The Concept of the Gene in Development and Evolution

Historical and Epistemological Perspectives

Advances in molecular biological research in the last fifty years have made the story of the gene extremely complex. The gene has become a curiously intangible object, defying any straightforward definition. Relating the gene as a molecular biological unit to the gene as a Mendelian factor produces internal inconsistencies; but genes have been deeply elusive entities even within the traditional Mendelian framework. Philosophers, historians, and working scientists approach the issue from a variety of perspectives. This volume provides evidence of the diversity of scientific disciplines that presently have a stake in the quest for the gene.

The essays collected here offer challenging perspectives on some of the most fundamental concepts of twentieth-century biology. Conceptual perspectives about the gene as it is presently known provide the substance of three contributions. The examination of pre-Darwinian heredity concepts, Goldschmidt's demission of the gene, and Seymour Benzer's work on the fine structure of the gene are also explored. A critique of the "genetic program" is presented as well as modern findings about the functioning of "master genes" during embryogenesis. In the final essay, Raphael Falk reviews the material laid out in this volume and lucidly summarizes the primary themes.

The Concept of the Gene in Development and Evolution is unique in that it is the first interdisciplinary volume solely devoted to the quest for the gene. It will be of interest to professionals and students of philosophy and the history of science, genetics, and molecular biology.

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Introduction

Everybody knows about genes. One can read about them in the press. Often we are told that genes are selfish and help themselves rather than the bodies they are housed in. Genes play their role in the nature/nurture debate and in health care. Also, there is an urgent need to conserve the biodiversity around us for future generations that has, of course, to do with genes. There is a big science industry of genome sequencing that is an inventory-taking of all of man's (and other organisms') DNA. Darwin searched a lifetime in vain for the hereditary units, and indeed, genes are indispensable in modern Darwinian evolutionary theory. Early this century, genes were inferred from the Mendelian behavior of traits. The year 1953 marked a breakthrough when Watson and Crick disclosed the double-stranded helical structure of DNA. This suggested an elegant explanation of how genes could replicate themselves from one generation to the next but also serve the purpose of building an individual organism in each generation. Henceforth, the gene came to be viewed as a piece of DNA that coded for a protein or, more generally, a functional or structural product. Genes were seen as inviolable messages passed down the generations (save for occasional mutations) and as the ultimate causal factors lying behind development. Once, these findings were considered evidence for one of the most successful research strategies in the life sciences during the first half of the twentieth century.

Molecular biological discoveries over the last fifty years have made this story vastly more complicated in the details. Somewhat detached from the gene as a public icon, but also unknown to many biologists, these new findings have caused a watershed during the

last few decades. The more molecular biologists learn about genes, the less sure they seem to become of what a gene really is. Knowledge about the structure and functioning of genes abounds, but also, the gene has become curiously intangible. Now it seems that a cell's enzymes are capable of actively manipulating DNA to do this or that. A genome consists largely of semistable genetic elements that may be rearranged or even moved around in the genome thus modifying the information content of DNA. Bits of DNA may be induced to share in the coding for different functional units in response to the organism's environment. All this makes a gene's demarcation largely dependent on the cell's regulatory apparatus. Rather than ultimate factors, genes begin to look like hardly definable temporary products of a cell's physiology. Often they have become amorphous entities of unclear existence ready to vanish into the genomic or developmental background at any time.

Indeed, we are thrown back into a position where we must renew the Socratic question, *What are genes?* It has frequently happened in the history of the sciences that basic concepts became so engrained and all-encompassing that their meaningfulness tended to decline. Today, who would seriously ask, What is life?, or, What is protoplasm? But the case of the gene seems to be in a different category, at least when viewed from the present perspective; and this provides the grounds for the present volume. Nearly all modern textbooks on molecular genetics show their authors' implicit awareness that there is a new (if not outrageous) issue of genes. Though it has been dealt with explicitly in more specialized journals by historians, philosophers, and working scientists as well, the issue has not been brought sufficiently into the open and probably has not received the attention it deserves from a broader audience. We want to provide a timely remedy to this situation by devoting a whole volume to the gene as a hot spot of issues. This volume, then, focuses on the gene and its difficulties as a subject of the sciences, not on the gene as a public icon. Though there is no longer any standard view of the gene, our undertaking is not iconoclastic. Far from destroying the image of the gene, this volume attempts to treat the gene as a focal point of interdisciplinary research.

The contributions to this volume have been arranged under four headings: In the first section the notion of genes in relation to traits

and the tension this relationship has engendered is discussed. Fogle re-examines the present molecular condition of the gene. He argues that it is impossible to bridge the gap between the gene as a molecular biological and as a Mendelian unit without producing internal inconsistency. Yet, some consensus definition of the gene may be reached within the molecular sphere by comparing patterns of biochemical architecture of actively transcribing DNA regions. Fogle reviews at some length the possibilities and heuristic limits of such a consensus. Schwartz and Gifford show that even within the traditional Mendelian framework genes have been in a sense deeply elusive entities: Because genes interact it is often impossible to specify which trait is caused by a particular gene. However, a phenotypic difference between individuals resulting from gene mutation usually can be traced back to the alteration of the single gene in question. Schwartz shows that already Morgan had a keen awareness of this problem and she develops some of the consequences of this insight. But even the construal of a gene as that which "makes a difference" is bound to reintroduce ambiguities because the expression of such differences is also environmentally – and therefore often population – dependent, as shown by Gifford.

We readily speak of the new issue of the gene, but it is not easy to trace its original sources. New insights also color the past, and in retrospect, a continuity of problems extends backward into the past. The second section contains the bulk of the historical contributions. Gayon traces the concept of heredity in a broad sweep from pre-Darwinian days, when it was seen as a magnitude, through its structural and particulate phase into the molecular biological dissolution of the gene. But he reminds us that even in the most convoluted cases of molecular biological gene editing it always must be true that a material structure is preserved from one generation to the next to provide the material basis for the existence of such a process. This, even Goldschmidt would not have denied. Dietrich gives an historical account of Goldschmidt's demission of the gene more than half a century ago. Yet in view of the new molecular findings this account reveals a remarkable modernity in Goldschmidt's thinking. Holmes reexamines Seymour Benzer's work on the fine structure of the gene in the bacteriophage T4 of *E. coli* at the end of the 1940s and during the 1950s. Shortly after Watson and Crick established their DNA

model in 1953, Benzer showed that the units of mutation, recombination, and function, all of which had been used previously to identify genes, were not coextensive in terms of DNA. With hindsight, then, the evidence provided by Benzer may be taken as a proof that there never was an unambiguous definition of the gene in terms of DNA.

The third section deals with questions of genes in development. Keller shows in a focused analysis how in the 1960s – largely as a consequence of the singling out of DNA as the genetic material – the notion of a developmental program was reduced to that of a genetic program. In contrast to this reductionist bias toward genetics, the last two decades have witnessed the unprecedented discovery of highly conserved "master genes" that make sense only in the realm of development. Such developmental genes control similar aspects of body structure across diverse phyla of the animal kingdom. Against this background, Gilbert puts forth an embryologist's perspective on the differences between the classical gene of neo-Darwinian thought and the reasserted developmental gene, while Morange gives a survey of the history of these recent findings. The conclusions are of a notable harmony: Master control genes do not exist independently but only as part of a highly complex regulatory network manifest in development (Gilbert); it is possible that they do not control anything and are no more than a response of molecular components to local configurations when used to build organisms (Morange); but even the whole developmental program lacks a specific location: As an entity it is "everywhere to be found" (Keller in a footnote). Where then are the genes?

In the fourth section, thoughts are presented on the conceptual prospects of the gene in view of the present impasse. Rheinberger, in a countermove against overzealous attempts toward integration, makes a virtue of the gene's fuzziness. In a short historical discourse he argues that it was the gene as a boundary object within a set of biochemical practices that ensured the spectacular success of molecular biology in this field, and so we should rather try to understand why fuzzy concepts work so well. Griesemer makes the novel and unique attempt to reduce genetics to development rather than the other way around. In the process, he introduces a variety of not-yet-familiar concepts that defy any short description (read the pa-

per!) and pursues various novel avenues of thought. One of the important upshots is that it is the stability of reproduction processes that causes the invariance in genetic coding and of genes rather than the other way around. Beurton argues that it is differences among individuals that bring genes into being. According to him, natural selection, in the process of working on adaptive differences among individuals, leads to a precipitation of genic structures in otherwise continuous DNA strings. If genes are secondary products of organisms as can be distilled from Griesemer and Beurton, this may also provide a powerful argument against genic reductionism.

The present state of the gene does not allow for a fully integrated story at the end. The final review by Falk is a one-man attempt at retelling this open-ended theme by picking up once more some of the threads laid out in this volume. It might be helpful for gaining some access to this diversity to read Falk's essay first. This volume is an interdisciplinary probing of perspectives on the gene by philosophers, historians, and working scientists. As editors we have been pluralists, though not necessarily in how each of us handles the gene in his own contribution; here differences will be discerned. Most of the contributions bristle with potential cross references, but we preferred not to press the authors very hard to be explicit. Cross referencing depends crucially on any one individual's own predilections, and more explicitness in this respect would have meant less suggestiveness and may also lower the exploratory initiative of the reader.

Books also have their own causes. This volume is the outcome of a project that was set up when the Max Planck Institute for the History of Science was founded in Berlin in 1994. Due to the initiative of the founding director Jürgen Renn and of Wolfgang Lefèvre, who constituted the bulk of the institute's personnel in the early days, a workshop on "Gene Concepts and Evolution" was organized in early 1995, and a second one on "Gene Concepts in Development and Evolution" for the fall of 1996. (We are grateful to Renn and Lefèvre for this original stage-setting.) All contributors to this volume participated in at least one of these workshops, and together, these workshops provided the indispensable intellectual setting and impetus for what followed. (The workshop material was made avail-

able to a broader audience in nos. 18 and 123 of the Institute's Preprint Series.) Yes, we set up these workshops because we wanted to produce a book on genes. It is a major part of this institute's trade to examine fundamental concepts in the sciences.

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