth-century experimental biologists differ fundamentally from the traditional naturalists who are interested in the *diversity* of lifeforms and whose research might involve hundreds or thousands of different species. Compared to natural environments and natural history collections, genetics and molecular biology laboratories are extremely impoverished in biodiversity. In fact, most laboratories work on only a single species, and a large number of laboratories work on the same species. While this is sometimes lamented as a deficiency (in addition to being a subject for scientific jokes), it is worth examining *why* model organisms played and continue to play such an important role in experimental biology.

There are at least three questions that can be raised concerning the role of experimental organisms in biological research. First, there is the question of why some organisms are especially well suited for studying certain biological processes. Second, we may ask why experimental biologists more often choose to work on an already established laboratory organism, rather than bringing a new organism into the laboratory and initiating research with this new organism. A third question concerns the notion of a *model* organism, that is, to what extent can certain experimental organisms function as models for other organisms, in particular humans?

In recent years, a number of historians of biology have focused on the use of model organisms as an important aspect of biological practice.[1] Most of them view such organisms as being part of a "material culture" of experimental biology. Like Rheinberger's experimental systems discussed in Chapter 5, the research materials and organisms employed by biologists can be units of historical analysis in their own right that can give the historian important insights into the dynamics and organization of laboratory practice. As we shall see (Section 6.2), some of these historians give a number of unexpected answers to the main questions concerning the role of model organisms that I have mentioned. First, they make substantial use of several economic and technological metaphors to describe the role of model organisms; for example, they describe them as "artifacts," "instruments," "craftwork," "tools," or "systems of production." Second, historians have found that it is far from clear that biologists deliberately choose certain organisms for solving specific biological problems. It may very well be the other way around: The choice of certain organisms defines what comes to be viewed as a relevant research problem. This choice is mainly determined by locally contingent factors. Thus, the historical course of experimental biology could have been driven in certain directions for largely contingent reasons. Possibly, our ways of thinking about life today could be quite different, if – more or less by chance – different laboratory organisms had been chosen at certain critical junctures in the past.

Obviously, the impact of such historical contingencies is reduced if it is the case that the knowledge obtained from model organisms is of a *general* or even *universal* nature, as some biologists have claimed. But how general is this knowledge really? If we look at the history of twentieth-century biology, we find many examples of biologists who overgeneralized findings that they obtained with a particular organism. For example, the Dutch Botanist Hugo de Vries based his "mutation theory" of speciation on just a single organism, the evening primrose *Oenothera lamarckiana*. *Oenothera* led de Vries to believe that new species can arise by single mutational events (Weber 1998a, Section 2.3). However, it turned out that *Oenothera* is a highly unusual example, because it contains ring-shaped chromosomes that make it genetically unstable. Another example is Wilhelm Roux's "mosaic theory" of development, which assumed that parts of an embryo specify corresponding parts in the adult animal. Roux based his theory on experiments showing that cutting frog embryos into half yields half frogs. However, Hans Driesch showed that, in sea urchins and other marine invertebrates, fragmented embryos can generate whole animals (Weber 1999b). To my knowledge, Roux and Driesch never resolved their disagreement as to which results were more biologically significant.

These historical blunders notwithstanding, it is a major characteristic of modern experimental biology that it aspires to have some kind of *generality*, or even *universality*. Morgan and his co-workers were not seeking to study the mechanisms of heredity of *Drosophila melanogaster* or the mechanisms of heredity of insects. They thought they were studying the mechanisms of heredity, period. Similarly, Paul Zamecnik and his laboratory – working in a hospital – did not primarily want to know how rats or bacteria of the genus *Escherichia* synthesized proteins; they were initially after the regulation of protein metabolism in human cancer cells, and later after *the* mechanism of protein synthesis (see Section 5.1). Presumably, these biologists assumed – or had reasons to believe – that the knowledge they would gain from experimenting with *Drosophila* flies, rat liver cells, or bacteria would be applicable to a wide range of biological taxa, including the species *Homo sapiens*. Therein lies one of the main differences between disciplines such as genetics, biochemistry, or molecular biology and field studies of the sex life of sea snails. However, it would be naïve to assume, for example, that the mechanism of protein synthesis is *exactly* the same in *E. coli* and in humans (in fact, it is not). Furthermore, there are biological mechanisms for which there must exist considerable differences between different organisms, because of the obvious differences in anatomy and physiology. Such phylogenetically variable mechanisms, too, have been studied with great success in various model

organisms, for example, embryonic development in frogs and memory and learning in *Drosophila*.

I try to develop a general framework for answering questions about the generality of biological knowledge obtained from studying particular model organisms toward the end of this chapter. Before I turn to this issue, I present another historical case study. In Section 6.1, I examine how the fruit fly *Drosophila* – already the favorite lab animal of geneticists in the first half of the twentieth century – was turned into a major model organism for molecular studies of development. This case study allows me to address several questions concerning the role of laboratory organisms and some more general points concerning experimental practice in biological research. In Section 6.2, I use the case to critically examine some of the claims recently advanced in relation to model organisms by historians of biology. In Section 6.3, I show that technological and economic metaphors are only of limited value in illuminating the role of experimental organisms. In Section 6.4, I introduce a new analytic concept in order to capture the role of experimental organisms more adequately: the concept of preparative experimentation. In Section 6.5, I take on the challenge posed by those historians who stressed the contingency of experimental organism choice. Finally, Section 6.6 examines the question of what can be learned from the study of model organisms.

6.1 THE MOLECULARIZATION OF *DROSOPHILA*

The early history of modern genetics is closely tied to the use of the tiny fruit fly *Drosophila melanogaster* as an experimental organism. Based on experiments with spontaneous *Drosophila* mutants, Thomas H. Morgan's group at Columbia University in New York produced the first genetic map in 1913. This map was constructed with the help of a genetic process known as "crossing-over" (see Section 3.2). That these so-called linkage maps really represented a physical structure, rather than just being mathematical constructs, was confirmed in the 1930s, when it became possible to map *Drosophila* chromosomes cytologically. Cytological maps were prepared on the basis of dyed giant chromosomes isolated from larval salivary glands (Painter 1933, 1934). These giant chromosomes show characteristic banding patterns that are visible under a light microscope. It was shown that the earlier linkage maps were co-linear to the cytological maps. Thus, the fact that two different experimental techniques provided corresponding results provided evidence that these maps represented real chromosomal structures (Weber 1998b; see also Section 9.2).

The view that the choice of experimental organisms is largely a matter of locally contingent factors while, at the same time, having far-reaching consequences for defining relevant research problems could mean that our perception of the biological world is strongly biased toward a small number of organisms that have not been chosen because they allow scientists to discover important biological principles, but simply because they happened to be part of some local "material cultures." What comes to be viewed as an "important" principle could also be determined by these contingent factors. However, this constructivist conclusion only follows if the knowledge obtained from certain experimental organisms cannot be *generalized* to other organisms. I discuss the problem of generalizing from model organisms in Section 6.6. Now, I argue that the impact of locally contingent factors may be more limited than some historians of biology have suggested.

What the historical analyses provided by Kohler and others suggest is that the *initial* choice of experimental organisms can be highly contingent and strongly influenced by locally contingent factors.[15] However, the later *vindication* of this organism as a system that is conducive for producing certain kinds of knowledge may be less dependent on local factors. The proof of the pudding is in the eating, and model organisms can only prove their worth after a while, by enabling fruitful research in many different laboratories, the results of which can again serve as a basis for further research. In such a distributed process, the impact of locally contingent factors may be reduced.

It is now time to move on to the question of what can be learned from laboratory organisms that goes beyond the biology of the species that serves as a model.

6.6 WHAT CAN BE LEARNED FROM STUDYING MODEL ORGANISMS?

How much truth is there in Jacques Monod's legendary saying, "What is true for the coline bacillus is true for an elephant"? To put it less allegorically, to what extent can the findings obtained from studies of a particular organism be generalized to other organisms, for example, to humans? Richard Burian (1993a, 366) has called this question "an especially acute version of the traditional philosophical problem of induction." Kenneth Schaffner, after examining some recent research on the genetic basis of social behavior in *C. elegans*, mating behavior in *Drosophila*, and the pathogenesis of a mouse analog of Alzheimer's disease, concludes that "animal models are ultimately used as a source for extrapolations to humans, though an important subordinate goal is to understand the biology of all organisms" (Schaffner 2001,

224). While the use of mice as an animal model for Alzheimer's disease seems somewhat plausible – given that mice, like humans, are mammals – what can biologists hope to learn about human beings from studying an organism such as the humble nematode worm *C. elegans*? In this section, I try to develop a general framework for answering such questions.

As a starting point, it is helpful to consider the conditions under which we would expect inferences from one organism to another to succeed. For obvious reasons, if all organisms were radically different in terms of their physiological, developmental, and genetic mechanisms, nothing could be learned about other organisms from studying a particular model organism. A model organism must have *something* in common with the organisms it is supposed to be a "model" for. Now, it is known today that all organisms are remarkably similar at the level of certain molecular mechanisms. For example, so far as is known today, all self-reproducing organisms contain DNA as their genetic material.[16] Furthermore, the genetic code is the same in almost all organisms. Known exceptions include only the mitochondrial genetic system and some protozoans. The molecular mechanisms of DNA replication, transcription (RNA synthesis), and translation (protein synthesis) are remarkably similar within the prokaryotes (bacteria) and within the eukaryotes (nucleated cells), whereas they differ between prokaryotes and eukaryotes. The same is true of many metabolic pathways, for example, oxidative phosphorylation (see Chapter 4). Although oxidative phosphorylation comes in different versions in bacteria, it is virtually the same in all the eukaryotes.

But what grounds do biologists actually have for believing that the mechanisms listed above are really the same, or almost the same, in many different organisms? In other words, what makes them think that they have learned some biological principles that are of *general* significance? It could be objected that life on our planet still consists of more than one million species. Only a tiny fraction of these have ever been studied at the molecular level. This seems like a rather thin induction base. In fact, if the generality of molecular biological principles had been inferred solely by *enumerative induction*[17] from the known cases, the grounds for this generality would be very weak indeed. However, I claim that the generality of certain biological principles over a large number of species is *not* inferred by enumerative induction, but by a more sophisticated kind of inductive argument.

This kind of argument proceeds by comparing organisms *phylogenetically*, in other words, by paying attention to their common evolutionary descent. If a mechanism is found to be the same in a set of phylogenetically very distant organisms, this is evidence that it is also the same in a great number of other organisms as well, namely all those that share a common ancestor with the

known organisms that are being compared. For example, the genetic code has been shown to be the same in organisms as phylogenetically diverse as mammals, fish, insects, plants, fungi, and bacteria. Now, it is assumed that this standard genetic code arose only once in evolution. This assumption is very likely to be true, because of the extremely large number of possible alternative genetic codes (i.e., possible assignments of nucleotide triplets to amino acids), which makes it highly unlikely that the same code arose more than once in evolution. Given these assumptions, it can be inferred that a large majority of organisms from all the kingdoms of life share the same genetic code. The deviant genetic codes found in a small number of genetic systems are very likely to be *derivative* traits that evolved only in a small number of taxa. For, if changes to the genetic code had occurred more often in evolution, we would not expect to find the same code in such phylogenetically distant organisms as humans and bacteria.

From a logical viewpoint, what we have here is an *argument from parsimony*; that is, we are inductively inferring to a statement from logically weaker premises by making an assumption of *simplicity*. In this case, the simplicity assumption is that the genetic code arose only once. While arguments from parsimony are not generally reliable, this one is: we have strong reasons to believe that the genetic code *did* arise only once. For a penetrating analysis of the problems of parsimony and phylogenetic inference, see Sober (1988).

The case of the genetic code is perhaps the most clear-cut one, because of its remarkable phylogenetic conservation and the extremely low probability that the same genetic code has arisen more than once in evolution. However, in principle, arguments of this kind can be applied to other mechanisms as well.

These considerations suggest that the usefulness of model organisms crucially depends on the extent to which the mechanisms in question are *phylogenetically conserved*. Any extrapolations from model organisms are only reliable to the extent that the mechanisms under study have the same evolutionary origin in the model organisms and in humans. However, we must be clear about what exactly the special kind of inductive argument that I have used on the example of the genetic code establishes. To be specific, what this kind of argument can show is that there is a high probability that a particular organism shares a certain mechanism with other organisms for which it is *known* that they have this mechanism. In other words, if we are asking whether some organism S_1 has a mechanism M, we can use this kind of phylogenetic inference by first checking whether organisms $S_2, S_3, \ldots, S_n$ have M. If we know the phylogenetic relationship of $S_1, S_2, S_3, \ldots, S_n$, we can then estimate the probability that S_1 has M. Alternatively, this kind of inference can be used

to estimate how widespread a certain mechanism is in the biological world, that is, in how many taxa it occurs (as in the example of the genetic code). It seems to me that the latter kind of extrapolation is more important than extrapolation to particular species (see below).

Thus, extrapolations or inductive inferences from model organisms to other organisms are possible and can be reasonably sound, provided that they are based on known phylogenetic relationships. Ultimately, the *generality* of molecular biological principles can only be established by such inferences.

It might seem that this conclusion basically answers the question of what biologists can learn from studying model organisms. However, I want to show that the role of model organisms in biological research does not stop here. That is, model organisms have epistemic functions over and above providing a basis for inductive inferences or extrapolations to other organisms (Weber 2001c). It is to these other functions that I turn now.

In order to show that model organisms are not good just for extrapolations, I return to my case study from Section 6.1. As we have seen there, two *Drosophila* laboratories have cloned some fly genes that, due to the drastic effects that mutations in the genes have on the fly's body plan, were implicated in the genetic control of development. It was found that three of these genes, *Antennapedia*, *fushi tarazu*, and *Ultrabithorax*, share a short, conserved sequence element called the "homeobox." By using DNA probes from *Drosophila*, Walter Gehring's laboratory then discovered that several organisms that are phylogenetically very distant from *Drosophila* also have genes containing a homeobox. This points to an important role of model organisms in modern biological research. Namely, research on model organisms provides important *research materials* for work on other organisms. The cloned DNA fragments containing homeobox genes from *Drosophila* are an example of such research materials. These cloned DNA fragments provided scientists with rapid access to the homeobox genes of other organisms (including humans). Namely, these DNA pieces could be used to "fish" for homologous DNA sequences in genomic libraries prepared from the nuclear DNA of a variety of other organisms (a procedure colloquially known as "zooblots"). It is hard to say whether mammalian homeobox genes could have been discovered without the DNA probes that the *Drosophila* workers had prepared. There are a small number of extremely rare mammalian mutants that are probably due to homeotic genes, for example, the mouse mutant *rachiterata* or people with inborn alterations in digit numbers at their fingers or toes. However, in the pregenomic age, cloning homeotic genes in *Drosophila* was a much easier task than cloning mammalian genes, because – as I have shown – chromosomal walking was greatly facilitated by cytological mapping methods (Section

6.1). Thus, model organisms such as *Drosophila* can provide biologists with valuable research materials that can be used to discover homologous genes in other organisms. This function of model organisms has nothing to do with extrapolation or inductive inference: it is an example of what I have called preparative experimentation (see Section 6.4).

In the example discussed above, a cloned DNA fragment that originated from *Drosophila* research was used to discover genes with similar functions in other organisms. This approach was useful at a time when genomic DNA sequence information was still comparatively scarce. Today, in the age of genomics, model organisms can provide even more direct access to the function of certain genes. Recently, the full genomic DNA sequences of humans, *C. elegans*, *Drosophila melanogaster*, yeast (*S. cerevisiae*), the plant *Arabidopsis thaliana*, and various bacteria have become available. Clearly, the sequencing of the model organisms was not done for pure biological interest in these organisms. Instead, the sequences of model organisms are thought to be of crucial importance for interpreting the human genome sequence. The rationale behind this approach results from the fact that all of these model organisms contain so-called orthologous genes. These are genes that can be traced back to a common ancestor. For example, an initial analysis of the *Drosophila* genome sequence revealed that the fly genome contains orthologs to 177 out of 289 human disease genes (Rubin et al. 2000). Similarly, a comparison of the predicted proteins of yeast and *C. elegans* suggested that "most of the core biological functions are carried out by orthologous proteins [. . .] that occur in comparable numbers" (Chervitz et al. 1998, 2022). Thus, it seems that most organisms share a substantial number of molecular mechanisms that are evolutionarily very ancient. At the molecular level, evolutionary history is "one of new architectures being built from old pieces" (Baltimore 2001, 816).

When the first draft of 94% of the full DNA sequence of the human genome was published in February 2001, biologists expressed surprise that humans contain only about 30,000–40,000 genes (International Human Genome Sequencing Consortium 2001, 860). This is only twice as many as in *C. elegans* or *Drosophila*, suggesting that the additional complexity of human beings is due to more complex interactions between genes, rather than a substantially larger number of genes. Human genes also appear to encode a larger number of proteins than worm or fly genes because of a mechanism known as "alternative splicing."[18] However, there appear to be few protein domains (functional modules of proteins) in humans that are not found in any of the major model organisms.

Thus, in the postgenomic age, biologists are dealing with a universe of genes, proteins, and protein domains many of which are present in a great

variety of organisms. A recently formed "Gene Ontology Consortium" writes: "Where once biochemists characterized proteins by their diverse activities and abundances, and geneticists characterized genes by the phenotypes of their mutations, all biologists now acknowledge that there is likely to be a single limited universe of genes and proteins, many of which are conserved in most or all living organisms" (Ashburner et al. 2000, 25).

Most, if not all, human genes have orthologs in other organisms. Therefore, understanding the role of any of these genes in model organisms can shed light on the function of the corresponding human genes. Biologists use the term "functional annotation" for this procedure, because it involves the ascription of biological functions to DNA sequences.

In order to see how the knowledge obtained from studying mechanisms in model organisms is relevant to other organisms, it is helpful to remember that biological mechanisms are often embedded in a *hierarchy* of mechanisms (Craver 2001; Craver and Darden 2001; Weber 2001c). For example, consider the neurological mechanism of long-term potentiation (LTP). This designates long-lasting changes in the readiness of neurons to transmit signals to neurons to which they are connected. LTPs are thought to be involved in learning and memory. The mechanism is part of a hierarchical structure of mechanisms that includes the basic mechanism of neural transmission (action potentials, see Section 2.1) at the next lower level and neural circuits at the next higher level. LTP operates in some very simple neural systems such as those of the sea snail *Aplysia* or *C. elegans*, as well as in the extremely complex central nervous systems of the mouse or humans. This means that a mechanism that has been elucidated in some simple model organism can be transferred into an explanatory structure for a more complex process in another organism. In other words, the basic mechanism of LTP could be worked out in *Aplysia*, where it is embedded in mechanisms such as the conditioned gill-withdrawal reflex. But the same (or almost the same) mechanism is also part of much more complex mechanisms in mammals, namely mechanisms that are involved in learning and memory.

It thus seems that biological mechanisms have a *modular structure*. The mechanisms of neural transmission or LTP are modules that can be part of different mechanisms of varying complexity in different organisms. The mechanisms or modules at the bottom end of the hierarchy are present even in the simplest organisms, whereas the mechanisms at the top end – such as memory and higher cognitive functions – are only found in more complex ones. Biologists have knowledge about a growing store of such modules out of which theoretical explanations of various biological processes can be assembled. Most of these modules have been investigated in model organisms.

The view of biological explanations as sets of modular mechanisms that can be assembled into hierarchies of different complexity can give us some hints as to what kinds of processes can be fruitfully studied with the help of model organisms. Since the mechanisms at the lower levels of the explanatory hierarchies (for example, the basis mechanism of neural transmission) appear to be phylogenetically strongly conserved, it does not matter much in which organism they are studied. For these mechanisms, biologists can choose the organisms that offer the most experimental resources. By contrast, the mechanisms at higher levels of the explanatory hierarchies are generally less conserved; they operate mainly in the more complex organisms. For these mechanisms, the value of model organisms is probably more limited.

To give an example, de Bono and Bargmann (1998) have described a gene from *C. elegans* called *npr-1* that explains some natural variation in the feeding behavior of the worm (discussed in Schaffner 2001, 205–207). Worms that have one variant of the gene feed socially, whereas carriers of a different allele are solitary foragers. Interestingly, there is an orthologous gene that codes for a receptor found in the human central nervous system (neuropeptide Y receptor). However, it is unlikely that that this finding has any significance for explaining human feeding behavior. It is much more likely that this receptor has a more general function in the human nervous system, a function that has nothing *specifically* to do with whether people prefer to eat alone or in large dinner congregations. In other words, in humans the *npr-1* homolog is probably embedded in a neurological mechanism more complex than that in *C. elegans*.

An even more striking, but similar example was provided by Barr and Sternberg (1999). The *lov-1* gene from *C. elegans* is necessary for male mating behavior. The closest human homologues for *lov-1* are *PKD-1* and *PKD-2*, which are kidney disease loci. As such, they are unlikely to be involved in human male mating behavior (I hope I will not be proven wrong on this one). Both the *npr-1* and *lov-1* genes seem to code for receptor molecules that are coupled to cellular signal transduction mechanisms. This suggests that, in terms of the lower-level mechanisms, these proteins perform a similar function in both worms and humans. However, these lower-level mechanisms are probably embedded in quite different higher-level mechanisms in humans, which limits the extent to which the worm is a good model for studying humans.

To conclude, model organisms play different epistemic roles in biological research, only some of which involve extrapolations or inductive inferences from a model organism to a different organism. By placing the knowledge obtained with the help of model organisms in an appropriate

comparative–evolutionary framework, extrapolations in the sense of inductive inferences to other organisms are possible and can be reasonably sound. However, such inferences seem to serve mainly for giving us confidence in the *generality* of certain biological principles such as, for example, the genetic code. The main roles of model organisms for illuminating the biology of *specific* organisms – such as humans – are distinct from their role in providing a basis for inductive inferences. Namely, model organisms provide *research materials* (e.g., cloned DNA fragments) and valuable information that are useful for research *directly* on the organism in question. Cloned DNA fragments can be used to isolate genes from other organisms. Comparing DNA and protein sequences with orthologous sequences with known functions, as determined by research on model organisms, can be used for *functional annotation* of genomic DNA sequences, for example, the human genome sequence. Furthermore, specific mechanisms can be studied in model organisms because they are phylogenetically conserved. This is possible because of the modular structure of biological mechanisms, which can be assembled into hierarchies of mechanisms of different complexity. Mechanisms located at the lower levels of this hierarchy tend to be more strongly conserved phylogenetically, and they can be embedded in higher-level mechanisms of varying complexity that are less conserved. This limits the extent to which simple organisms can serve as "models" for more complex ones.

SUMMARY

Experimental organisms such as the laboratory fruit fly *Drosophila melanogaster* play a central role in biological research. In this chapter, I have examined how the fly was transformed from an experimental organism for classical genetic analysis into a model organism for molecular biology, in particular the molecular basis of development. This transition required recombinant DNA technology, which was developed in the 1970s using *E. coli* and bacteriophage. I have shown that, in addition, classical mapping methods and the material resources of traditional *Drosophila* genetics also played an important role. These methods were combined with recombinant DNA technology for the molecular cloning of some *Drosophila* genes that had been implicated in the genetic control of development.

In order to analyze this case, I have first tried to apply the general framework developed by Robert Kohler, who has brought an economic and technological perspective into the historical study of experimental organisms. On such a view, *Drosophila* was transformed from being an instrument for producing

genetic maps into an instrument or tool for producing specific cloned DNA fragments. I have then argued that the view of lab organisms as "instruments" or "technological artifacts" is metaphorical and, therefore, of limited value. Instead, I have proposed that there is an important mode of experimentation in biology, namely *preparative* experimentation. This kind of experimentation involves the production of research materials and knowledge about these materials that are required for controlled biological experiments. The great value of laboratory organisms for biological research can be explained by the cumulative character of preparative experimentation. Furthermore, I have argued that economic terms such as "production" or "resources" are not metaphorical in the present context; however, their explanatory scope is limited. Specifically, these concepts fail to illuminate the *epistemic* roles that experimental organisms play.

Finally, I have examined what can be learnt from studying model organisms. The generality of biological knowledge that was obtained by studying model organisms can be established on evolutionary grounds by a special kind of inductive argument. However, model organisms are not just useful for providing a basis for such extrapolations or inductive inferences; they have additional functions in biological research. Namely, they can provide research materials and valuable information (e.g., DNA and protein sequence information) for research directly on other organisms such as humans.