PROMISES AND LIMITS OF REDUCTIONISM IN THE BIOMEDICAL SCIENCES

Edited by

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Preface

This volume contains the presentations made by scientists and philosophers of science at the Philippe Laudat Conference on 'Promises and Limits of Reductionism in the Biomedical Sciences', held at the Abbey of Royaumont, north of Paris, on 22–24 May 2000. Several Philippe Laudat Conferences (laudat@tolbiac.inserm.fr) are organized yearly by INSERM (the French Biomedical and Health Agency). The aim of the present Conference was to have scientists and philosophers discuss both the merits of reductionism as a useful research methodology and the limits of reductive explanations in molecular biology, genetics, evolutionary psychology, and in the practice of medicine. Particular attention was given to the alleged social implications of the Human Genome Project. The presentations were followed by several Round Table Discussions and the transcripts of these discussions are also included in this volume. This will give the reader a flavour of current debates between reductionists and anti-reductionists regarding the appropriate level of analysis of complex integrated biological systems.

Marc H. V. Van Regenmortel

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About the Editors

Marc Van Regenmortel was for 20 years Director of the Immunochemistry Laboratory at the CNRS Institute of Molecular and Cellular Biology, in Strasbourg, France. Educated in Brussels, Belgium, he received his PhD degree (1961) in virology from The University of Cape Town, South Africa, and has held professorship appointments at several universities in South Africa and France. The author or editor of 14 books in virology and immunochemistry, he has published over 350 scientific papers and reviews. He is editor-in-chief of *The Journal of Molecular Recognition* and of *Archives of Virology*, an executive editor of *Analytical Biochemistry*, and serves on the editorial boards of seven other journals. He was for nine years (1990 – 1999) Secretary General of the International Union of Microbiological Societies, and for three years (1987 – 1990) chairman of its Virology Division. Since 1996, he has been the President of The International Committee on Taxonomy of Viruses and is currently an emeritus director at the CNRS in The Biotechnology Institute of The University of Strasbourg.

David L. Hull received his PhD degree in 1964 from the Department of History and Philosophy of Science at Indiana University, in Bloomington, Indiana. He taught first in the Department of Philosophy at The University of Wisconsin-Milwaukee for 20 years, and then in the Department of Philosophy and the Program in History and Philosophy of Science at Northwestern University, Evanston, Illinois, for 15 years. While at Northwestern University, he occupied the Bertha and Max Dressler Chair in Humanities. He is currently emeritus professor in the Department of Philosophy at Northwestern University. He has been President of The Philosophy of Science Association (1983–1984), The Society of Systematic Zoology (1984–1985), and The International Society for the History, Philosophy and Social Studies of Biology (1991–1992). He is a Fellow of the American Association for the Advancement of Science, a member of The American Academy of Arts and Sciences, and a past member of The Sub-Committee on Scientific Conduct of The American Academy of Sciences. He has published nine books and over a hundred papers, and beginning in 1985, he has edited 40 books for The University of Chicago Press in their *Series on the Conceptual Foundations of Science*.

Chapter 1

Introduction

David L. Hull and Marc H. V. Van Regenmortel*

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The authors in this anthology agree with each other on some very basic issues. First, in the developed world 'Reductionism Rules'. Scientists who use reductionist methods predominate in raw numbers, publish the most papers, are cited the most frequently, get the most grant money, etc., while more holistic scientists are increasingly shut out. For example, the University of Leiden recently closed five of the nine research groups in its Institute for Evolutionary and Ecological Sciences. Whether or not one thinks of these closures as an instance of the unfortunate effects of reductionism on science, depends on one's view of evolutionary theory. Is evolutionary theory a bulwark against reductionism, or is it itself reductionist to its core? Contributors in this anthology represent both sides of this dispute.

A second point on which the authors in this anthology agree is that reductionism, as successful as it has been on a host of counts, is seriously inadequate. It must be *supplemented* with more holistic science. To understand nature in all its vicissitudes, methods from the most reductionist to the least reductionist must be used. Hence, anti-reductionists are forced, like it or not, to advocate pluralism. For example, Robert Williams concludes that 'We must not despise reductionism. However, it has to be put in a proper perspective'. Too often reductionism and anti-reductionism are presented as if they are in diametric opposition when all that separates them is degree of emphasis. As Alfred Tauber observes, 'reductionism' and 'holism' cannot be defined in isolation from each other. An unsteady balance exists between the two. 'Holism and reductionism are inexorably coupled and cannot be defined independent of each other'. As a result, like so many other contributors to this volume, he embraces a 'pluralistic approach'.

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Some of the more enthusiastic reductionists disagree. As they see it, reductionism is the only game in town. Their message to their fellow scientists is either get on the bandwagon or be left behind. Calls for pluralism simply show how feeble the alternatives to reduction have become. Anti-reductionists would not be calling for pluralism if they had any chance of winning. Pluralism is the last resort of losers, at least so claim the more enthusiastic reductionists. Dorothy Nelkin quotes a whole series of such exuberant pronouncements by reductionists: behavior is to be reduced to cell biology, beliefs are chemical events in the brain, and genes can be found for everything from alcoholism to heterosexuality. How literally we are to take the claims made by reductionists is not always easy to tell.

Philosophers and scientists: pooled resources

In the past, philosophers have expressed their views on reductionism, whether pro or con, in terms of the traditional philosophy of science, the sort of philosophy of science that arose in the works of Sir John Herschel and continued to at least Carl Hempel. Philosophers working in this tradition acknowledge numerous differences of opinion on philosophical issues, but they tend to address the same sorts of problems and produce variations on the same variety of themes. As Claude Debru remarks, the terms which were used in the 'nineteenth century discussions remain the ones which we use now'. For example, philosophers in this tradition tend to view science in terms of the 'wedding-cake model' and interpret reductionism as a relation between laws and theories (see Alex Rosenberg and Kenneth Schaffner). However, philosophers within this tradition can be found arrayed on both sides of the dispute over reductionism. They accept the general outlook of the traditional philosophy of science, but some conclude that reductionism is a viable position while others conclude that it is not. In this anthology, those authors who rely most heavily on traditional ways of carrying out the philosophy of science nevertheless reject reductionism. Hence, accepting the methods of traditional philosophy of science does not automatically make one a reductionist, or worse yet, a 'positivist'.

Philosophers are not the only ones who have involved themselves in the dispute over reductionism. From the first, scientists have also joined in the fracas. In fact, throughout its history, both scientists and philosophers have made major contributions to the philosophy of science. The two groups have pooled their conceptual resources. This arrangement has not always run smoothly. Scientists can be found huffing that 'philosophers of science would not talk such nonsense if only they got their hands dirty and learned a little science', while philosophers can be found reminding

scientists that the dispute over reductionism is a philosophical dispute. Debru, in his brief history of the transition from nineteenth century ideas on reduction in physiology to non-reductive explanations in twentieth century biochemistry, complains about how molecular biology has been parodied. After all it is molecular biologists who have shown that biological molecules are 'not only very complicated molecular machines', but also the 'results of the whole history of life'. So the 'quarrel of reductionism which is raised by some philosophers against molecular biologists is entirely unfair'. Stanley Shostak warns of philosophers 'bearing gifts'. Rosenberg concedes that biologists are 'unlikely to be interested in philosophical disputes about the nature of explanation', but regrettably 'they have to be, if they wish to decide intelligently about whether to embrace reductionist or non-reductionist methodology'.

The contributors to this anthology present an appropriate balance between science and philosophy. Several papers include extensive discussions of particular areas in science, showing the difficulties of possible reductions. For example, Marc Van Regenmortel examines the immune system in great detail to show how far reductionist modes of explanations can be extended and why they are not sufficient. Constructing one-dimensional profiles that allow the prediction of successful antigenicity rarely exceeds a 60 % success rate, while the approximate location of binding sites in the folding protein is achieved in only about 50 % of the cases. Schaffner explains how overly simple views of molecular biology led early philosophers to reject reductionism – the relation between Mendelian genetics and molecular biology are many–many. However, as molecular biology developed, the apparent simplicity of molecular mechanisms gave way to mind-boggling complexity. Schaffner describes attempts to deal with this complexity that rely on genetic chip technology. However, 'genes and mRNA levels are too indirect a measure of the phenotype, which is where the action is', and concludes that the initial focus on DNA and genetics has been misleading. Biological activities and interactions take place not at the level of genes but at the level of proteins, including post-translationally modified proteins. The rise of 'proteomics', which is the study of the expression and function of proteins in different biological contexts, is a clear indication that scientists have realized that they need to move beyond genetic reductionism.

One important point of disagreement among reductionists and anti-reductionists concerns 'emergent' properties. The latter are properties possessed by a complex whole but not by its parts. Van Regenmortel lists a whole series of emergent properties. First on his list is the viscosity of water. Water is viscous, while individual molecules of water have no such property. The issue is which emergent properties can be explained in terms

of their constituent parts, including their relations, and which cannot. Water is about as simple a molecule as one is likely to find. If it withstands reductive analysis, then one need not worry about proteins and molecules of DNA. The record here is mixed. Williams argues that on the basis of quantum theory, we can provide a complete explanation of the structure of water in its gaseous phase, but not in either of its condensed phases. Thus, none of the properties of water vapor are emergent, regardless of what people thought in the past, but some, if not all, of the properties of liquid water and ice may turn out to be unreducibly emergent. The message is that deciding which properties are emergent and which are not is far from easy. Debru tells a comparable story for hemoglobin. However, it is clear that a melody arising from notes, the salty taste of sodium chloride and the antigenicity of a protein are emergent properties.

Function, selection and laws of nature

One difference between reductionists and anti-reductionists is that reductionists tend to express their position in terms of processes and laws, while anti-reductionists prefer to talk of mechanisms and systems. On the 'wedding-cake model', phenomena at various levels are related by inference – laws at higher levels are deduced from laws at lower levels. Complex systems to the contrary are made up of parts. Deriving a higher-level generalization from a lower-level generalization is not the same thing as dividing a whole into its parts. Evolutionary theory deals with various processes, e.g. the influence that population size has on the rapidity of evolutionary change. However, it also deals with structure, e.g. population structure. For anti-reductionists finding out how the machinery works is explanatory in and of itself, even in the absence of a knowledge of the process laws governing this machinery.

As Van Regenmortel observes, in contrast to 'reductionists who emphasize causal explanations, anti-reductionists favour functional and selectionist explanations for biological phenomena'. Anti-reductionists emphasize structures and their emergent properties. Among these structures are functional systems. The latter are not only systems, but the peculiar way in which they are individuated provides an additional barrier to reduction. Functional systems are currently defined in two ways – as Wright functions and as Cummins functions. Wright functions (Wright, 1976) are delineated in terms of descent via selection processes. They are naturally selected effects. As both Van Regenmortel and Rosenberg remark, natural selection for adaptations is 'blind' to differences in physical structure that have the same or roughly similar effects. Hence, no regularities relating structures can be found in functionally defined systems. Any laws must relate functions, not structures.

One additional complicating factor is that organisms seem to exhibit many fewer functions than structures. This asymmetry may be due to the emphasis that biologists have placed on structures in the past, or it may reflect a fundamental difference in the living versus the non-living world. In any case, the presence of functional explanations in biology and the analysis of 'function' in terms of selection 'makes biology an essentially historical discipline' (Rosenberg). Just in case anyone might think that functional explanations are reserved only for higher levels of analysis, Rosenberg presents a functional explanation entirely in the context of molecular biology.

Reductionists couch their explanations in terms of processes. One problem with reductionism is that the old positivist notion of laws of nature has fallen on hard times. It has never seemed all that appropriate for biology anyway. In fact, numerous biologists and philosophers of biology have argued that biology has no laws. If laws are as central to our understanding of the external world as positivists have supposed, this is a damning conclusion. As a result, several biologists and philosophers of biology have argued that once the notion of a law of nature is freed from certain simplistic assumptions, biological laws do exist, e.g. the basic principles of selection (see Sober, 1993 and Rosenberg in this volume). Others agree that there are no biological laws but that is all right because there are no laws in physics either! Even the most fundamental laws in physics require all sorts of provisos, including *ceteris paribus* clauses. Even these laws apply only to the most fundamental and general characteristics of natural phenomena. We take laws governing planets as seriously as we do because they are special instances of more fundamental processes, i.e. the relation between masses as such. Of course, as general as these laws may be, we humans can solve them for only three, possibly four bodies at a time.

Van Regenmortel objects to linear reductionistic causal laws in which one factor is singled out and given undue weight as *the* cause when all the various factors play a role, frequently a necessary role. Van Regenmortel, Steven Rose and Kenneth Schaffner take issue with the claim that genes are self-replicating molecules. Van Regenmortel objects that genes 'provide information only in the context of other genes and they are expressed only in the context of a particular cellular, extracellular and extraorganismic environment. Genes certainly do not act alone and they are not even self-replicating'. Rose agrees. 'One of the central features of DNA as a molecule is that it cannot simply and unaided make copies of itself; it cannot therefore ''replicate'' in the sense that this term is usually understood . . . What brings DNA to life, so to speak, is the cell in which it is embedded' (see James Griesemer and Schaffner for similar objections).

Of course, no one would object to any of the preceding claims about DNA. They can be found in any introductory textbook. However, there are two issues with respect to self-replication: the warrant for selecting one part of the complex story and terming it *the* cause and the connotations of the term 'self-replication'. Although numerous factors play a role in any causal situation, frequently we select one as the cause and demote all others to supplementary conditions. For example, one afternoon I come home from work and find my house burnt to the ground. I might ask, 'What caused my house to burn down?'. To be told that oxygen did it would be clearly wrong-headed. Of course, oxygen is a necessary part of the entire story. So is the fact that my house is built of flammable material, has no sprinkler system, and on and on. However, if a space heater set some curtains on fire, I want to know about that. It was the cause of the fire. An insurance broker may nevertheless want to argue that I caused the fire by keeping the heater on and placing it too close to the curtains.

Perhaps the message of the 'self-replication' objection is that scientists must always give complete explanations all the time. Quick, shorthand references are never good enough. Another message is that 'self-replication' carries inappropriate connotations. For example, one of the most common examples of self-replication is photocopying machines (see Griesemer). A page is copied, this copy is copied, and so on. However, it seems strange to refer to this process as 'self-replication' because all of the work is being done by the machine. The paper copies are almost incidental parts of the process. The message for the self-replication of genes is that reference to the relevant developmental machinery is being omitted (see Schaffner). One response to the above arguments is that in both cases all of the machinery was devised to fulfill one purpose – passing on information via copies – and it is this information that is crucial to selection processes.

Even if one is willing to accept as laws of nature the sort of hedged bets that we find in both physics and biology, a difference remains between the two. With respect to quite a few of the most general laws in physics, only a very few additional assumptions need to be made. We know what they are and how to take them into account. Comparable laws in biology are noteworthy by their absence. Too many factors matter, and they vary too rapidly and in too many different ways. Reductionist explanations in terms of a single causal factor are thus singularly deficient in biology.

History, selection and laws of nature

One commonly hears that biology is fundamentally historical in a sense missing in physical phenomena. Of course, both biological and purely physical processes have histories. Just as paleontologists reconstruct phylogeny,

cosmologists reconstruct the history of planets, star systems, and even the entire universe. All of these activities are equally historical in the sense that historical reconstruction is central to the activity (see Rosenberg).

A second source for the conviction that biology is historical in a sense different from physics is a deep and pervasive misunderstanding about biological taxa such as Vertebrata and *Homo sapiens*. Until quite recently, everyone has treated biological taxa as beings kinds of some sort. Just as gold consists of all the atoms with the atomic number 79, trumpeter swans have certain sorts of feathers, eggs, and mating calls. Although it has taken a while, biologists have finally recognized the implications of evolutionary theory for biological taxa. The latter as monophyletic groups diagnosed by homologous characters are not classes like electrons or substances like gold, but historical entities. They are historical entities in that they have a beginning in time, survive for a while and then become extinct, never to recur. However, in this respect they are no different from purely physical historical entities like the Earth or Alpha Centauri. Biological taxa seem to pose problems for biology only if one puts them in the wrong metaphysical category.

However, biology does differ from physics in one very fundamental way, i.e. the crucial role that selection processes play in biology. In response to our changing understanding of biological taxa, those who want to argue that laws can be found in biological phenomena move up a level from biological taxa to kinds of taxa, e.g. peripheral isolates. According to one prevalent view in evolutionary biology, small populations isolated at the peripheries of species are the best candidates for the production of new species. All natural phenomena take place in time and in this weak sense have 'histories', but most natural phenomena need not be characterized in terms of these histories. However, in cases of selection processes, histories are crucial. In order for selection to perform the functions that it does in biological evolution, the relevant entities must be related by descent (see David Hull and Rosenberg).

A common device used to explain statistical frequencies is an urn filled with balls of various colors. You take out a ball and see what color it is. You toss the ball back into the urn again, stir the balls and take another ball. As you proceed, you can become increasingly confident that you are discovering the relative frequencies of the balls in the urn. This is not how selection works. Starting at the genetic level, numerous genes of various sorts are produced. These genes proliferate. Only a small percentage of these genes succeed in producing copies of themselves which proliferate in the next generation, and so on. No balls get thrown back in the urn. The genes that do succeed in surviving and reproducing are connected through time. All

phenomena have histories. These histories can be studied, but what makes selection processes 'historical' in a special sense is that they incorporate in their make-up an historical element – replication. Parallel observations hold for the immune system as well. It too embodies a selection process (Van Regenmortel; for a differing view, see Griesemer).

Many aspects of life on Earth are contingent, e.g. that all proteins used by organisms are *levo* rather than *dextro*. However, if biology is to count as science in the sense left over from the early days of philosophy of science (e.g. from Herschel to Hempel), some very fundamental phenomena that are uniquely biological must be characterizable in terms of laws. Of course, these laws need not be 'lawful' in a sense more rigid than comparable laws in physics. *Ceteris paribus* clauses will be necessary. If Newton's laws count as laws only *ceteris paribus*, then we cannot expect more of the basic laws governing selection processes. However, these laws must be very general. Reference to genes is even too particular. All genes here on Earth are either DNA or RNA, but other molecules might well serve this same function. In fact, prions might well turn out to be gene-like molecules already existing here on Earth. In any case, one reason why Dawkins introduced the notion of a replicator is to make sure that selection processes are general enough to incorporate something very much like lawful regularities (for an extensive criticism of Dawkins, see Rose).

Given the requirement that the traditional laws of nature must be spatiotemporally unrestricted and monophyletic taxa are necessarily spatiotemporally localized, then it follows that monophyletic taxa cannot function in laws of nature. This is the reason why there can be no law of the aardvark. Few people would be all that upset about this conclusion for aardvarks, fruit flies and slime molds, but if *Homo sapiens* is a biological species, this conclusion follows for it as well. There can be no laws of human beings qua human beings. Unfortunately, many systems, both in science and outside of science, depend on *Homo sapiens* being a natural kind of some sort. Many of the social sciences turn on discovering 'universals', things that are true of all human beings and only human beings. For example, evolutionary psychologists insist that there is such a thing as the monomorphic mind, a belief that Rose finds particularly puzzling. If human beings evolve the way that other species do, then one should expect the human species to be genetically quite heterogeneous. Hence, it is at least possible for behavioral differences to be in some sense 'genetic'. However, these very biologists turn around and claim that numerous adaptations, such as a fear of snakes, are 'universal'. If so, how did all the genetic variability that surely played a role in the evolution of the human brain somehow get weeded out?

Evolutionary psychology

Several contributors to this volume, especially John Dupré, Rose and Nelkin, set their sights on evolutionary psychology and find it reductionistic of the worst sort. Like Rose, Dupré distinguishes between behavioral genetics and evolutionary psychology and also notes that these disciplines seem naturally antagonistic to one another in that 'evolutionary psychology is officially concerned with the search for human universals whereas behavior genetics is typically addressed to differences between humans'. However, they think that this hostility is largely illusory.

In his paper, Dupré proposes explaining the inadequacy of reductive explanations of human behavior in terms of single factors, in particular those at lower levels of analysis, e.g. explaining the behavior of people at the annual meeting of the Tunbridge Wells Contract Bridge Club in terms of the genes for metabolizing ethanol. Perhaps the effect of ethanol on people may explain some of the behavior in such social groups but not all by a country mile. Dupré reiterates the acknowledgment that for everything that counts as human behavior something must be going on in the nervous system, but such explanations are not always relevant and appropriate even when we have them. As the fire example above indicates, necessary conditions are not always explanatory.

Rose finds evolutionary psychologists scientifically deficient because they misunderstand evolution, development and neural function. He faults them for uncritically accepting the more theoretically abstract formulations of evolutionary theory produced during the modern synthesis. In addition, evolutionary psychologists reason too facilely from these highly abstract formulations to overly specific adaptationist claims. The weakness of such adaptationism is never more apparent than in the treatment of human beings, in particular the behavioral traits of human beings. These connections are not stated baldly in terms of genes coding for a particular behavior but leave room for environmental effects. Genes do not determine, they only dispose, possibly predispose. For example, primates turn out not to be innately fearful of snakes. The first time that a young primate sees a snake, it does not flee in terror. However, primates are predisposed to become afraid of snakes given only minor environmental cues from their congeners. However, Rose finds that these modified versions of gene-based evolution allot too much importance to genes (see also Griesemer). Selection occurs at a wide variety of levels of organization, not just at the genetic level (see also Hull).

Everyone knows that not all traits are adaptations, but Rose thinks that his fellow biologists need to be repeatedly reminded of this fact in order to neutralize their tendency toward adaptationist scenarios. Needless to say, at

least some of these colleagues take offence at being reminded of the obvious. In addition, the distal stories preferred by evolutionary psychologists must be supplemented with the specification of more proximal causes. For example, a distal story can be told for stepfathers killing the children of their new wives more frequently than their own biological children, but more proximal causes such as the complexity of multiple relationships with their attendant economic and social insecurity may be even more relevant. Do rich, well-placed men kill their children, whether biological or adopted, less frequently than poorer, less prominent men? Within these numbers, is there a difference in murder rates between biological and adopted children?

Nelkin provides a litany of unwarranted reductionist claims about the implications of the innate predispositions of human beings to social policy. Most of the most infamous examples occurred in the past, e.g. the implications of craniometry, phrenology and eugenics for immigration and sterilization. However, she also sets out some more recent examples. With the power of hindsight, we can see the effects that reductionism has had on human beings in the past. Present-day examples are frequently not so obvious. Racism and sexism may have distal causes of the sort postulated by evolutionary biologists, but they also have even more significant proximal causes, and Nelkin argues that our attention should be directed at these modifiable proximal causes, in part because they are modifiable. Nelkin concentrates on the most egregious examples of the harm that reductionism has done. If such things as anti-reductionism, holism, pluralism, open immigration policies, the Great Society Programs of the 1960s, the democratic experiment in America which assumes the perfectibility of human beings, nurturing educational programs, a belief in free will and social causes as distinct from individual responsibility, have ever been misunderstood by the general public or done any harm, no one in this anthology mentions it. Reductionism may indeed lead to social problems but so do fundamentalist religions. In order to be properly 'pluralist', must Bible stories be taught in biology courses? As powerful and malevolent as such evolutionary psychologists as Steven Pinker, Leda Cosmides and John Tooby may well be, picture them lined up to do battle with the Taliban.

Reductionism and medicine

Elisabeth Lloyd, Tauber and Schaffner address the issue of reductionism in the practice of medicine. Tauber asserts that a fundamental demand of clinical practice is 'viewing and treating the patient in his biological entirety'. It is unlikely that any clinician would claim otherwise. It does no good

to continue to remove a patient's appendix if he is already 'brain-dead'. Van Regenmortel makes a comparable claim about the immune system. Vaccination is an 'immunological intervention that is meaningful only in the context of the whole organism'. If all of the details of the incredibly complex workings of the immune system are spelled out but no mention is made to the effect that all these mechanisms have on the health of the organism, something desperately important has been left out.

However, Tauber goes on to argue that among the legitimate claims of holistic medicine is that the highest faculties of human beings must also be taken into account – the social, psychological, moral, and even spiritual aspects of human beings. A large percentage of physicians are likely to have some reservations about this higher calling. Such needs might well deserve to be met, but perhaps not by physicians, especially those currently being turned out by medical schools in developed countries. More strongly, given the contingencies of the settings in which medicine is practiced today, patients are lucky if they get their biological needs met adequately, let alone these higher needs. Tauber takes his position to be more than epistemological; it is also a moral imperative. This is how clinicians *should* treat their patients, whether they *can* or *do*.

Lloyd concurs and adds the patient's social entirety as well, citing a series of studies that show that ecological factors also matter, most surprisingly the income gradient of a society. What matters is not simply the difference between the richest and poorest people in some absolute sense, but the relative difference in their own society. People living in a relatively poor society can lead healthier lives than people living in a richer society if the difference between the richest and the poorest in their society is less. What really matters is how much poorer poor people are in a society relative to the richest people. However, Lloyd's later appeal to data drawn from primate studies might lead some to cry 'reductionism'. The human species is unique. No inferences can be made from other species, even primate species, to us.

Schaffner indicates the consequences that recent work in molecular biology has had on our hopes for understanding human illnesses and treating them. For example, genes responsible for cystic fibrosis turned out to have many more mutations than anyone had expected, and some of the genes that were thought to influence this disease did not because of differences in the genetic background of the host. Even though geneticists have discovered two genes related to breast cancer (BRCA1 and BRCA2), how much they increase the likelihood of developing breast cancer in women who have them and how to advise female

patients who have a history of breast cancer is 'mind-numbingly complex'. Genetic knowledge is *knowledge*, but we are a long way from being able to use this information. Our increasing knowledge of the influence of genes on development seems only to replace one set of problems with another.

Disagreements versus differences in emphasis

In intellectual disputes, presenting the views of one's opponents sympathetically is not easy. Parody and defeat is too effective a strategy to reject totally. Dupré takes the debate over genetic reductionism to be:

> *. . . one of the more notoriously sterile exchanges in contemporary intellectual life. Both sides accuse the other of one or other versions of reductionism, and both generally claim that they, unlike their benighted opponents, really acknowledge a rich interactive conception of human life.*

Apart from insisting that he himself advocates a 'subtle and richly interactive conception of human life', Dupré does not go deeply into the intricacies of this debate. Carrying on in this same vein, Debru complains, 'Nowadays reductionism is often used as an insult which is uttered by people from various tendencies who have no real idea of biology, most of the time for ideological, social, or political reasons with little scientific relevance'. Michel Morange also distinguishes between 'simplistic reductionism' and the more sophisticated views being developed by molecular biologists today. It will be obvious that the term 'reductionism' is used in many different ways by the various authors. Shostak in particular uses terms like 'reductionism', 'monophyly' and 'cladistics' in a rather idiosyncratic manner.

The picture that emerges in this anthology is that what at first seems like hopeless disagreements turn out to be differences in emphasis. Everyone acknowledges that genes play an important role in the living world. Without genes, we would be in real trouble. However, certain scientists seem to place too much emphasis on genes, as if they were close to sufficient to understanding everything about living creatures. Reductionistic science is not all bad. It has been responsible for huge strides in our understanding of the world in which we live, but some phenomena do not lend themselves to this sort of investigation and for that reason they are commonly ignored. If reductionist methods won't do the trick, then some investigators conclude that the corresponding phenomena do not exist or are not worth

investigating. The consensus view, however, leads to pluralism: both reductionist methods and a more holistic approach to biological complexity are required, depending on the questions being asked. It is undeniable that both approaches will continue to bring forth valuable biomedical knowledge.

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Chapter 2

Emergent Properties of Biological Molecules and Cells

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Introduction

While in this lecture I do not wish to denigrate in any way the reductionist approach to living organisms, I do wish to explain its limitations. Life, I shall state, is a *property* of a particular combination of dynamic processes involving chemical and energy flow in a confined space. The processes must be co-ordinated by messages between them giving rise to organised activity within structural constraints. Hence, any analysis of it must examine the nature of this property and these accompanying processes to reach an appreciation of what life is. As an alternative, the reductionist might wish to say that understanding of a coded molecule, such as DNA, is sufficient for us to understand life. This impression is given in the popular press by discussing life as being open to understanding through genetic sequences. At times, some scientists of considerable standing use a similar language and under the heading of molecular biology give the impression that through the genome project and a detailed description of molecules we can understand life. The genome project is a reductionist approach but I shall state that no such analytical examination of separated single molecules can be at the correct level of description to appreciate the particular property which is life. As I shall show, it is inadequate in many respects. To repeat: my thesis will be that life is a property of a system as described above and that to date we understand this special type of system poorly. It follows that we need to uncover *a systems description, parallel to the thermodynamics of non-living equilibrated chemical properties*. Let me explain why reduction of such systems to molecular terms is an impossibility.

Promises and Limits of Reductionism in the Biomedical Sciences
Edited by M.H.V. Van Regenmortel and David L. Hull

Molecular chemistry and systems

By about the year 1800, it was realised that all substances were open to quantitative chemical analysis and could therefore be given formulae. It took many years to convince all chemists that these formulae represented the composition of material in terms of atoms. However, through an analytical study of all chemicals on Earth and numerous synthetic procedures it was discovered that there are less than 100 different types of atoms from which all of these substances are made. The simple materials studied at first were found to have formulae based on laws of combining proportions of atoms, for example, water was shown to be, and is, H_2O. This is a remarkable feat of reductionism. Today, its finality is backed by the detailed theory of atomic structure based upon quantum mechanics, which also allows a full understanding of the Periodic Table shown in Figure 2.1. Moreover, quantum theory allows a complete explanation of the structure of the H_2O molecule in the gas phase in terms of forces. Of course, this knowledge about the water molecule is extremely valuable but we must also look further and ask how does the formula of water relate to the properties of water in condensed phases, and then we need to enquire how can we approach the even more difficult descriptions of the compositions and the phases of polymers, alloys and minerals? Unfortunately, even the simple combining laws are not general.

In order to appreciate the physical properties of water and not just its composition, we have to investigate the effects of variables, e.g. temperature and pressure, the energy content of the phases and the disposition of the material in space. Now this is not a study of single molecules but of huge assemblies of molecules in liquids and solids, as well as in gases. The treatment of these properties was developed in functional form from about 1850 to about 1900 when Gibbs formulated equilibrium chemical thermodynamics. In the period from 1900 to 1950, thermodynamics was reformulated as a quantised treatment, and the statistical essence of systems became established. The explanation of the behaviour of water over temperature and pressure ranges (phase diagrams) was then seen to be only possible in terms of *functional variables of systems*, such as free energy, enthalpy and entropy. These contain collective as well as co-operative force properties of large numbers of single molecules. The connections between these functional variables, which are not the properties of isolated molecules of H_2O since the variables are statistical and interactive, allow us to see why water (and similar materials such as NH_3, NO, CH_4, CO_2, etc.) has a melting and boiling point but they are far from providing us with a solution to the problem of why the melting point of water is 273 K and the boiling point is 373 K. The description of the systems is in terms of these

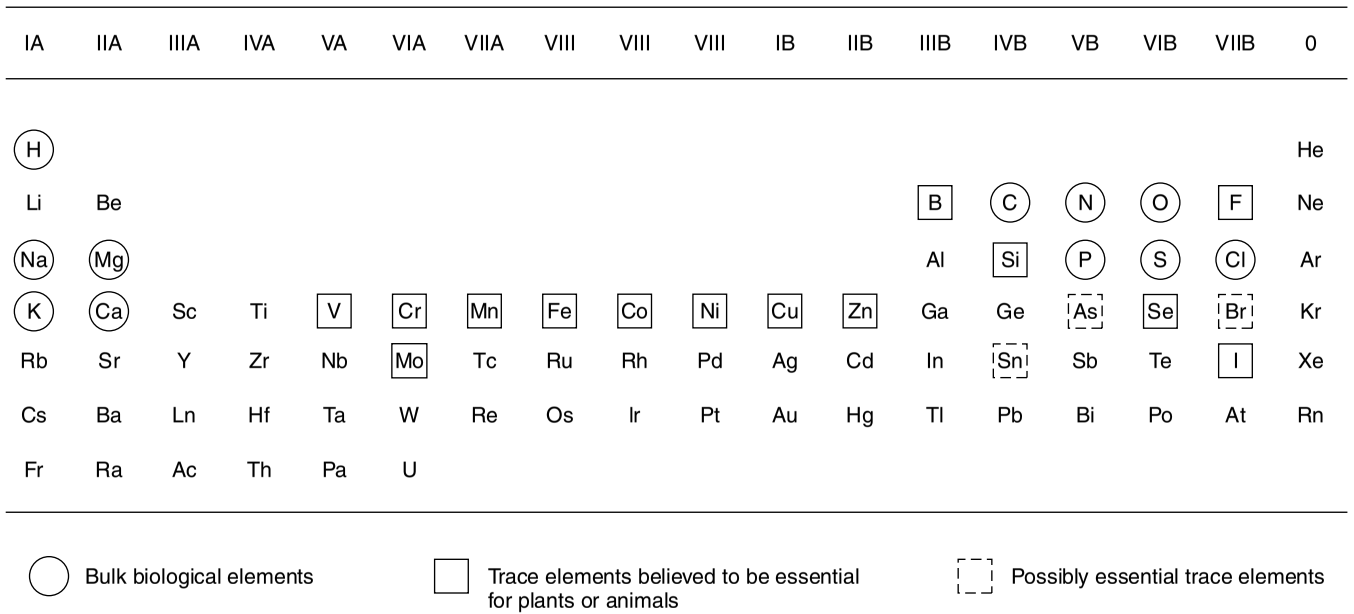

FIG. 2.1. The Periodic Table of the elements, the full understanding of which provides ideally a reductionist approach to the explanation of chemistry. The essential bulk and trace elements for living cells are also shown but knowledge of them is not in any way adequate for an explanation of biology

quantitative functions and is not reducible, even in a complex way, to the properties of single molecules, although in principle we know how to do it. We refer to such properties as being emergent. It is fair to say only that we thoroughly understand water in terms of *systems* variables (ΔG, ΔH, ΔS, ΔC_p, T and p). Notice that one feature of the understanding we desire includes a *knowledge of the environment*, for it is open systems which we wish to appreciate when we study life. The general problem with reductive analysis is then that while in principle all chemicals are understood in terms of atoms, in practice none are fully understood in such atomic or molecular terms in condensed phases due to the complexity of the functions. We note immediately that the properties associated with water and its liquid range were absolutely critical for life to begin and still are so for life's existence today.

The extension of this description to polymers and complicated alloys and minerals is now of great interest, as an understanding of life requires a treatment of very complicated polymer and small-unit mixtures, as well as of water.

All biological polymers, including proteins and DNA (RNA), are made from monomers. If we ignore the structural complexity of the monomers and assume that we understand them completely in isolation, that is we liken them to gaseous H_2O, we can describe a linear polymer as a joined string of such units with random motion about the joints. This is known as a random-coil polymer. The great beauty of these polymers in life is that they are stoichiometric in their atoms, like H_2O, so that the composition of any single polymer is not a variable. Now, the polymers of concern in biological systems also fold into shapes with considerable residual motion of side-chains upon which their properties depend. The unfolding is often called 'melting', since it is a co-operative order/disorder transition, and as such is an *emergent* property of the polymer in water in a given environment. (However, it is probably better described as 'boiling' if the high-temperature state is a random coil.) Polymers such as proteins therefore cannot be described by single structures in any state, except for convenience. (This is the crystallographic approach.) It is then clear that reductionist analysis is not possible where attempts to describe properties of folded proteins or DNA (RNA) are made by force-field calculations starting from monomers. Similar reductionist analysis of folding in terms of monomer properties is bound to fail. The studies of polymers concern the equilibria of mini-phases requiring functional analysis with two added difficulties over the macro-phase studies, as described above. First, the study is in water (and electrolytes), not in isolation, and hence the analysis of the polymer property has to include hundreds of H_2O molecules in free and bound states. All

of the difficulties associated with the description of liquid water given above are involved. Secondly, in describing macro-phases, i.e. conventional phases, the degrees of freedom are assumed to be independent of the size of the (large) system under study so that no account is taken of the relative contribution of the surface. The interior is totally dominant. In the examination of proteins or DNA (RNA), the surface energy is an important part of the stability of any state. Since the surface energy is a separate variable comparable in magnitude with the internal energy, there is one additional variable to include in the phase rule for bulk material. We see that the condensed states of any polymer are difficult to describe, except in terms of functional properties.

Alloy and mineral solid phases are different again since they are generally non-stoichiometric and can exist over ranges of composition. The situation arises even in the crystalline state due to the ease of substitution of one atom for another in a lattice of fixed structure. Some obvious examples are Cu/Zn alloys and silicates. This means that their thermodynamic functions behave as smooth continuous variables with composition, at least over limited ranges, and without points of inflexion. In addition, there may be points of inflexion in these functions as the composition is varied and these lead to the formation of separate phases, i.e. species with idiosyncratic shape and physical properties, such as melting points and boiling points. These are again *emergent properties* of the system, now at a given composition. Note that in all cases the analytical composition is a reductive property to be given in terms of atoms, while other properties of the system can only be analysed functionally. Now many alloys and mineral compositions give similar structures. Given these problems and our knowledge of macrophases, we should not be surprised that many different sequences of proteins give very similar folds, nor that many mutational substitutions of amino acids or bases do not affect folds. The examination of the phase diagrams of such compounds should be undertaken before the study of cells, since the latter are also somewhat variable in composition, although DNA is not. Polymers and cells, i.e. mixtures of chemicals, clearly need very strict functional analysis (ΔG, ΔH, ΔC_p, ΔS, etc.) with variation in temperature, pressure and composition. Once again, the environment of cells like those of the proteins is a major concern, now extended to include water, salts and fields, and affects these variables.

Only against this background can we turn to living cells to examine them as systems. We shall presume that the steps in understanding any chemical system, living or dead, have to be the same, and with the above history of chemistry behind us and the future of biology in front of us, we can state them clearly as follows:

(1) The analytical composition of the system must be known and its degree of variability determined. This is the chemical *composition* variable (see Figure 2.1).

(2) The effects of the systems' environmental physical variables have to be understood in order to appreciate the observed properties. The variables for stationary systems are temperature and pressure, but for biological systems we must include fields and time-dependencies (see below). A cell produces chemicals.

(3) Material and energy input and output are required to be known since the object under study, a cell, grows or develops.

(4) A knowledge of the cells' chemical as well as physical environment is essential as is apparent from (1) and (3) above.

(5) Processes go in well-defined directions spontaneously.

It is clear that an appreciation of *chemical stationary systems* with respect to (1), (2) and (5) is virtually complete as explained above in terms of thermodynamic variables, although the analysis of cells is not, since the equations linking the functional variables are missing. Even if we are sure that the variables are known, we do not know their functional connections.

Turning then to the biological world of interacting chemicals, we should be wise enough to pursue at first the same discipline as that which has led to a satisfactory understanding of chemistry. It is for this reason that the present-day reductive approach has to be followed but it can only yield very limited answers. Subsequently, we wish to understand the emergent property of these chemical systems which is *life*. Before we can understand such a property we need the following:

(1) A full appreciation of composition of a given form of life. *Note* – this may not be very closely knowable. It is not to be found from DNA, RNA or protein content alone but has to be uncovered as a complete analysis of all chemicals. How far is this possible? It has not been carried out for any organisms in a systematic way. To what extent are organisms of variable composition dependent on the environment?

(2) Temperature (300 K) and pressure (1 atm) to be taken as fixed.

(3) Knowing the composition, we need to know the structures that are present. In the first instance this is a matter of the different containers or compartments of the system which we may take as fixed, and can thus let their temperatures and pressures be fixed. Later, we could also allow that internal and external filaments fix the shape of the containers.

(4) Since there is a flux even in the steady state, we need to know the flux of material and energy. Here, we hit very difficult problems but without these flows there is no life, and no development. Since there is flux of energy and material from and to the environment, the system is not open to description in thermodynamic variables alone – we require time-dependencies.

(5) The definition of the system requires a knowledge of the environment, since it is an *open* system. When the system is of comparable size and chemical activity to the environment, then they change together, *inseparably*.

Immediately, we can state that a reductive analysis of life is impossibly difficult. We shall now illustrate the difficulties, which are best seen against an analysis of the simplest cell first, and then from an examination of evolution, not in terms of species, but in some form of systems analysis, which we consider to be the way forward. We start as we must from the simplest property – the composition.

Chemical composition of simple primitive cells

Unfortunately, the analytical composition of what we take to be the simplest cells we know is based on existing anaerobic (archaeic) bacteria. There may well have been many types of such cells existing together. The clearest statements that can be made are the *essential* ingredients of the most primitive cells:

(1) Water is some 80 % of the cell.

(2) A number of essential organic molecules is required and represents more than 15 % of the cell. They are all made from the elements, H, C, N, O, P, S and Se, all of which except phosphorus are in coded form in amino acids. From their simple inorganic forms in the environment they give rise to all DNA (RNA), lipids, saccharides and proteins, and all small molecules participating in their synthesis.

(3) The remaining 5 % includes essential bulk minerals, Na, K, Mg, Ca and Cl, plus essential trace elements, including Mn and Fe for sure, but possibly Ni, Co, Mo(W) and a small amount of Zn (see Figure 2.1). The failure to understand trace element absolute requirement is a major gap in our appreciation of life as a system.

All of the above essential elements, in non-stoichiometric and maybe somewhat variable ratios, are necessary for structure, energy capture, catalysis, coding, osmotic and electrolyte stability, and confinement in space

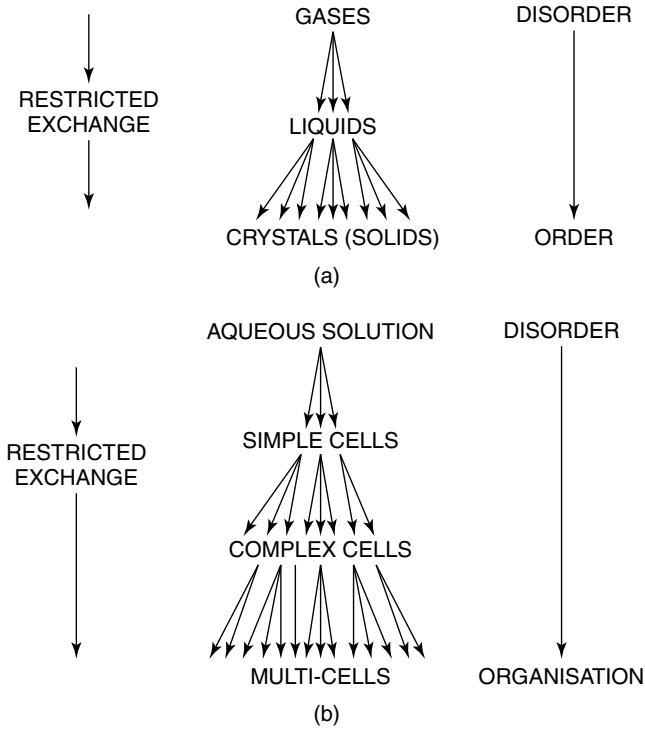

FIG. 2.2. (a) The effect of changing the variables, i.e. temperature and pressure, on atomic chemical element mixtures. There is a systematic sequence of events leading to many materials of different chemical composition and physical properties but a full reductionist explanation is not possible. The system can be described in a time-independent equilibrium manner. (b) The effect of time at constant temperature and pressure, but allowing a cellular biological system. Different cells of different chemical composition and structure can evolve. To what level of reduction can the change be analysed?

(membranes). So life is a chemical system of some 15 to 20 elements, even in its most primitive form. Of course, the elements must now be placed in the compounds we observe in cells and then combined into larger structures, i.e. *miniphases*. The question then arises as to the degree of compositional variation which is permitted in them for life to exist. We can relate this problem to that of phase structures in minerals and alloys. Each phase may have a certain broad or narrow range of composition and there can be hundreds of phases if many elements are involved (Figure 2.2). They can be treated as the sum of the interaction energies of order and disorder and have distinctive *emergent properties* such as melting points. Thus, we may appreciate in a non-dynamic system (i.e. not living) the stability of the

observed composition. It may be the case that the mixture of very primitive single cells, 'bacteria', could have a rather variable composition and maybe they could exchange chemicals, even DNA, so that there were no species. (Some minerals and alloys are like this even as solids and are very much like this in the liquid phase. Again, separate liquid phases may not mix but may exchange molecules readily.) On the other hand, many species may have arisen coincidentally and existed within defined chemical composition ranges and may not have mixed. In this case, they could well have had defined separate properties such as shape, temperature stability, and so on, just as chemical crystals do. Very intriguingly, if they could exchange they could develop better (more stable) systems incorporating either simple units or processes or even compartments separate from one another so that the combination had greater survival strength. This is an almost Lamarchian progression of compositional gain from the environment – an increase in order within a local (enlarged) space. Note that none of this is a treatment of living dynamic systems.

Now we must move on from the discussion of composition to that of functioning cells. The primitive structure had to be a simple confined space if the systematic capture of energy and material to maintain the composition was to be possible, from which many flows could occur and had to be controlled. Note that controlled flow is impossible without structure, and so structure arose first. The life properties arise through these features plus a variety of additional factors which have nothing to do with thermodynamics. The flows have to be *organised* (not ordered) co-operatively by feedback and so the system also requires internal messengers between flows. The living cells had the same or a very similar chemical environment but selected flows could and did eventually give rise to speciation. Adding coded molecules (DNA/RNA) controlled a part of the compositional and flow variations through their coded feedback instructions and generated survival through reproduction. The rest of the flow is controlled by internal feedback between selected elements. These are of two major kinds, namely acid/base exchange of material fragments and energy-based, often on phosphate compounds, and redox exchange, often based on iron compounds, but using organic material, of course, in both cases. We shall call this a P/Fe system. We need to be able to appreciate which flows of chemicals within a structure can be compatible. Hence, a quick appreciation of the types of flow which allow life as we know it to exist is needed.

As far as I can judge, all *primitive* cells had a basic reducing cell metabolism: glycolysis, a citric acid cycle or its reverse, amino acid and base synthesis, while all maintained high K^+, low Na^+ and Cl^-, moderate Mg^{2+}, and very low Ca^{2+} (see Figure 2.3) by input and output pumps. Chemical

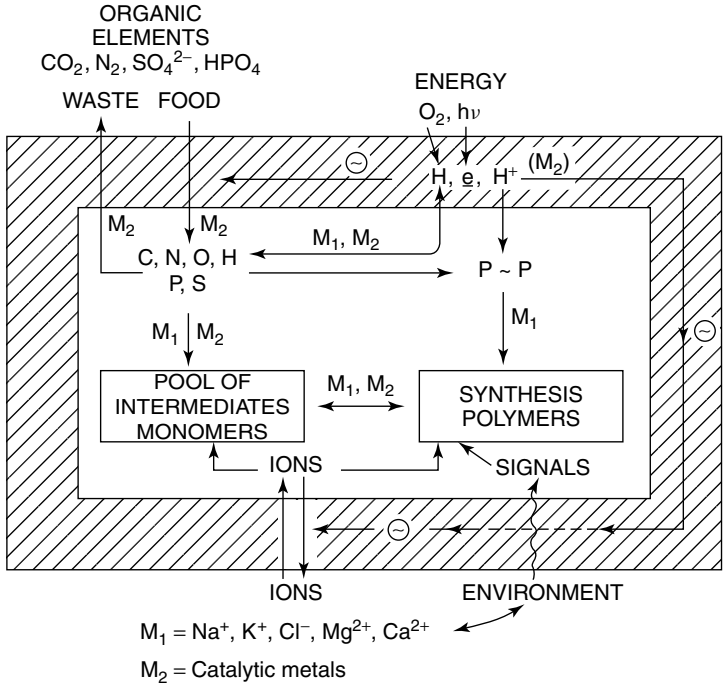

FIG. 2.3. The essence of cellular flow toward synthesis – note the involvement of 15–20 elements (see Figure 2.1). In addition, note that energy could well have been introduced in stages represented by geochemical change, light, and O_2 reactions

reduction is essential since the polymers are made from environmental CO_2, N_2, H_2O, and more recently, SO_4^{2-}. The subsequent synthesis to monomers and polymers is on well-defined routes by using energy to this day. Moreover, energised uptake pumps and rejection pumps are required to incorporate K^+, Mg^{2+} and HPO_4^{2-}, and to reject Na^+, Ca^{2+}, Cl^- and many other ionic species. Much of this activity depended on ATP-ases. Requirements are for a closely fixed level of all of these entities in the primitive cell, plus essential catalysts involving Fe, Mn, Ni, Co and Mo(W) as we see the system in archae. Much of this activity depended on iron.

It is here that we hit a central feature of every organism as well as the most primitive. There has to be spatial structure, there has to be flow, and there has to be communication to co-ordinate the activities of the cell. The communication has to link the metabolic paths and consists in the primitive cell of feedback controls by small molecules (mobile coenzymes and substrates) and ions, where up to 20 elements are involved. By seeing

the organisation of a cell and its networks, one sees immediately that we need functional parameters to describe the system which cannot be reduced to the activities or properties of single molecules, or to the functions of equilibrium thermodynamics. We need to have new, if possible simple, variables to describe such systems. It may well be that looking at species, which is a level of reduction, may only be one way of trying to understand life by examining life as evolving in spreading patterns – a tree. There is the obvious hope that by working backwards in time through the branches of the tree and its growth from an elementary species, e.g. a seed, we can understand life. An alternative approach, an examination of a total ecosystem in time, is just as valuable. This would be comparable to examining the cooling of the gaseous elements of our planetary system with time as it gave rise to more and more chemical species through cooling (see Figure 2.2). We shall see where this functional approach leads us. It will help us to see the difficulties of reductionism, even in reducing evolution to a developing tree-like series of species.

A global view of evolution

In the above sense, evolution cannot be described by reference to molecules much though speciation may be referenced by DNA (RNA) or protein content. Speciation may be only a way to characterise evolution and not the way in which to understand it. The global evolution of an ecosystem of living chemistry is an alternative approach. The parameters which can evolve and did evolve are as follows:

(1) chemical composition;

(2) spatial division;

(3) communication networks;

(4) co-operation between spatial divides, organisms;

(5) the environment.

Of these, (2) and (3) and (1) and (5) must develop together and we see this in Table 2.1. The mixture of primitive cells from which we start our discussion all used as messengers in the cytoplasm various phosphate compounds, various substrates and the levels of minerals such as Fe^{2+}, Mg^{2+} and K^{+}. We labelled this above system as the P/Fe system of communication in the earliest life system. It may be better to view the system as diversifying at first through combination rather than as progressing. There is a part of the

TABLE 2.1 Ecosystem development

(a) Spatial division	
Compartments	*Co-operative chemistry*
1. Simple single cell	Cytoplasmic feedback
2. Complex single cell	(1) + vesicle and organelle feedback
3. Multi-cellular organism	(2) + extracellular fluids
4. Mankind's industry	(3) + external systems
(b) Chemical change	
Internal chemistry	*Environmental chemistry*
1. Reductive chemistry with no functional use of Ca^{2+}	Loss of CO_2 and H_2; gain of S_n and FeS_2
2. Reductive chemistry with Ca^{2+} message	Little change
3. Initial use of O_2, SeO_4^{2-}, SO_4^{2-} and Zn^{2+}	Liberation of Zn^{2+}, generation of SO_4^{2-} and SeO_4^{3-}, loss of Fe^{2+}, etc.
4. Final use of O_2; Cu in higher oxidation states	O_2, (O_3) and NO_3^-; liberation of Cu^{2+}
5. External industry; all elements	Pollution

system which once started hardly changes. (In a sense, the initial variety of cells which we presume to have existed is to be likened to a set of gaseous molecules which evolve on cooling (see Figure 2.2).)

We have to appreciate that once such a structural organisation as the primitive prokaryote cells had appeared – I am not concerned with its origin which could have been by one-off fluctuations – then the evolution of variety is extremely probable. Remember that any such organised flow system once started will, through combination or variation, by using existing environmental energy and chemicals, generate novel structures. Within the primitive cell it is easy to imagine that accidental budding of the membrane will lead to vesicles and that the variety of synthetic reactions will lead to separation of different metabolic pathways and to filaments in the cell. Filaments themselves will arise since they stabilise structure and thereby increase the survival of flow patterns. Is it essential for this development to be coded or might it just survive on its own quite well? Effectively the new vesicles contain environmental fluids – high Na^+, Cl^- and Ca^{2+} – which were rejected from the cytoplasm of the most primitive cell. This more complicated structure will have greater survival value per single cell, i.e. a longer lifetime, than the simpler original cell. It can have separated reaction paths in the vesicles reducing confusion and the nucleus, if any, can be protected by a membrane. Sooner or later, such cells, eukaryotes, were bound to appear once prokaryotes existed since in essence this is but a greater use of spatial organisation (equivalent to cooling a gas). The innovative eukaryotes do not easily displace the original prokaryotes, however,

since a second requirement for greatest survival strength is not just organisation but speed of reproduction, which we base on DNA. Here the prokaryote in all its simplicity has a greater chance of survival. Fitness of a flow system is many-faceted and hence diversity arises, not replacement. When we take the view of a primitive global ecosystem there is no tree in such evolution and not even a diverging bush springing from inorganic chemical base level flows since each imagined stem can exchange with every other stem or even merge with it. Hence, for example, bacteria and early eukaryotes gained by symbiosis, or incorporation to give mitochondria and chloroplasts in eukaryotes, once a filamentous interior evolved. Meanwhile, bacteria could rapidly utilise degraded eukaryotes and a kinetic balance was established.

We stress again that the whole system was partnered by the environment. Due to inward accumulation, the cell trapped and generated chemicals and energy but outward rejection generated gradients of, for example, Ca^{2+} and Na^{+}. These elements are poisonous at certain concentrations and had to be rejected. Gradients across cytoplasmic and vesicle membranes can be turned to valuable assets in signalling (see, for example, Figure 2.4). Now the increase in size of the cell, inclusion of vesicles and filaments and mobility of the outer membrane, which are all part of a eukaryote, created a signalling

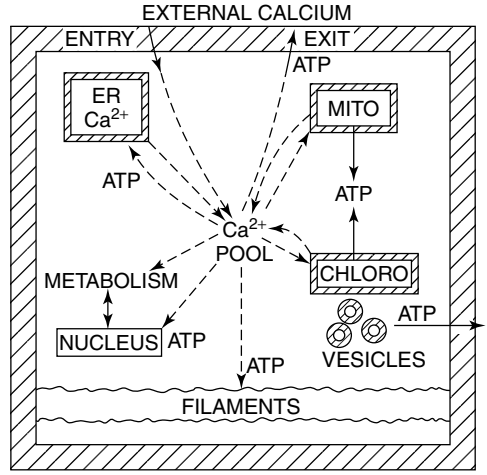

FIG. 2.4. The network of calcium connections. The outward pumping of calcium by the most primitive cells made for an energy and chemical store in the environment which later could become the means of knowing about the environment in eukaryotes. By developing vesicles or incorporating prokaryotes as organelles, the cell needed further information transfer and this was again based on calcium gradients. Calcium became an essential player in evolution

problem since the co-ordinated activity of the prokaryote cytoplasm P/Fe system could not be used outside of the cytoplasm, yet still had to be maintained there. Phosphorus, iron and substrates are hardly rejected but kept in the cytoplasm. The obvious new system which is available for message transmission is the large and sensitive Ca^{2+} gradient, developed for protection, which then has to be coupled to the P/Fe network, but now in eukaryotes calcium was also stored in vesicles. The consequence is a calcium electrolytic current networking the internal cell activity with the environment as well as internally through vesicle–condenser discharge, where the vesicles are rich in calcium (Figure 2.4). The calcium pulse became the major second messenger. The cell was no longer at the mercy of the environment but responded to it through the information that these pulses provided. Of course, in order to secure continuity through reproduction the whole network, now Ca/P/Fe, had to be coded in the DNA in qualitative essentials. How did this come about? Through random-mutation or (better) directed-mutation? What pressure forced the development of a calcium channel and ATP-ase pump? Once the eukaryote system with incorporated prokaryotes, and dependent on prokaryotes for certain chemicals (symbiosis), had been achieved, with little change in basic cytoplasmic chemistry, larger and larger organisation, further evolution, became possible but this was forced into new directions by another inevitable development – the change in the chemistry of the environment. This environmental change due to the prokaryotes fed through the environment in many ways and then back to the cells, as it must, equally to prokaryotes and eukaryotes. A cell cannot escape its environment – it is an open system, and whether it is a prokaryote or a eukaryote there was the possibility with new environmental chemicals to introduce new living chemistry in new compartments. All the existing eukaryotes and prokaryotes developed, that is, the whole ecosystem. Did they do this by exchange or via separate but similar mutations? How did the varieties of DNA find the similar solutions to these problems of the advent of dioxygen in all the different eukaryote species?

The new environmental chemistry

At some stage in the existence of primitive prokaryotes they commenced using H_2O rather than H_2S as a source of hydrogen for reducing carbon and nitrogen compounds (Figure 2.5). The consequence was a gradual accumulation of dioxygen in the atmosphere. As we have pointed out elsewhere, this change of the environment led to the successive change in the oxidation states of available metals and non-metals (Figure 2.6). The forms of life had to diversify to survive and benefit. Hence, there are

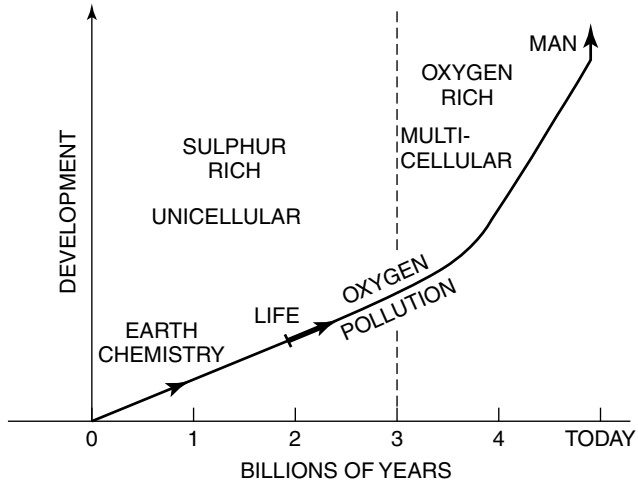

FIG. 2.5. The development of cells and types of cells with time has been grossly affected by the energy and chemical store of dioxygen and then a host of other chemicals in the environment (see Figure 2.6 below). Man has discovered new ways of using all the elements in the environment and all energy stores in a second wave of evolution which has just begun

additional, both reductive and oxidative, metabolic paths and they appear throughout prokaryote and eukaryote kingdoms, being very similarly based on the same novel pathways. The suggestion is that they shared one common gene pool, swapping valuable assets. The novel elements which became available and are of greatest importance in this discussion are copper and zinc, due to the removal of sulphide as sulphate. The element which became most seriously less available was iron; however, various other elements became difficult to obtain, including nitrogen from N_2, sulphur from SO_4^{2-} and selenium from SeO_4^{2-}, while halides became open to oxidation to halogens. We have detailed these developments of chemistry, but they allowed advance in structure and communication in the cellular systems. While all of the cytoplasmic major reaction pathways, internal filaments and internal messenger networks found in primitive prokaryotes remain, a number of add-on developments from the eukaryote Ca/P/Fe system was fashioned together while keeping connection to this Ca/P/Fe system. The obvious change is to multi-cellular eukaryote organisms although one should not lose sight of the changes in single-cell prokaryotes and eukaryotes. Some examples of these follow.

The connective filaments needed to link cells together are dependent upon copper oxidases for cross-linking and zinc enzymes for hydrolysis,

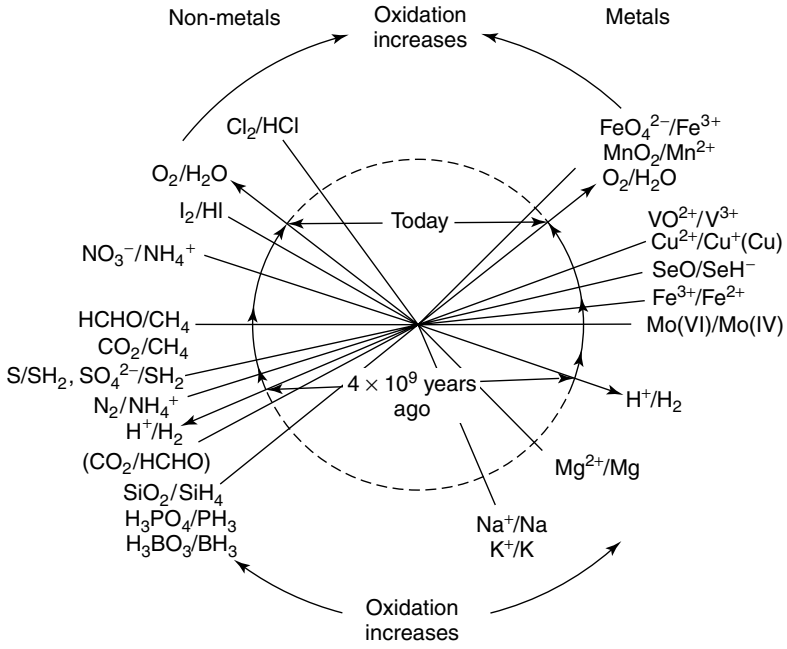

FIG. 2.6. The redox potentials of chemical element couples in the environment at pH 7.0; non-metals are on the left, with metals on the right. The slow change from 4×10^9 years ago to today has been almost continuous. As a result, the switch on the left is from H^+/H_2 toward O_2/H_2O and in passing generated SO_4^{2-}, SeO_4^-, NO_3^- and I_2, while on the right it generated MoO_4^{2-}, Fe^{3+} (precipitated), Cu^{2+} and VO_4^{3-}, plus the possibility of using high oxidation states while it liberated Zn^{2+} and Cd^{2+}

so as to allow cell–cell expansion. Again, the development of membranes depended on the oxidation of sterols to produce cholesterol. Novel oxidised protein side-chains appeared which are not coded. Novel fats arose which require oxidation.

While the primitive energisation of the cell versus the external environment gave rise to a natural mode of communication with the environment – a calcium gradient on top of the P/Fe internal networks – later messenger modes from outside to inside the cell depended on the use of organic messengers, many of which are produced by *oxidative* metabolism associated with vesicles (Figure 2.7). There were no residual inorganic elements remaining for messenger use in chemistry (although see sodium below), so synthesis now gave gradients. Even the major use of peptide messengers, production and removal, is very dependent on zinc which was released into the environment by oxidation of insoluble zinc sulphide to soluble zinc

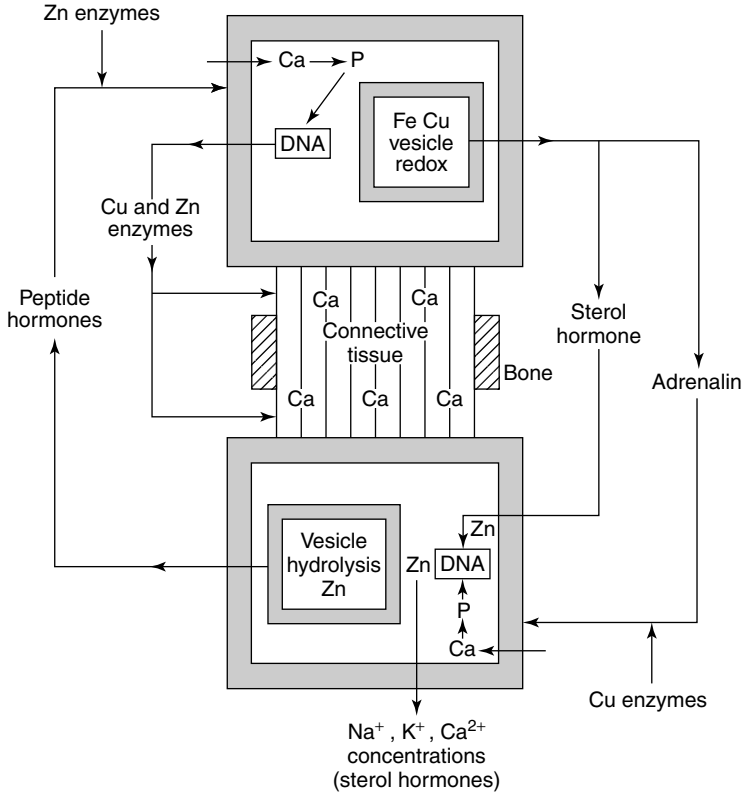

FIG. 2.7. Illustration of the way in which multi-cellular organisms combine their cells physically through extracellular connective tissue, often calcified, to give shape and developed cell–cell communication through elements and chemicals. Note that all this evolution was made possible by oxidation following inevitably from the release of O_2

sulphate. Other messengers, aromatic compounds and amidated peptides, are products of copper oxidases. Note that iron is much less used as it is fully engaged in the original reductive cytoplasmic systems. Adding-on is of the essence since the copper and iron systems inter-communicate.

Finally, the ability to build complicated spatial structures and to keep it all in flow with communicating messengers requires more energy. The full use of light and the intermediate production of dioxygen in bacteria give rise to a huge energy gain over anaerobic systems through oxidative phosphorylation. The novel system came first in bacteria which were then taken in from *the environment* into eukaryote cells and made into organelles – hardly a Darwinian event.

Now each evolution of a more complex system is slower in reproduction, needs more protection, and due to its complexity, is subject to internal breakdown. Within the ecosystem, the achievement of greater survival of these 'higher' organisms was to utilise lower organisms as sources of primary products such as co-enzymes (vitamins), fats, sugars and amino acids. Mutual feeding became the essence of the ecosystem for the 'higher organisms' after death were degraded by the lower or were used as niches for their nutrition. Species are *not* independent forms in evolution. The whole can be looked upon as a succession of diversification in the use of flowing chemistry in spatial compartments, some within one species and others between species, with increasing possibilities due to chemical changes of the environment.

Almost simultaneously, a huge variety of animals with skeletons (see Figure 2.7) and plants with multitudinous different forms arose so that either parallel mutations occurred in many species or the transfer of genes allowed the very similar chemical changes in many eukaryotic plants and animals. Was the only mode of advance Darwinian? No matter, the clear implication is that by utilising chemical composition change, *mainly of trace elements*, the system could produce new forms of increased spatial organisation with new structure and new messengers. At the same time, the essential features of the cytoplasm are maintained to this day. The interdependence of this part of the ecosystem on the 'lowly' forms of prokaryotes and eukaryotes is clear. Seeing it all as a unity with diversity of functional responsibility has advantages over seeing it as evolution of independent forms. Thus, reductionist discussion of species has a disadvantage as well as an advantage over an analytical simplification.

We see evolution as a way of energising chemicals in compartments. The internal cytoplasmic system we described as the P/Fe system is a one-off even if it occurred in a multiplicity of interchanging primitive forms. It remains to this day a chemically reducing activity making DNA, RNA proteins and so on, where energised chemicals are kept inside. However, through its rejection of calcium, generating gradient energy *connected to the environment*, it made novel communication possible. Then, through the rejection of dioxygen and the consequent changes of environmental chemistry of very many elements, the prokaryotes by themselves, or within eukaryotes, gave rise to a hugely energised environment. Once again, this energised environment drove evolution to the forms we see today. However, the primitive system had generated one more valuable functional possibility – it had rejected sodium, thus giving an energised state of sodium across the membrane which eventually allowed the nervous system and the brain to evolve.

This overall picture of evolution is not complete without an account which leads to the brain and mankind. Early steps led to a cell having contact with the environment in eukaryotes through calcium gradients, while later steps led to cell–cell co-operation through organic molecules dependent on oxidation-based changes, although communities of individuals depend on further changes. Now cell–cell communication based on chemical release of organic molecules is slower than electrolytic connection. The elongated nerve cell was a natural development once a large structure of cells was in place and where the organism needed co-ordinated movement. This depends on the primitive electrolyte gradient of Na^+ versus K^+ gradients needed to control osmotic and electrolyte balance but it was reinforced and given novelty by the Na^+/K^+ ATP-ase. The organisation of nerve cells in the brain then allowed the environment to become part of the organised system. Many kinds of external dead structures were built by animals as nests or burrows or even tools. We see this develop up to man when suddenly an understanding of chemistry and physics allows the environment to be almost totally linked to the living system. New chemistry (by man) allows new materials, new structures, and new communication modes in space disconnected from the organism itself. The chemistry is now that of all of the elements of the Periodic Table and all space is put to full use. It is the last step that can occur – all composition and space, movement of material in time with application of energy, are being thoroughly explored, as are the modes of energy generation. The whole progression from primitive cell to mankind was inevitably the way organisation had to evolve to utilise space and chemicals fully, much as cooling the gaseous early sun-system gave rise to the planets in an inevitable progression via liquids and solids. Species are not particularly important when compared with this global advance which is present or incipient in the primitive organisation development. The brain finally developed memory and transferred culture, and not DNA, through generations by using new means of communication (not chemical). The idea of mutational evolution cannot handle this development but the use of functional variables makes it obvious and inevitable (see Table 2.1).

We must see that all of it has indeed been a global advance of chemistry in compartments. To be more effective, an organisation must compartmentalise and communicate. The above illustrates the general sense of this change, although the whole picture is more complicated. Compartments need not belong to the same organism, although all organisms must have the same cytoplasmic metabolism. An obvious development is symbiosis. There is no life without bacteria because they are simple manufacturing units for basic chemicals for all life forms to this day. It is only good sense in an ecosystem that the more complex systems give up elementary chemical

synthesis but provide their dead material for lower systems to recycle. Man is more sophisticated than any other organism but he is less chemically competent. He cannot make a range of amino acids or fats; even co-enzymes are vitamins for this organism. Again, he needs minerals from food through the digestion of other organisms. Advanced plants cannot fix nitrogen. The conclusion is that the evolution of organisation of the sophisticated depends upon the use of organisation of the under-developed. Does this not resemble modern civilisation? To what degree is the whole a matter of dependence, not independence, where speciation is not the important point? Have we tried to reduce life too far, just as the chemist tries to reduce everything to chemical formulae?

To conclude – we must not despise reductionism. However, it has to be put in a proper perspective. We know that all of chemistry including life can be reduced in one sense to the properties of the electronic properties of the elements of the Periodic Table. Unfortunately, this is an exceedingly unhelpful view of life since in practice it cannot be done. Organic chemists do not attempt to describe their chemistry from the properties of H, C, N and O atoms. They start from *evolved* molecules, alcohols, ethers, ketones etc., in classes of combined units. Physical chemists use thermodynamic functions to examine and help to explain properties of matter not related to molecules as such. Biologists must know what atoms and then what molecules exist in cells but this knowledge will not lead directly to an understanding of biological systems, i.e. life. DNA is a recognisable changing molecule through time but it does not allow understanding of evolution – it only relates to it in a somewhat dangerous way. Today, we do not have an appropriate functional analysis to put beside it. Perhaps when we do we shall come to see evolution as an inevitable diversification within organisation. Once it was started, the way chemicals and space were used was certain to appear as we see them today – it was just a matter of time. Life and its evolution are just emergent properties of flow. What man does today outside living cells is exactly parallel to what happens inside life. Organisation is built up by increasing sophistication of flow inside structure with communication networks. Just because such feedback is essential, so then life cannot be linked linearly to molecular properties.

Reference

The work described in this article is presented in full in the text, Williams R.J.P. and Frausto da Silva, J.R.R., *Bringing Chemistry to Life*, Oxford University Press, Oxford, UK, 1999. All detailed references are to be found there.

Chapter 3

From Nineteenth Century Ideas on Reduction in Physiology to Non-Reductive Explanations in Twentieth-Century Biochemistry

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My purpose in this presentation is to ask the question, 'Whether biology as a science is reductive, non-reductive, or both?'. In contemporary philosophy, reduction and reductionism are the subjects of formal and very general distinctions made by analytical philosophers dealing with issues in general epistemology, like reduction, explanation and so on. How easily these distinctions, even if they are very relevant or appropriate, do apply to the actual workings of biology remains to be demonstrated, because a very general and formal philosophy of reduction gives a somehow reductive view of science, and it is not always easy to recognise biology in these distinctions. Much before being a topic of analytical philosophy, reduction was the subject of many discussions in the nineteenth century, and I would like to stress that the terms which were used in these nineteenth century discussions remain the ones which we use now. It is very striking to notice that these discussions were especially vivid in the fields of biology and medicine, in the context of the progresses made by the physical and chemical approaches of life, as we shall see later. The terms of the debate were defined and set at this time. I think it is important to notice this, because one could be tempted to draw the conclusion that the present scientific context has nothing in common with the nineteenth century context and that consequently reductionism has lost its scientific relevance.

Promises and Limits of Reductionism in the Biomedical Sciences
Edited by M.H.V. Van Regenmortel and David L. Hull

Nowadays, reductionism is often used as an insult which is uttered by people from various tendencies who have no real idea of biology, most of the time for ideological, social, or political reasons with little scientific relevance. I would like to say in this respect that the ideological relevance of the quarrel about reductionism is much clearer than its scientific relevance. Biology has many dimensions – it is like a multidimensional space which even the greatest minds cannot distinctly and entirely perceive, and a network so complicated that we perceive only its major lines of force. Scientists who are considered as reductionists obviously do not ignore that. Molecular biologists are the first ones who know that biological molecules are not only very complicated molecular machines, the workings of which are not presently entirely understood, but also the results of the whole history of life, which means an enormously complicated series of events. So, the quarrel of reductionism which is raised by some philosophers against molecular biologists is entirely unfair. It is absolutely clear that biology cannot be reductionist in the sense of 'reducing' something to something else which would be much simpler and much more limited in complexity than the thing to be reduced, or which would be more abstract and more general like a law. Biology does just the contrary in its workings. It produces a more and more complex, rich and subtle view of things which is more and more difficult to grasp in a single theoretical scheme and which has many theoretical dimensions. Reductionism is a misrepresentation of science. It is antiscience really. There should be no propaganda for such a word, reductionism, as it is so commonly used and understood.

The quarrel about ontological reductionism is meaningless in biology, since biological organisation is characterised by a hierarchy of levels (this is a point which was made very forcefully by Paul Weiss) and by the emergence of new properties, as has been shown so beautifully by Professor Williams in his lecture. With these conceptions, biologists have the means to avoid the quarrel about ontological reductionism, since multi-level causality is a major conception in biology which allows us to understand the appearance of new properties or behaviours. The issue of epistemological reductionism, of science as being an essentially reductive process, seems much more serious. Would it be possible for a science to be non reductive in its progress? Does reductionism hold true in cases of heterogeneous descriptions of the same reality, which are still irreducible to each other as is the case of biology? Could incomplete understanding still be named a reduction? Is biology as a science reductive or non-reductive, or both? I would tend to think it is both, and consequently to concentrate on the concept of this model, which I will do later.

First, let us consider the way in which the problem of reductionism was introduced in biology and medicine. It was particularly discussed by one of the founders of modern experimental medicine, Claude Bernard, in very striking terms, and I wish to discuss this briefly. Bernard reflected on the relationships between physics and chemistry on the one hand, and medicine on the other hand, and the terms in which he discussed these themes set largely the stage for future discussions. Due to the particular influence of Bernard, he may be held partly responsible for what happened next, but the enormous cultural stability of language is also partly responsible. The point I wish to make here is historical. I mean that the issue of reductionism was raised in the middle of the nineteenth century because chemistry was unable to deal with the synthetic part of animal metabolism (which was considered as the typically vital part of metabolism), and also because such a physiologist as Bernard had only a very limited view of chemistry, surely a much less prophetic view of chemistry as his fellow chemists at this time. It is clear that after the highly sophisticated developments of organic chemistry, biophysics and biochemistry in the twentieth century, it is quite impossible to keep Bernard's views, vocabulary, and ways of defining the problem alive. This would be my basic argument in this presentation. The question I wish to ask consequently is the following – Is there still a problem of reductionism in biology? I would like to mention in this respect that each time more elementary levels are revealed in biological research, they are always more complex than expected. This is likely to weaken the arguments regarding reductionism, because the difference in complexity between levels is perhaps smaller than expected. The problem is to calculate this difference. This is an extremely complex problem but a purely cognitive one, and one of pure science.

I did not find the word 'reductionism' in Claude Bernard's *Introduction to the Study of Experimental Medicine* (Bernard, 1966). However, there are several occurrences of the verb 'to reduce' as well as occurrences of a verb with a close meaning, 'ramener', which means to bring back or reduce. These occurrences are found in very important passages of the work, where Bernard discusses the relevance of physics and chemistry for medicine. I wish to make another comment here. One of the words which is found most frequently in the *Introduction* is the word 'complexity'. Surely the sense of complexity in biology and medicine, which is so common nowadays, has nothing new in it. The issue of complexity appears closely linked to the issue of reduction in the passages dealing with the relevance of physics and chemistry for medicine. In the *Introduction*, Bernard expresses repeatedly his programme of laying the foundation of the science of life on the science of non-living things. The principles and aims of both kinds of sciences

are the same, and they share the same method, i.e. the experimental one. This method allows us to determine the conditions of existence and/or the proximate causes of the phenomena, and thus to influence or control their production (Bernard, 1966, pp. 100–101). According to Bernard, these conditions of existence are determined in an absolute way in the living as well as in the non-living beings. One of the aspects of this discussion is the issue of vitalism versus materialism (Bernard, 1966, p. 110). From this viewpoint, Bernard's polemics against vitalism do not result in a total rejection of vitalism, but only to a qualified rejection. In one way, he says, vitalism is pure superstition, when it denies the efforts aimed at reducing vital phenomena to determined organic, physical and chemical conditions. This is perhaps the first appearance of reductionism in the *Introduction*.

However, Bernard goes on to say that he would agree with vitalists if vitalists could recognise only that living beings offer phenomena which are not found in non-living things and are thus particular to them. He says that vital manifestations cannot be elucidated by the only physical and chemical phenomena which are known to exist in non-living things. Here he introduces the important and subtle idea that living and non-living beings are different by certain determined or determinable conditions, some of which are peculiar to living beings. Consequently, the sciences of life can be distinguished from the sciences of non-living matter only by their special explanations or laws, but certainly not by the scientific method itself, which consists of the experimental method based on the idea of determinism, also introduced by Bernard. Now, the idea of determinable conditions which are peculiar to living beings is at first sight both very plain and very strange. What does this mean, being a condition? Is this something peripheral, an external cause having some kind of influence on the production of phenomena, or something more essential? We will see that the answer is not clear, and that both aspects are involved, although in different ways. At first sight, it is not something essential. In Bernard's view, and this is one of the major themes of the *Introduction* and one of Bernard's greatest inventions, it is something environmental. This is the idea of the internal environment which allows us to keep the validity of the scientific method applied to the realm of life. Let us follow the path leading to this idea.

To establish this, Bernard starts with the idea of complexity and mobility, fugacity or transience of living phenomena. Complexity, he explains, is not such a great obstacle. It can be dealt with by the method of experimental analysis which decomposes successively all complex phenomena into simpler and simpler phenomena, until their reduction to only two elementary conditions, if possible (Bernard, 1966, p. 114). Why two conditions? This idea of two conditions is very striking. The first meaning of condition is

a defined and necessary condition for the production of a phenomenon. There may be several of these conditions. In physics, they are ideally represented. In chemistry, they are simple or compound bodies which are irreducible and the most elementary conditions for the phenomena. Biology has to follow the same path, reducing complex phenomena to the most elementary and irreducible conditions, organisms to organs, tissues, and the so-called immediate principles which are the subject of organic chemistry. However, Bernard goes on, arguing that in the present state of science it is impossible to establish any relationship between the vital properties of bodies and their chemical constitution. This situation began to change mainly after Bernard's death, as everybody knows. Anyway, in Bernard's view, the so-called immediate principles of the organic chemist are not the active physiological elements. They are only passive elements.

The physiologically active elements are anatomical or histological elements, which are the real and simplest carriers of the simplest known vital properties. So Bernard draws a clear borderline between chemistry and histology. Life is bound to histology as to its proximate condition.

Now, again, what is a condition? In this respect, Bernard's positivistic tendency is very clearly stated. Indeed, Bernard goes on saying that when the physicist, the chemist or the physiologist reach their goal in determining the irreducible elements of the phenomena, the scientific problem is simplified but remains essentially the same, because the scientist does not come closer to an absolute knowledge of the essence of things. However, the scientist has gained something most important for him, meaning the knowledge of the conditions of existence of the phenomena under study and the determination of a defined relationship which exists between the body which expresses a certain behaviour or property and the proximate cause of this expression or manifestation. Bernard's pharmacological experiments on the paralysing action of curare or carbon monoxide poisoning are good examples of this, since in both cases a defined action and a defined agent are correlated without any real knowledge of the mechanism of this action at the chemical molecular level. So we have just discovered that the meaning of a condition is something influencing a phenomenon in a still unknown way, and secondly, we have also discovered that material conditions are one of the two sets of conditions defined by Bernard. What about the second set of conditions?

In order to identify these other conditions, Bernard develops philosophical ideas on the nature of phenomena which are relationships between bodies, requiring at least two bodies to achieve any kind of existence, like in mechanics (attraction and gravitation), electricity, chemistry, and so on. The same is true for life. Life, Bernard says, is the result of the contact

and interaction between two things, the organism and the environment (Bernard, 1966 p. 118). This contact and interaction may be described in the different kinds of organisms in biology, and here Bernard introduces his famous idea that more complex organisms develop an internal environment which protects them from being harmed by external environmental variations. The idea of the internal environment, which is one of the major themes of the *Introduction*, is conceived of as a condition or a cause on which it is possible to act in physiology or medicine. This is the real medium for regulation and action. So the study of life includes two things or conditions: the properties of the anatomical–histological elements and the properties of the environment, in particular the internal environment. It is enough at this present moment of science for the scientist to describe the laws which govern the interactions between these two things.

We still have not finished with Bernard. Indeed, Bernard is not such a straightforward thinker. He has such a sense of complexity that he remains often very ambiguous. Now he faces the 'black hole' of the unknown structures underlying life. The creative aspect of life, which is perhaps the most characteristic one, for instance, regarding metabolism, remains out of the physiologist's hands. The conditions surrounding the black hole are defined, the black hole remains unknown, but perhaps not unknowable. When Bernard, in the *Introduction*, says 'life is creation' (Bernard, 1966, p. 142), he adds that we give the name 'vital' to organic properties which we still cannot reduce to physical and chemical considerations, but there is no doubt that we will succeed in doing this some day in the future. Consequently, he displaces the problem of the essence of life, which does not reside in how complex physical and chemical properties may be, but in an idea which governs the creation and development of the organism, a creative idea which directs vital evolution, development, and so on (Bernard, 1966, p. 143). Commentators have seen in this passage a premonition of the idea of genetic programming.

To summarise these typically nineteenth century ideas on science as reduction to irreducible elements which might be further reduced in the future in spite of their internal complexity, I would like to stress finally the fact that behind all this lies an ideal of science which is defined by simplicity (another word frequently used by Bernard) and determinism (a word which was seldomly used before him and to which he gives a new meaning and a new prominence, as shown by my colleague Jean Gayon (see Gayon, 1996)). I would be tempted to conclude from this discussion about Bernard that reduction of vital phenomena to irreducible physical and chemical elements and/or relationships is both a necessary and an insufficient condition of science, because of the emergence of features, like developmental patterns

or 'creative ideas' which are more distinctly perceived without being suitable to a scientific experimental approach. So one gets the impression that science is not a game with two terms, reduction and the irreducible, or complexity and simplicity, but rather with three terms, a phenomenon, its conditions, which are of two kinds, and the black hole which can be perceived and approached but remains largely undefined and out of our hands. The black hole of Bernard's thinking may be defined as developmental biology and heredity, as well as evolutionary biology. These dimensions are basic and essential but foreign to experimentalism. Bernard formulates a reductionist programme for physiology. However, at the same time he perceives in biology dimensions which are, in his view, of a different order since they do not belong to chemistry or physics (Bernard, 1966, p. 143). I wish here to emphasise that the problem of reduction, which may be defined as the difficulty of reducing vital properties to ordinary physical and chemical properties, was set in this particular nineteenth century scientific and epistemological context, characterised by the very limited power and relevance of physics and chemistry for biology. So why should this problem survive at a time when the context has entirely changed and when molecular biology has solved so many problems by penetrating into the core of biological structures and functions? Did molecular biology play a role in the revival of the reductionism issue in philosophy in the 1950s and 1960s? This would be an interesting question to discuss.

My point here will be that while molecular biology may be considered as the completion of the nineteenth century reductionist programme, its own progression during the last 40 years created a picture of life which is essentially foreign to the simplicity principle stated in the nineteenth century reductionist programme and which creates new methodological and cognitive challenges. In such a context, the question as to whether biology as a science is reductive or non-reductive, or both, seems relevant. I will try to defend a mixed view, based on the study of recent models and studies in protein biophysical chemistry. Moreover, I would like to argue that reduction is definitely not a good term to describe the actual workings of biology and to convey its special charm. My point will be that reduction of physiological to molecular properties is not reductive at all, in spite of the impression it can create, because it is not a reduction of a complex to a simple representation but a reduction of a complex to a complex thing or representation, or even perhaps a reduction of a more simple representation to a more complex thing.

In spite of their structural complexity, proteins do exhibit lawfulness and order in their behaviour. This lawfulness and order can be mathematically described and conceptually understood at the phenomenological level

of thermodynamics, thanks to the theory of linked functions elaborated by one of the masters of protein biophysical chemistry, the late Jeffries Wyman. A basic functional interpretation is thus available, in the mathematical sense of a function. Jeffries Wyman was the co-author of the famous Monod–Wyman–Changeux (MWC) model of allosteric transition in proteins, published in 1965. Wyman, who like Max Perutz devoted his whole scientific life to the study of a single molecule, i.e. haemoglobin, further developed in a very elegant way the fundamentals of the thermodynamics of biomolecules, particularly of proteins, which he presented in a recent book with Stanley Gill, *Binding and Linkage. Functional Chemistry of Biological Macromolecules* (Wyman and Gill, 1990). This sense of mathematical theory is also exemplified by other masters in this field, such as Manfred Eigen, whose *Hypercycle* was a landmark in many fields of biology (Eigen and Schuster, 1979). However, because of their structural complexity, the behaviour of biological molecules like proteins remains out of the reach of actual computation or simulation. The behaviour can be modelled, but it cannot be calculated. The abstract language of thermodynamics and the structural description overlap only partially. These different levels of description remain somehow heterogeneous. There is no unified theory of protein behaviour. This situation seems to be very general in biology, at least in other fields of protein biophysical chemistry like protein folding, which I will mention later. These points will be illustrated by the example of the haemoglobin molecule, which remains paradigmatic for all discussions of protein biophysical chemistry. I wish to present some comments now on the Monod–Wyman–Changeux model (Monod *et al*., 1965). (For an historical presentation of protein chemistry, see Debru (1983)).

This model is a mixture of structural hypothesis and statistical treatment regarding the behaviour of oligomeric proteins, meaning proteins made up of several subunits. The behaviour consists of the binding of different kinds of ligands on the subunits. This binding is regulated in such a way that it is mainly facilitated. This is the well-known co-operativity phenomenon, which is exhibited in the saturation curves, typically the oxygen saturation curve, of the haemoglobin molecule. This regulation property expresses underlying energy transduction properties of the oligomeric protein. The haemoglobin molecule is a tetramer, which exists under two different quaternary conformations depending on their deoxygenated or oxygenated state (the so-called *T* and *R* conformations). The most important assumptions in the model are the following ones. First, there is a symmetry hypothesis in the structural arrangement of the subunits, the monomers. This hypothesis plays a major role in the model. Secondly, the monomers (the subunits) are able to exist in two different conformations endowed with different

affinities for their ligands. Thirdly, the overall symmetry of the oligomer is conserved during the transition between the two quaternary conformations *T* and *R* of the tetramer. This symmetry conservation hypothesis has been greatly admired and widely discussed. The symmetrical arrangement has the effect of exerting constraints on the subunits. These constraints are different according to the different quaternary conformations. The switch between the two quaternary conformations is the highly co-operative result of conformational changes in the tertiary subunits. Intermediate forms, by which I mean mixtures of different kinds of tertiary conformations in a single quaternary conformation, are excluded. In this respect, Max Perutz's preliminary data on the two crystallographic structures of oxy- and deoxyhaemoglobin played also a major role in the MWC model.

How can we describe such a model from an epistemological standpoint? Is it reductive? First of all, it is unifying, because it brings together data from physiology and enzymology. Secondly, it is a theoretical treatment, characterised by a mixture of structural, topological, statistical and thermodynamical considerations which it unifies in a very nice way. It has a great explanatory power. However, I must confess I am extremely reluctant to consider this wonderful theoretical construction as a 'reduction' of the physiology of respiratory transport to molecular biology. Compared with the classical physiological description of respiratory transport, it focuses the discussion on molecular properties, and in a way it 'reduces' the size of the problem, but there is an irony in the fact that by 'reducing' it, it means that by purposely neglecting many other aspects, it creates an entirely new problem of unexpected complexity which is not presently entirely solved. This model helps to reveal the mixture of order and complexity which is rather typical in biochemistry, but I am extremely reluctant to describe this as a reduction. It is rather a non-reductive explanation, because it reveals complex phenomena which are not entirely understood or are understood only at a certain level of explanation. It induces questions concerning these phenomena which lead to great debates on the detailed molecular mechanisms of allosteric transitions, which are far from being settled. These debates were fueled by Max Perutz's crystallographic data and interpretations. In these debates, very different philosophies were expressed, like the induced-fit model, which was presented a little later by Daniel Koshland (with the Koshland–Némethy–Filmer (KNF) model) and is very different in its spirit from the original MWC model.

I am surely not going to describe all of these complicated discussions which took place after the famous Monod–Wyman–Changeux paper, with the result that an increasing number of molecular states were introduced and that both kinds of processes, the induced-fit one, the 'concerted' or

allosteric one, and combinations of both, were also introduced. Structural data provided by Max Perutz's crystallographic studies provided much material for the discussion of molecular mechanisms at the atomic level. Findings about co-operative interactions within the haemoglobin dimers (half-molecules) were also important in qualifying the original MWC model. The fact that the haemoglobin allosteric mechanism makes use of elements present in both the MWC and KNF models was mentioned recently by Gary Ackers, a specialist in this field, in his presentation of his own thermodynamical work on haemoglobin mechanisms (Ackers, 1998 p. 191). This presentation may be found in one of the recent issues of the series *Advances in Protein Chemistry*, devoted to 'Linkage Thermodynamics of Macromolecular Interactions', which is just the subject developed by Jeffries Wyman. Ackers's thermodynamical work leads to the new conclusion that previously unrecognised features play an important role in the haemoglobin switch.

The haemoglobin molecule is made up of four subunits arranged in two dimers, each of which is constituted of two different, i.e. alpha and beta, subunits. The haemoglobin molecule may exist under 10 unliganded and partially or totally liganded forms. This means that eight partially liganded forms exist. Using thermodynamical as well as structural data, Ackers concluded that the binding of one ligand generates a tertiary conformational change involving both subunits within the dimer. When a second ligand binds itself to the second subunit of the dimer, the effect is much smaller and the tension exerted on the quaternary interface is not much increased, so that the quaternary *T* conformation remains the same. However, when the other dimer is also ligated, at least by one ligand, the interface between both dimers switches from the *T* to the *R* conformation. Such a switch is the consequence of unfavourable free energy – this is known as the *symmetry rule*. If we introduce the identity of the ligated monomers, then it happens that the *T*–*R* quaternary transition occurs at six reaction steps in the overall binding process. This means also that other reactions in the overall process of 16 different reactions are not accompanied by a quaternary switch. The switch itself is the consequence of two kinds of triggers, occurring at both tertiary and quaternary levels. To quote Ackers, 'the formation and release of tertiary constraint is thus a fundamental driving force of co-operative binding in Hb. Whereas the *T* interface can withstand one dimer having tertiary constraint, it cannot accommodate two such perturbed dimers' (Ackers, 1998, p. 196). This general picture remains to be elucidated in its molecular basis and details. I am not going to enter into too many of these details now, as they are really very complicated. The only point I wish to make here is the increasing number of states and factors which are

considered when compared with the original models which were designed more than 30 years ago.

In the original MWC model, only two states were introduced. It was assumed that both of the quaternary forms, *T* and *R*, exist in thermodynamic equilibrium, and that in these two conformations all monomers exist in the correspondent tertiary conformation. The basic idea was of an overall equilibrium between different and homogeneous states. The KNF model postulated an increasing conformational change accompanied by a corresponding change in ligand affinity when the binding reaction goes further. Max Perutz's crystallographic data revealed that the oxygen binding on the haem part of the haemoglobin molecule induces important conformational changes which are mediated by the protein part of the subunit to the interfaces with the other subunits. This discovery was more in favour of a mechanistic model than in favour of the MWC thermodynamic equilibrium model, because it stressed the role of site specificity in the binding of oxygen. Many different kinds of experiments have been designed in more recent years to test these alternative views. They were carried out with analogues, hybrids, mutations, or with ligands other than oxygen. At the present time, the results produced by these different kinds of experiment are not always entirely homogeneous, and controversies are still going on, although major facts emerge, including co-operative binding within the dimer, which is incompatible with the concerted two-states model of Monod, Wyman and Changeux. In these new conceptions, the dimer is considered as an autonomous structure within the tetramer. In addition, the symmetry rule means that the switch between quaternary conformations takes place when each dimer carries one ligand. To quote Ackers, these 'new findings have provided a foundation for the more detailed analyses that must eventually provide an ultimate understanding of Hb mechanism' (Ackers, 1998, p. 247).

From Gary Ackers's conclusion, one can get the idea that the haemoglobin mechanism is not entirely understood presently in its molecular details. The progress towards such an understanding rests upon a truly multidisciplinary approach, which can hardly be described as reductive. This is surely an extremely complicated problem, like many other complicated problems of this kind, the protein folding problem for instance, which as a combinatorial analysis problem cannot presently be solved in a rigorous fashion by the available statistical methods applied in an exhaustive search. Regarding the multiplicity of molecular states, which is already clear in Ackers's discussion, I would like to mention studies on the internal dynamics of proteins which were started by Martin Karplus many years ago. These studies revealed that molecular structures like proteins are not 'frozen' in something which

could be described as a state, but that they are continuously vibrating and fluctuating. Karplus discovered that the number of states of minimum energy in the vicinity of the overall minimum, which was reached by myoglobin during 300 ps was 2000 (Elber and Karplus, 1987). Is the word 'reduction' really suitable to describe the evolution of science towards such a complex picture? I wonder if we really need to keep these scholarly terms, reduction, reductionism, alive. The lesson of this is that we still do not have the cognitive tools to understand completely the structures of life. If our limited understanding of things can be called a 'reduction', it is surely not the sign of a complete success, but rather of a partial failure.

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Chapter 4

Pitfalls of Reductionism in Immunology

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Introduction

The scientific analysis of biological systems usually involves the dissection of complex entities into their simpler constituent parts. After describing a complex system in terms of its constituents, a biologist may be led to believe that he has 'reduced' something complex to its simpler components, especially if he subscribes to the ontological view *that the whole is nothing but the sum of its parts*. When cells and organelles are described in terms of their molecular constituents, it may, indeed, seem plausible that biological entities are nothing but physico-chemical systems and that biology should be reducible to chemistry and physics. Along similar lines, it is sometimes claimed that physiology can be reduced to biochemistry or psychology to neurophysiology. In immunology, reductionist thinking leads to the expectation that it should be possible to describe all immunological phenomena in terms of the molecular properties of entities such as antibodies, T-cell receptors, major histocompatibility complex (MHC) molecules, cytokines and proteasomes.

The development of vaccines is one of the most successful practical applications in immunology and in this field it is currently fashionable to make the reductionist claim that it will soon be possible to design effective synthetic vaccines on the basis of our knowledge of the molecules involved in immunological interactions. It seems to me that this claim arises from an unwarranted faith in the power of a reductionist approach for solving complex biological problems. Such a claim does not take into account that the protection against disease that can be achieved by vaccination is a

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biological phenomenon which is meaningful only in functional terms at the level of the organism as a whole and which cannot be described adequately solely in terms of molecular interactions.

According to reductionist thinking, it is possible to make biological phenomena intelligible by reducing them to simpler chemical phenomena that are more easily understood. It is not always clear, however, which aspects of a problem are being reduced, i.e. whether the reduction pertains to biological concepts, entities, properties or explanations. The most commonly accepted view is that reductionism is a relation between causal explanatory theories and that the motivation for the reduction is to defend the primacy of physical explanation over biological explanation (Lennon and Charles, 1992). The higher-level properties are believed to be determined by properties at the lower level. The reductionist's credo is that the behaviour of wholes is causally produced by the behaviour of parts.

Reductionists believe that since biological systems are solely composed of atoms and molecules, they can be fully described and understood in terms of the physico-chemical properties of their constituent parts. Such a view disregards the fact that all biological systems, because of their complexity, also possess so-called emergent properties that arise through the multiple relations existing between individual components of the system. These emergent, relational properties do not exist in the constituent parts and cannot be deduced or predicted from the properties of the individual, isolated components (Holland, 1994). Examples of emergent properties are the viscosity of water (individual water molecules have no viscosity), the colour of a chemical, a melody arising from notes, the saltiness of sodium chloride, the specificity of an antibody and the immunogenicity of an antigen.

In my analysis of reductionist thinking in immunology, I will not consider the one issue that has received considerable attention from philosophers of science, namely that of theory reduction. According to Nagel's classical account (Nagel, 1961), reduction consists of an explanation in terms of one theory of why another theory works. This requires that the axioms and laws of the reduced theory must be deduced from the reducing theory. Discussions of intertheoretic reduction involve issues like the connectibility of terms used in the reduced and reducing theories and the possibility of logically deriving laws from the reducing theory that are applicable to the reduced theory (Schaffner, 1993). Such discussions are of secondary importance if one takes the view that natural selection is the only *bona fide* theory or law in immunology. I will stay clear of the issues that are currently the subject of intense debate in theoretical immunology (Tauber, 1994; Podolsky and Tauber, 1997) and will concentrate instead on what I see as

a reductionist bias in the thinking of many practitioners of experimental immunology today.

Dissecting the immune system into its constituents severs the connections that link the various parts to each other in a functionally integrated manner. As a result, essential and irreducible aspects of the system's behaviour are destroyed and it is no longer possible to understand and explain the workings of the system as a whole. This is not to deny that when the immune system is dissected into its components, a wealth of useful information is obtained regarding the different mechanisms at work in individual parts of the system. What is debatable, however, is the extent to which descriptions of the isolated components in molecular terms are able to give immunologists the type of explanation, the level of understanding and the predictive ability they would like to have. In order to settle this question, one must agree on what counts as a relevant question, an adequate explanation and a sufficient degree of understanding. Reductionists and anti-reductionists tend to disagree about what the relevant questions are and about what would constitute adequate answers to these questions. Reductionists try to understand how a system works by analysing its constituents in isolation and without interference from the environment, whereas anti-reductionists focus on why a system actually functions the way it does in a particular biological context.

An example will illustrate the differences in approach that can be followed in the case of vaccine development. It is generally accepted that a good vaccine must mimic the natural immune response that occurs when an individual is infected with a pathogen and which can lead to life-long protection against a second infection by the same pathogen (Bloom and Widdus, 1998). In order to be able to mimic a natural immune response, some investigators take the view that one should first understand what causes protection against the particular disease. This leads them to search for a causal explanation, for instance, in terms of neutralizing antibodies or cytotoxic T-cell responses. They will therefore dissect antigenic sites and cellular receptors into their atomic constituents in an effort to unravel the physico-chemical basis of specific binding reactions. Antigen–antibody complexes will be studied by X-ray crystallography to throw light on the mechanism by which one particular neutralizing antibody is able to attach to its target antigen. In this way, considerable information is obtained regarding the structural correlates of some of the many interactions that occur during infectivity neutralization. However, this knowledge does not explain why the ability of the pathogen to infect its host is abolished by the immunological interaction, nor how the required neutralizing antibodies can be elicited by vaccination. Mechanisms of infectivity neutralization and of escape from neutralization are still poorly understood (Dimmock, 1993)

and it is a sobering thought that none of the existing, successful vaccines has had its mechanism of action fully elucidated.

Instead of concentrating on the reductive analysis of single causal factors that contribute to the emergent phenomenon of infectivity neutralization, an alternative approach consists in studying the dynamics of the integrated system of pathogen, vector, host cell and immune response as a complex, functional whole. Several ingredients of a potential vaccine are combined in a trial-and-error approach (choice and dosage of immunogen, adjuvant, route of immunization, etc.) and tested simultaneously in recipients. Single causal factors then no longer hold the center stage and understanding is sought in terms of functional explanations instead of causal explanations. Some understanding is deemed to be achieved if positive results are obtained and vaccine efficacy is successfully predicted, even if the complexity of the system does not allow one to identify all the causal, mechanistic relations that are involved (Berger, 1998).

Causal explanations versus functional explanations

A causal explanation is reductive in the sense that one factor is singled out for attention and is given undue explanatory weight on its own. Since biological systems are complex, any observed effect always results from a complex network of interactions and an analysis in terms of a single cause is rarely satisfactory. Instead of invoking causes, it is more appropriate to refer to the many factors that simultaneously influence the features of a biological system. In biology, network causality is a more useful explanatory category than linear causality of the push–pull variety which is prevalent in physics.

It is not always appreciated that causality is a relation between successive events and not between two material objects or between a structure and an event. A biological event such as the neutralization of an infectious agent can, therefore, not be caused by something that is not an event, for instance, the structure of an antibody molecule. There is, in fact, no unique causal relation between the structure and activity of a biomolecule. A single chemical structure or protein fold can have a multiplicity of activities or functions and a single activity can be generated by a variety of structures (Martin *et al*., 1998). When molecular biologists investigate so-called structure–function relationships, they should look for correlations rather than for causal relations (Van Regenmortel, 1999a).

Another reductionist fallacy is the claim that a biochemical process can cause a physiological process. As pointed out by Rose (1998) a biochemical reaction such as the interaction between actin and myosin is not the cause of a physiological event such as muscle contraction. The biochemical process does not precede muscle contraction and therefore cannot cause it:

it simply describes the physiological event in chemical terms. Biochemical and physiological processes occur simultaneously and the claim that the one causes the other overlooks the fact that both are descriptions, at different levels, of the same reaction. According to Achinstein's classification of explanations, the biochemical event cannot provide a causal explanation for the physiological event but only a type of identity explanation (Achinstein, 1983). In contrast to reductionists who emphasize causal explanations, anti-reductionists favour functional and selectionist explanations for biological phenomena. According to the aetiological account of biological function, item X has the function of doing Y when item X is now present as a result of causing Y; in terms of biological evolution by selection, X has been naturally selected by a mechanism which picks out things that cause Y (Papineau, 1992). To attribute a function to an item is to say that the item has that behaviour because it has a certain evolutionary history and produced certain consequences in the past; those consequences themselves had the effect of reproducing items with that behaviour (MacDonald, 1992). It is because of its effects that the property is selected for and retained during evolution (Kitcher, 1998).

The functional explanation for the behaviour of a biological entity is that it contributes to the health, performance, survival or reproduction of that entity, the ultimate 'goal' of any biological entity being to reproduce more of its kind. It is true that selection can only favour some pre-existing trait at the expense of others, although each selected trait has itself an evolutionary history which could be invoked to explain its presence at any particular time. Accounts of functional explanations thus follow the good consequence doctrine according to which the performance of a function must confer some good to the system (Achinstein, 1983). The selection mechanism is blind to structure: it selects for effects and cannot discriminate between different structures with identical effects. The same effect can be produced by different mechanisms involving a variety of genes and gene products. Biologists search for a functional explanation for a presently observed biological structure in terms of superior fitness in the past rather than for a structural explanation for a currently observed function. Evolution is seen to operate on the DNA sequence through feedback from its effects (Rosenberg, 1994), akin to a backward causation relationship where the effect is interpreted as a cause and the cause is selected for the effect it produces.

All biological functions in an organism are interdependent and internally regulated and since their occurrence is context-dependent, they cannot be understood in isolation. Functional explanations are therefore more appropriate for understanding complex systems exhibiting many coupled interactions than are causal explanations which focus on a single factor.

The interactions between the parts of a complex system tend to be non-linear, which means that the overall behaviour of a biological system cannot be deduced by summing the behaviours of its isolated components (Holland, 1994). Since the number of possible interactions between the parts is very large, the complexity of any observed response cannot be analyzed using classical mathematical tools based upon assumptions of linearity and additivity and it is necessary, instead, to use non-linear, computer-based simulations. This means that the goal of understanding something as complex as the workings of the immune system through individual mechanistic descriptions of its isolated parts is simply not attainable. Many features of the immune system involve complex interconnections and relationships that are absent when the constituents are analyzed separately and it is thus rarely possible to control the system adequately by modifying a single causal factor.

A functional explanation for a particular trait does not stipulate by which mechanism within the organism a particular effect is produced. The function can be realized in physically different ways and the only relevant feature is that it must enhance fitness, i.e. serve survival and reproduction (Macdonald, 1992). Various causal factors can then be invoked to explain how the function is performed, although these factors cannot explain why the traits are present unless an appeal is made to selection pressure.

Reductionists tend to focus on causal explanations to describe how particular biological functions are performed while anti-reductionists concentrate on functional explanations that must necessarily take into account the past and present benefits of a trait for the system as a whole. When analyzing the presence of antibodies able to neutralize the infectivity of a pathogen, an anti-reductionist will ask questions that require functional explanations, such as – why do such antibodies exist, do such antibodies suffice to protect an organism against infection, or how can antibodies with such activity be induced? Answers to these questions cannot be obtained by, for instance, analyzing in great detail the internal structure of antibodies. The answer as to why antibodies are organized the way they are and are functionally active does not lie inside but outside the antibody molecule and it cannot be uncovered by a reductionist approach (Cohen and Stewart, 1994).

Reduction and the occultation of dimensions, relations and context

The capacity of antibodies to recognize myriads of different antigens in a specific manner is one of the characteristic features of the immune system. Since most antigens of biological interest are proteins, the present

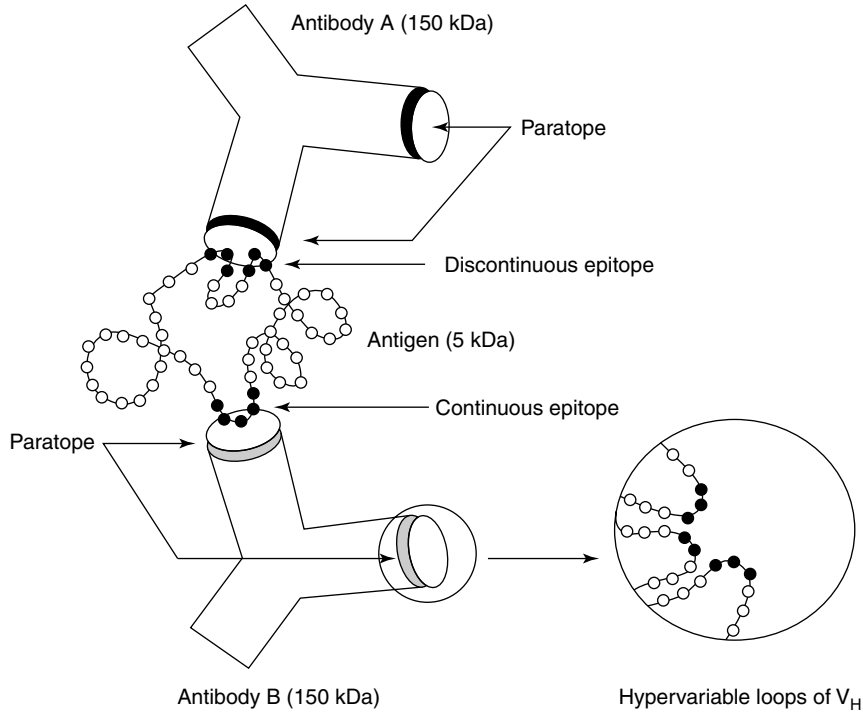

FIG. 4.1. Schematic representation of two antibodies reacting with a continuous and a discontinuous epitope of a protein antigen; interacting residues are indicated in black. If the individual loops of a discontinuous epitope are able to bind to the antibody paratope on their own, they may be given the status of continuous epitope. The inset shows the three loops of an antibody VH chain which form part of the paratope

discussion of immunological specificity will be restricted to proteins. The antigenic reactivity of a protein refers to its capacity to interact specifically with the functional binding sites or paratopes of certain immunoglobulin molecules. When a particular immunoglobulin is found to bind to a certain protein, it becomes known as an antibody specific for that protein. The portion of the protein antigen that is recognized by the paratope of the antibody constitutes an antigenic determinant or epitope of the antigen. It is customary to classify protein epitopes as either continuous or discontinuous, depending on whether or not the amino acid residues in the epitope are contiguous in the polypeptide chain (Figure 4.1). The label 'continuous epitope' is given to any linear peptide fragment (5–10 amino acid residues) capable of binding to antibodies raised against the intact protein. The second type of epitope, termed as 'discontinuous', is made up of residues that are

not continuous in the sequence but are brought into spatial proximity by the folding of the polypeptide chain (see Figure 4.1). Usually, antibodies to discontinuous epitopes will recognize the antigen only if its native conformation is preserved. In general, it is accepted that an antibody is directed to a discontinuous epitope if it fails to react with any short, linear peptide fragment of the protein antigen. The distinction between continuous or discontinuous epitopes is widely used, although it is a rather fuzzy one (Van Regenmortel, 1998). Discontinuous epitopes often contain several stretches of a few contiguous residues that could be viewed as continuous epitopes and conversely, so-called continuous epitopes often contain a number of indifferent residues that are not implicated in the binding interaction, and which, therefore, make the epitope discontinuous in a functional sense.

The crystallographic analysis of a number of antigen–antibody complexes has revealed that a significant amount of induced fit or mutual adaptation of the two partners occurs during the binding process. This means that antigenic specificity cannot be solely described in terms of three-dimensional structures, but that it is necessary to incorporate the fourth dimension of time in order to accommodate the binding process itself (Van Regenmortel, 1996). The three-dimensional structure of an epitope is thus only a visual time slice in a dynamic process of interaction. The structure and activity of a binding site cannot be dissociated and they should be viewed in an integrated manner as a structure-functioning complex. It is a reductionist oversimplification to picture binding sites as two-dimensional flat areas at the surface of proteins, or worse still as unidimensional linear sequences forming continuous epitopes devoid of any conformational features (Van Regenmortel and Pellequer, 1994). Considerable efforts have been made to predict the location of continuous epitopes along the polypeptide chain of proteins by constructing one-dimensional profiles of the sequence that depict certain physico-chemical propensities of the amino acids, for instance, their hydrophilicity. The level of successful antigenicity prediction achieved in this manner rarely exceeds 60% correct prediction (Pellequer *et al.*, 1994). This mirrors the limited success of attempts made to predict protein tertiary structure from sequence information. It should come as no surprise that the occultation of dimensions that occurs when antigenic sites are reduced to unidimensional models is not conducive to a satisfactory understanding or prediction of antigenic specificity.

A second type of occultation concerns the relations that exist between biomolecules. In the same way that the antibody nature of an immunoglobulin molecule becomes evident only when its complementary antigen has been recognized, the epitope nature of a set of amino acids in a protein can

be established only by finding an immunoglobulin capable of binding to it (Van Regenmortel, 1998). Both epitopes and paratopes are relational entities defined by their mutual complementarity and identifiable only through the process of binding to a complementary partner. They cannot be described by a structure identifiable before the interaction has taken place since they exist as binding sites only by virtue of a particular relational nexus. A single atomic substitution in an epitope necessarily leads to an altered complementary paratope by virtue of this relational definition. Furthermore, antigenic sites in a protein and antibody combining sites in an immunoglobulin are fuzzy recognition sites, each one consisting of several individual epitopes and paratopes, respectively. The potential combining site of an immunoglobulin available for interaction consists of about 50 amino acid residues located on six loops of hypervariable sequences known as complementarity determining regions (CDRs). Only about 15–20 of these 50 residues participate directly in the interaction with any particular individual epitope. This implies that about two-thirds of the CDR residues of the immunoglobulin are potentially capable of binding to other epitopes that may bear little or no structural resemblance to the first epitope. This gives rise to antibody multispecificity and explains why the relation between an antibody and its antigen is never of an exclusive nature. In the same way that an epitope can only be defined in terms of its complementary paratope, it is equally meaningless to speak of the affinity of an antibody without mentioning which particular antigen–antibody pair is under consideration. Similarly, antibody specificity is a ternary relational property that acquires meaning only with respect to the antibody's capacity to react differently with two or more epitopes and thereby to discriminate between them (Van Regenmortel, 1998).

Occultation of context can also complicate the analysis of binding site activity. It is frequently found that residue substitutions introduced far away from the discrete regions that are in contact when an antigen and its antibody interact are able to alter the binding activity (Choulier *et al*., 1999; Lavoie *et al*., 1992). The flanking residues of an epitope that are not directly involved in the binding process are nevertheless able to modulate its immunological reactivity (Moudgil *et al*., 1998). The activity of an isolated epitope, when removed from the context of the whole protein in which it is normally embedded, tends to differ significantly from the original activity it possesses in the intact protein. Context is important in all biological interactions since a biological activity can only be expressed in a particular chemical and cellular context. Genes, for instance, provide information only in the context of other genes and they are expressed only in the context of a particular cellular, extracellular and extraorganismic environment. Genes

obviously do not act alone and they are not even self-replicating. Similarly, biological functions are meaningful only in an integrated system since they must contribute to fit and to the survival and reproduction of the organism as a whole.

When a protein antigenic site is studied in isolation and is dissected into its atomic constituents, it may be difficult to relate its binding activity to that of the intact protein. One of the aims of studying the binding of an isolated epitope is that the investigator may wish to enhance the binding affinity of a synthetic version of the epitope intended to be used as a potential vaccine. Binding experiments are then performed in order to discover how changes introduced in the structure of the epitope affect its ability to bind to the complementary antibody. This can be achieved by site-directed mutagenesis of the protein antigen whereby each amino acid of the epitope is replaced in turn by other residues. If the epitope is represented by a synthetic peptide, it is possible, by using combinatorial synthetic strategies, to produce a very large number of peptides where each residue at every position is replaced by all 19 possible amino acids. By testing each peptide for its binding activity, it is then possible to determine how a change in chemical structure is related to change in antigenic activity. This allows the derivation of so-called quantitative structure-activity relationships (QSARs) which can lead to the identification of peptides possessing a superior binding activity compared to that of the original peptide. Instead of testing many peptides in a random manner, which is time-consuming and expensive, it is possible to select the peptides to be tested according to a factorial, statistical design. This reduces considerably the number of peptides that must be tested while providing the same QSAR information.

A factorial design which varies several structural elements in a peptide simultaneously is a vastly superior approach to the simple strategy of changing one element at a time. This is illustrated in Figure 4.2, which describes a study aimed at discovering what is the optimal setting of two factors necessary for reaching a maximum response (Hellberg *et al.*, 1991). Using the classical approach of changing one structural factor at a time, the effect of factor A is analyzed while holding factor B constant at the value b1. The response curve for factor A indicates an optimum in response when A = a1 (Figure 4.2(a)). Factor B is then studied (Figure 4.2(b)) while holding factor A constant at the apparent optimal value of a1. This will lead to the erroneous conclusion that there is an optimum response at the settings a1 and b1 and that a decreased response would be obtained at other values of factors A and B. When both factors are changed simultaneously (for instance when two amino acid positions in a peptide are changed simultaneously according to a 2^2 factorial design), a surface response

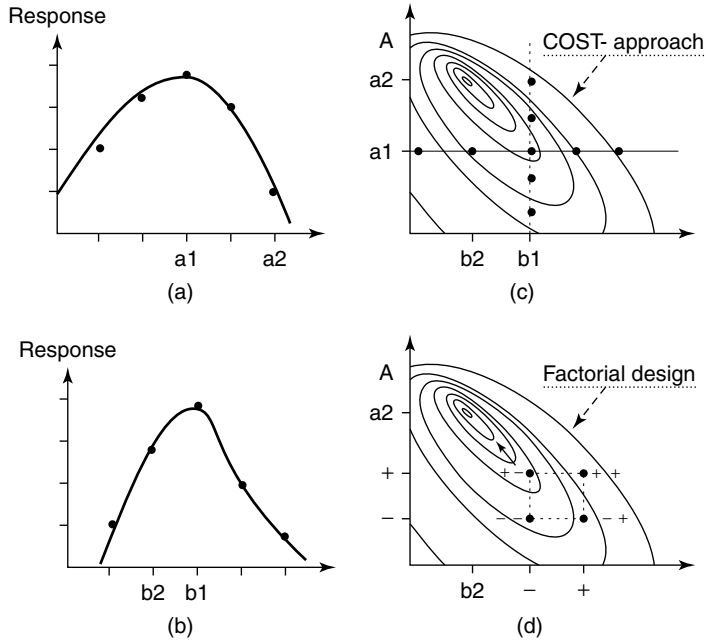

FIG. 4.2. The process of determining the optimum setting of two factors, A and B, required to obtain a maximum response. (a) When one factor is changed at a time, factor B is kept constant at value b1 and the response curve for factor A indicates an optimum in response when A = a1. (b) Factor B is then studied, while factor A is held constant at the apparent optimum a1. (c) Changing one factor at a time (the COST approach) leads to the erroneous conclusion that there is an optimum response at the settings a1 and b1. (d) When both factors are changed simultaneously (factorial design), a surface response plot is obtained pointing to the real optimum at settings a2 and b2. From Hellberg, S. *et al*., *Int. J. Peptide Protein Res.*, **37**, 414–424 (1991). Reproduced by permission of Munksgaard International Publishers Ltd, Copenhagen, Denmark, © 1991

plot is obtained showing that the response is influenced by interactions between the two factors. Mathematical modelling based on as little as four experiments will produce a non-parallel response surface pointing in the direction of the high-activity area and to the real optimum at settings a2 and b2 (Figure 4.2(d)). At present, the analytical strategy of varying one factor at a time is nearly always used in this type of study, in spite of the fact that this approach is not suited for analyzing complex systems characterized by non-additive effects of each constituent. When non-linear computer-based simulations are used, it is usually found that the dynamics of the model agree with the experimental behaviour of the system. The system can then be said to be 'explained' to the extent that similar relationships hold

between the variables in the model and the components of the physical system. Explanation is thus achieved by dynamic modelling instead of by a deductive, causal account (Berger, 1998). Although non-linear systems are usually too complex to allow the identification of all the causal, mechanistic relations that are relevant, it may nevertheless be possible to predict how the system will behave under many different circumstances. Since relevant information for making successful predictions is obtained, a degree of understanding will be achieved even if it is not possible to allocate a defined portion of the overall activity to each constituent part of the system. In most cases, the effects of site-directed mutagenesis on binding activity are not predictable, because of non-additivity (co-operativity) of the effects of individual mutations (Rauffer-Bruyère *et al*., 1997; Tobin *et al*., 2000).

Is it possible to predict biological function from the structure of biomolecules?

Molecular biologists who subscribe to a reductionist agenda tend to believe that it will soon be possible to deduce the function and biological role of any gene or gene product. This optimism stems from the belief that a linear causal chain links the sequence of a gene to the biological function of the product of that gene (Table 4.1). According to this view, the gene sequence is solely responsible for the appearance of a co-linear protein sequence, independently of the cellular and extra-cellular environment and of regulatory genes. The protein sequence is assumed to dictate the three-dimensional structure of the protein, independently of the chemical and

TABLE 4.1 The vagaries of predicting biological functions from DNA sequences

Pseudo-causal chain	*Factors that tend to be overlooked*
Gene sequence	
↓	⟵ Cellular and extra-cellular environment; regulatory genes; transcription control
Protein sequence	
↓	⟵ Influence of chemical space on folding; role of chaperones
3D protein structure	
↓	⟵ Multiple sites
Binding site	
↓	⟵ Varied chemical composition of ligands
Ligand	
↓	⟵ Binding activity does not amount to biological function or value; importance of biological context; multiple functions appear during evolution
Function	

cellular context. Although our ability to predict the folding of a protein from its sequence is improving constantly, the best that can be done at present is to correctly predict the structure of about 75 % of the residues in a protein (Koehl and Levitt, 1999). In order to predict biological activity, it is also necessary to find the probable location of binding sites in the folded protein, a goal that is achieved in only about 50 % of the cases. Since most proteins contain a number of binding sites specific for different ligands of varied chemical composition, it is only rarely possible to predict binding activity on the basis of the fold similarity between related proteins (Russell *et al*., 1998). An even more serious problem lies in the fact that binding activity does not necessarily entail functional activity.

When analyzed at the molecular level rather than the cellular or organismic level (Bork *et al*., 1998), the function of a protein, which is probably better described as its *functioning*, is defined by what it binds to, as well as by when and where it binds (Murzin and Patthy, 1999). However, a biological function can also be equated with the biological value of the molecule for the organism as a whole. Such functions are internally regulated and since their occurrence in the cellular environment is context-dependent, they cannot be assumed to take place at higher levels simply because structural features make a particular binding interaction possible.

Although a necessary condition for the occurrence of an immunological reaction is that various components of the immune system such as cellular receptors, antibodies and cytokines must bind to their specific ligands, this is not sufficient to guarantee that a beneficial function will ensue in the organism. Binding is a necessary but not sufficient condition for the occurrence of a beneficial biological activity. For instance, many of the antibodies elicited by a vaccine will bind to the infectious agent but they will nevertheless fail to neutralize its infectivity. In the case of molecular mimicry, which occurs when foreign epitopes closely resemble self-epitopes, the two binding reactions observed when the cross-reacting epitopes interact with the same antibody are very similar but in one case a useful protection against infection is obtained, whereas, when the self is recognized, a harmful reaction and autoimmune disease may ensue. It obviously is not the function (selected by evolution) of an antibody to destroy the self and the binding reaction must be dissociated from the possible subsequent occurrence of a useful function or detrimental effect. Small differences in the biochemical and cellular context in which a binding reaction occurs can change a beneficial response into a harmful one. For instance, a small difference in the affinity of a peptide for a T-cell receptor can turn a peptide agonist into an antagonist and radically alter its functional activity.

What level of biological and chemical organization is relevant in immunology?

Table 4.2 lists some of the topics in immunology that are currently the subject of intensive research. Vaccination is the single, most cost-effective application of immunological knowledge. Since it is the organism that needs to be protected against disease, vaccination is an immunological intervention that is meaningful only in the context of the whole organism. Successful vaccination can only be demonstrated by determining to what extent vaccine recipients are protected against a challenge infection. Measurements of the cellular immune response or of the concentration and specificity of antibodies elicited by the vaccine are at best surrogate assays that must be validated by protection trials that are a prerequisite for establishing vaccine efficacy.

Autoimmune disorders (see Table 4.2) are also meaningful only at the level of the organism as a whole. Small differences in the cellular and organismic context in which immune recognition occurs are able to turn a beneficial immune reaction into a harmful one, thus leading to autoimmune disease. The reactivity of a vaccine or of an autoimmune antigen involves a complex network of biological interactions that cannot be reduced to the discrete, molecular features of an individual component of the immune system. In a similar vein, concepts like the immune self (Tauber, 1994) or the protecton (Cohn and Langman, 1990) are meaningless if internal regulatory mechanisms operating at the level of the organism are left out of the picture.

When the lower levels of organization listed in Table 4.2 are examined, it appears that a phenomenon like the activity of IgA antibodies during a

TABLE 4.2 What level of organization is relevant in immunological investigations?

Level	*Phenomenon*	*Explanation*
Organism	Vaccination; autoimmunity	Functional
Organ	Local IgA mucosal immunity	Functional
Cell	Killer cell activity	Functional
Organelle	Antigen processing	–
Protein	Antigen–antibody recognition	Structural
Amino acid	Specificity of immune recognition	Structural
Atom	Fine specificity	Structural
Elementary particle[a]	–	–
Quantum mechanics[a]	–	–

[a]These levels are irrelevant for explaining the properties of biomolecules.

mucosal immune response pertains to the level of particular organs and tissues, while the activity of killer cells is only relevant at the cellular level. Immunological phenomena at these three levels of complexity (see Table 4.2) are best analyzed in terms of functional explanations involving so-called ultimate causes (Mayr, 1982).

The next lower level of complexity is found in antigen processing which takes place in certain organelles and proteolytic multisubunit assemblies and which involves the transportation of antigen fragments to particular regions of the cell. Further down the complexity scale, the interactions between antigens and antibodies are described in terms of their molecular and atomic features. At this level, the specificity of an immunological reaction will be explained by the three-dimensional structure of the interacting molecules and is often said to entail so-called proximate causes (Mayr, 1982). Since the phenomenon under study now involves only molecular and atomic forces, it is debatable whether the analysis still belongs to the field of immunology rather than protein chemistry. Studying the interaction between a protein antigen and an antibody molecule, itself also a protein, may be classified as an immunochemical investigation but this does not make it an example of a biological rather than a chemical study. What may be considered to be a reduction from biology to chemistry in fact is simply a shift in subject matter whereby any attempt at describing and understanding a biological phenomenon such as pathogen recognition and elimination or self–non-self discrimination has been abandoned. For the same reason, it could be argued that much of what is today called research in molecular biology does not really belong to biology at all. In recent years, it has become increasingly recognized that the appropriate conceptual framework for biological investigations involves notions of complexity and emergence (Holland, 1994; Casti, 1994). This may in due course alter the distinct reductionist flavour of much of contemporary biological research.

The so-called rational design of vaccines

Our increasing knowledge of the molecular structure of antigenic sites recognized by antibodies (Davis and Cohen, 1996) and T-cell receptors (Garcia and Teyton, 1998) has given rise to the belief that it should be possible to develop vaccines following the molecular design strategies used in structure-based drug design (Kuntz, 1992; Gschwend *et al*., 1996; Amzel, 1998). Such a belief disregards the fact that the relationship between a drug and its receptor or target molecule is fairly unique. In this case, once the molecular details of the interaction have been elucidated, it may be feasible to alter the structure of the drug slightly in order to improve

its biological activity, a procedure known as *rational design*. In the case of antigen–antibody interactions, however, recognition is always a highly degenerate type of process. Antibodies are always polyspecific and in addition to recognizing the epitope against which they were elicited, they are always able to bind to a large number of structurally related or unrelated epitopes (Van Regenmortel, 1998).

In order to use a molecular design strategy for developing vaccines, it is necessary to possess detailed structural information on the relevant antigens. In the case of several viruses, the three-dimensional arrangement of the atoms present on the outer protein surface of the virus particles has been established by X-ray crystallography (Chiu *et al*., 1997). This makes it possible to describe in molecular terms the viral antigenic sites that are recognized by the immune system and has led to the suggestion that these antigenic sites, in the form of synthetic peptides, could replace intact virus particles for vaccination purposes (Arnon, 1987; Nicholson, 1994). Compared to classical vaccines that require the cumbersome handling and containment of large amounts of infectious material, synthetic vaccines made up of inert chemicals would be very stable and would be cheaper, safer and easier to use. As a result, there has been considerable interest in the possibility of replacing classical vaccines by peptide-based vaccines (Van Regenmortel, 1999b).

A molecular design approach could, in principle, be applied to improve the capacity of a peptide antigen to bind to a particular monoclonal antibody which neutralizes the infectivity of a virus. Antibodies endowed with neutralizing capacity are the type of molecules that a viral vaccine must be able to elicit in order to be effective. However, it should be emphasized that when the binding properties of a peptide are optimized with respect to one neutralizing antibody molecule, this does not ensure that the same type of antibody molecule will be elicited when the peptide is used as a vaccine immunogen. The reason for this is that a peptide vaccine must possess adequate immunogenicity – a property very different from its antigenicity.

The ability of a peptide to react specifically with a complementary antibody is known as antigenic reactivity or antigenicity. This type of reactivity can be improved by optimizing the degree of steric complementarity between the peptide and a single antibody molecule. The situation is quite different with immunogenicity, which is the ability of an antigen to induce an immune response in a competent host. Whereas antigenicity can be reduced to the chemical level of an interaction between a peptide and a particular antibody paratope, such a reduction is not feasible in the case of immunogenicity which depends on many complex interactions with various elements of the immune system. The immunogenic capacity of

a peptide, in addition to being dependent on intrinsic properties of the peptide, also depends on the potentialities of the host being immunized, i.e. on extrinsic factors such as the immunoglobulin gene repertoire, self-tolerance, cytokines and various cellular and regulatory mechanisms that have no meaning outside of the context of a functioning immune system. These factors cannot be controlled by adjusting the structure of the peptide in a predetermined manner. For instance, one cannot predict which sequential order of the T and B cell epitopes included in a synthetic peptide construct will produce the most effective vaccine immunogen (Denton *et al*., 1994; El-Kasmi *et al*., 2000). Furthermore, it is not sufficient to elicit a strong anti-peptide immune response since what is required is the induction of a particular type of antibody that also recognizes the infectious agent and neutralizes its infectivity. Unfortunately, there are no rules for designing peptide immunogens that elicit neutralizing rather than non-neutralizing antibodies (Van Regenmortel, 1999c).

Another difficulty is that a peptide may be able to bind to an existing neutralizing monoclonal antibody by an induced-fit mechanism that is somehow driven by the pre-existing structure of the antibody paratope. However, the same induced-fit process may not take place when the peptide is used as the immunogen and is confronted in the host by a large population of B cell receptors allowing a variety of other interactions.

Many attempts have been made to develop peptide-based vaccines against viral diseases. Such studies have been carried out with foot-and-mouth disease virus, influenza virus, human immunodeficiency virus, measles virus, poliovirus and canine parvovirus (Van Regenmortel, 1999b), and usually involve the initial selection of peptides that bind strongly to certain neutralizing monoclonal antibodies. In the case of measles virus, for instance, some peptides were found which corresponded to the known epitopes of the virus (El-Kasmi *et al*., 2000). By using random and combinatorial peptide libraries, other peptides were selected which showed no sequence similarity with the viral antigen and were therefore labelled as mimotopes (El-Kasmi *et al*., 1999). Irrespective of whether the peptides showed a sequence similarity with the viral antigen or not, most peptides selected because they bound strongly to the antibody were unable to induce neutralizing antibodies when used as immunogens (El-Kasmi *et al*., 1999, 2000). In most studies of this kind, it is found that the selected peptides are rarely able to induce antibodies that possess the required neutralizing capacity.

In the rare case when a peptide showing some promise has been identified, further immunization trials are necessary to establish its value as a practical synthetic vaccine. Since peptides are usually poor immunogens and do not mimic well the conformation of the corresponding antigenic site in the

virus, the level of neutralizing antibodies that can be induced by peptide immunization tends to be rather low. In order to improve the ability of the peptide vaccine to induce protection, various strategies are then followed such as introducing chemical modifications in the peptide to increase its stability and the use of various delivery routes and adjuvants. None of these approaches, however, amount to a rational design strategy requiring information on the structure of the molecules implicated in the immune response. There are many additional reasons why the molecular design of synthetic vaccines is not a realistic enterprise (Van Regenmortel, 1999c).

In conclusion, it appears that the knowledge derived from a reductionist analysis of the physico-chemical principles underlying immunological recognition is not sufficient to allow immunologists to design new vaccines. The elicitation of a neutralizing immune response in a vaccinated individual cannot be reduced to a specific chemical recognition process between an antigen and its antibody.

Whereas molecular design is a strategy applicable to the chemical level of epitope–paratope interactions, it cannot be used for optimizing the many cellular interactions required for achieving an immune response that leads to infectivity neutralization of a pathogen. As a result, the future development of vaccines will continue to rely more on the empirical testing of the protection afforded by candidate vaccine preparations than on the rational design of biomolecules defined in a reductionist manner by their chemical structure.

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Chapter 5

Reductionism in Medicine: Social Aspects of Health

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Introduction

I review in this paper a number of empirical findings which show that not all appropriate or powerful medical research is done at the molecular or even clinical level. Socioeconomic factors turn out to be powerful predictors of health outcomes, both for the rich and the poor, and these factors cannot be investigated if all research funds are concentrated at problems conceived at the molecular level. I first review some relevant but surprising facts, and then summarize some current hypotheses concerning how social-level phenomena become embedded in individual organisms. I conclude by reiterating a well-designed research program to explore these phenomena that appear well above the molecular level.

What we know

Socioeconomic gradients and health

There is a socioeconomic gradient in health status. Those with higher income, better education, and jobs with more status, prestige, and decision latitude provide the best ecological niche for adult human beings. Those with less of these things enjoy progressively higher morbidity and mortality.

This in itself is not too surprising. What is much more surprising is that a number of cross-national surveys have shown that the degree of income inequality in a given society is strongly related to the society's level of mortality. The more steep the income gradient (the more severely the poor

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are poorer than the rich), then the worse off everyone is, not just the poor. The health status of each social class within the population seems to be better than the classes below, and worse than the classes above, regardless of the actual level of material wealth. Thus, middle-class people in a very rich society may die sooner than upper-class people from a less rich society, even though they have more material goods.

We would expect absolute levels of income to be related to morbidity and mortality, but there are many new studies showing strong associations between levels of *income inequality* and mortality (after adjustments for absolute income differences) in the 50 states of the US. The results show that *increased mortality at all per capita income levels* is associated with higher income inequality (Kaplan *et al*., 1996; Lynch *et al*., 1998; see also Kennedy *et al*., 1996). That is, the size of the gap between the wealthy and the poor (vs. the absolute standard of living held by the poor) matters in its own right. A higher per capita income was still significantly associated with lower mortality ($r = -0.21$), but this association was *weaker* than the effects of income inequality on mortality. In other words, being in the top 10% of income in a society with a steep income gradient increases your chances of morbidity and mortality, compared to living in a society with a less steep difference between the rich and the poor.

Areas with high income inequality and low average income had an excess mortality of 139.8 deaths per 100 000, compared with areas with low inequality and high income. In 1995, the magnitude of this mortality difference was comparable to the combined loss of life from lung cancer, diabetes, motor crashes, HIV, suicide, and homicide combined (Lynch *et al*., 1998, p. 1079).

The conclusion is that there is a high mortality burden associated with income inequality. In other words, the greater the gap in income between the rich and the poor in any given society, then the lower the average life expectancy, while the latter is relatively unrelated to average national income. The life expectancy is lowered even for the richest tenth, in societies with steep income gradients. This result has been confirmed in a number of cross-national studies (Kawachi *et al*., 1997; LeGrand, 1987; Rodgers, 1979; Wilkinson, 1986, 1990, 1992, 1997).

The range of diseases which display this phenomenon is astonishingly broad, and includes the following: accelerated aging, allergies, angina, arrhythmias, asthma, atherosclerosis, cancer, coronary artery disease, epilepsy, essential hypertension, Grave's disease, headaches, herpes, multiple sclerosis, myasthenia gravis, myocardial infarction, peripheral vascular

disease, post-traumatic stress disorder, rheumatoid arthritis, stroke, systemic lupus erythematosus, and type 2 diabetes mellitus (Kelly *et al*., 1997, p. 438).

The results regarding socioeconomic gradients undermines the hypothesis that the principal social class influence on health is material deprivation. In fact, the social class gradient in health cuts deeply into the affluent middle classes. The implication is that the conditions under which people live can affect human health directly, and not only through material deprivation. 'Early childhood experience, one's place in the social environment, and the experiences of daily life must be powerful determinants of the length and healthfulness of life' (Kelly *et al*., 1997, p. 438).

If all this is correct, then there must be some process of 'biological embedding' wherein life experiences condition individual biological responses, which lead to systematic differences in resilience and vulnerability to disease across the range of social class experience.

Studies examining the relationship between socioeconomic status and health have also been carried out comparing various US states, e.g. comparing the degree of household income inequality and state-level variation in all-cause and cause-specific mortality. In an independent study, Kaplan *et al*. (1996a) examined the association between income inequality and state-level and household-level variations in total mortality rates. In all cases, increased steepness of inequality was associated with higher death rates overall.

Common myths

Several factors have long been believed, both popularly and in public health, to be decisive contributors to the health gap between the wealthy and the poor. The real questions regarding population health were thought to revolve around identifying which aspect of people's material circumstances were responsible for the social gradient in health, e.g. occupational hazards, differences in diets, housing, and air pollution? Reviews of some recent findings regarding determinants of population health from the 1980s are therefore in order. First, medical services 'were not a major determinant of population health – and certainly not of the substantial social gradient in health found even in countries providing universal access to medical care' (Wilkinson, 1999, p. 48). Another common myth is that well-known behavioral risk factors, such as smoking, obesity, and lack of exercise, explain the social gradient in health; in fact, these well-known risk factors left most of the social gradient in health unexplained. Finally, social selection

(reverse causality, wherein sick people tend to become poor) made only a minor contribution to health inequalities (Wilkinson, 1999, p. 48).

The puzzles

One puzzle that arises from these results is to understand the mechanisms by which *relative* socioeconomic position leads to variations in health. Degree of income inequality is an 'ecologic' variable – it is a property of the population and not of the individual. This is not how we ordinarily think about health, which is conceptualized as a property of an individual body, while socioeconomic level is usually conceptualized as a property of an individual or a family, and is measured by income, education, occupation and social class. Large conceptual changes in our understanding of the biology of disease have been required, in order to account for these new findings. I review below several key theories put forward to explain the challenging findings revealed in these cross-populational correlations between socioeconomic status and morbidity and mortality.

Hypotheses

The biological problem is that the pathways and mechanisms of the association between income inequality and mortality levels are still unknown. These questions are, nevertheless, fundamentally biological, as they must address how social influences can somehow enter into or embed themselves in the functioning body.

Wilkinson

Richard G. Wilkinson's hypothesis is that the key lies in understanding the biology of social anxiety. It is not the absolute standard of living that is important, but the levels of depression, isolation, insecurity and anxiety that are associated with relative poverty, which he describes as *psychosocial characteristics*. During the 1990s, it became established that there were important psychosocial influences on health e.g. 'life events', social support and sense of control were all closely associated with health. The questions for epidemiologists thus became – what ideational states were damaging to health? Wilkinson concluded that anything contributing to chronic anxiety was likely to affect health.

The crucial investigative questions for Wilkinson are as follows. How hierarchical is the social hierarchy? What are the depths of material insecurity and social exclusion tolerated by society? What are the direct and indirect psychosocial effects of social stratification?

He believes that the clinching pieces of evidence where psychosocial pathways may make the largest single contribution to the socioeconomic gradient in health came from the evidence regarding income and health. Specifically, income was found to be related to health within developed countries (and within US states), but not between them. Thus, it seemed likely that the relationship was not one between absolute living standards or material circumstances, 'so much as a relationship with relative standards or with relative income serving as a marker for social status' (Wilkinson, 1999, p. 49). Independent confirmation for this theory came from evidence that, 'although mortality rates in developed countries were not closely related to average income, they were related to income distribution. [Thus], Measures of income inequality can plausibly be interpreted as measure of the burden of relative deprivation on health in each society' (Wilkinson, 1999, p. 49).

Further independent confirmation came from studies of the biological effects of social status among nonhuman primates. R. M. Sapolsky's studies of wild baboons, and C. A. Shively's studies of macaques in captivity showed that a number of physiological risk factors had similar associations with social status among animals as those among human beings. The reason that these animals studies are so compelling for those studying risk in human beings is that the physiological risk factors associated with social status among nonhuman primates and people are pretty much the same. Characteristics reported to be associated with social status among *both* human beings and non-human primates include the following: worse HDL:LDL ratios, central obesity, glucose intolerance, increased atherosclerosis, raised basal cortisol levels, and attenuated cortisol responses to experimental stressors (Wilkinson, 1999, pp. 49–50).

In addressing the basic question, then, of why more egalitarian societies tended to be healthier than less egalitarian ones, Wilkinson believes that the most plausible explanations focus on the way that the social environment is affected by inequality. He emphasized cases in which unusually healthy and egalitarian societies provide circumstantial evidence that more egalitarian countries were more socially cohesive than less egalitarian ones. Data observed from several sources have strongly confirmed this pattern (Wilkinson, 1996; Kawachi and Kennedy, 1997).

For instance, Wilkinson found that people are much more likely to feel trustful towards others in those US states in which income differences were smaller. Similarly, the hostility scores for 10 US cities found by R. B. Williams *et al*. (1995) were related to city mortality rates ($r = -0.9$), which have also been found to be related to the extent of income inequality in those cities. In addition, R. D. Putnam studied the functioning of regional governments in Italy, and notes that his index of 'civic community' (measure of the strength

of people's involvement in community life) was closely correlated with the extent of income inequality (Wilkinson, 1999, p. 51).

There is also evidence from a large number of studies that homicide and violent crime are substantially more common in less egalitarian countries. (A meta analysis carried out by Hsieh and Pugh showing violent crime and homicide rates related to income inequality covers 34 studies (Hsieh and Pugh, 1993).) All of this evidence strongly suggests that as social status differences in a society increase, the quality of social relations deteriorates. The countries studied included the US, UK, Italy, and Japan, plus a number in Eastern Europe.

However, what is it about social status and social integration that makes them so important to health? One proposal is that social status indicates social capital, and that it is a person's social capital which is most important to health. Wilkinson rejects this hypothesis, stating that 'social capital' is an epiphenomenon 'and that we still have to identify the causal factors underlying it' (Wilkinson 1999, p. 52).

According to Wilkinson, 'No one has yet provided a plausible explanation of why either social cohesion/capital or friendship and the quality of social relations are important to health. Good social relations of all kinds – from close 'confiding' relationships, to having more friends, to involvement in community associations – all seem to be beneficial to health' (Wilkinson, 1999, p. 52).

Looking for the direct results of social status is also difficult. 'The fact that a number of the same physiological risk factors are associated with low social status among humans as have been reported among monkeys, means that they are unlikely to be explained by smoking, unemployment, bad housing, and the like. Among monkeys, the physiological risk factors associated with low social status can be confidently attributed to the chronic anxiety that comes from the constant threat of being attacked and bitten by superiors. However, the sources of the chronic anxiety inherent in low social status among people are rather different and usually more subtle' (Wilkinson, 1999, p. 52).

Wilkinson concludes, 'We do not really know why social affiliation matters to health, we do not know why social cohesion is associated with better health, and we have not yet identified what is inherently stressful about low social status' (Wilkinson, 1999, p. 52).

So how does Wilkinson propose to fill these gaps in our biological knowledge? He is sure that, once we have identified the main sources of chronic anxiety, there are a variety of plausible biological pathways from there to physiological illness and death. He also believes that, when the 'stress reaction' (fight or flight) is activated for brief emergencies, little harm

is done. 'But when the anxiety and worry lasts for months and years, and the body is frequently in a high state of arousal, there is likely to be a variety of health costs' (Wilkinson, 1999, p. 53). This is because, among other things, when the body is mobilizing resources for muscular activity, other system-maintenance and repair processes (such as growth, tissues repair, immunity, digestion, reproductive functions, etc.) are put on hold (Sapolsky, 1998). Risk of blood clots is also increased, and therefore risk of heart attacks. If the energy resources that are mobilized are not used, they increase accumulation of cholesterol in blood vessels. All of this means that the variety of physiological processes affected by chronic anxiety mean that its health effects are analogous to more rapid aging. 'Our aim then is to understand the central sources of chronic anxiety related to the main risk factors for population health in the developed world' (Wilkinson, 1999, p. 53).

One of the primary sources of anxiety considered by Wilkinson is violence. He notes the association between income inequality and homicide. Among the 50 US states, it accounts for half of the very large variations in homicide rates between states. The higher violence was not between rich and poor. 'The violence associated with greater inequality occurs largely among the most deprived' (Wilkinson, 1999, p. 54). This makes sense, according to Wilkinson: 'Where more people are denied access to the conventional sources of respect and status in terms of jobs and money . . . people become increasingly vulnerable to signs of disrespect, that they are being treated or regarded as inferior, insignificant, and worthless' (Wilkinson, 1999, p. 54). Wilkinson sees all this as very significant, because it shows how much social status matters to people, and can perhaps start to show how low social status may be a direct source of anxiety.

Wilkinson also notes the importance of emotional development in early life: poor attachment and emotional trauma in early childhood affects health. As he notes, there are observed associations between health and social status, between health and friendship, and between health and early emotional development. All three of these must be considered prime candidates for sources of social anxiety.

One mistake which Wilkinson urges us to avoid is to picture human characteristics as having evolved in relation only to a physical environment; one of the primary hostile forces has always been other human beings. The importance of social interactions should not be underestimated. One example that he gives is that blood pressure tends to rise when people are interviewed by a higher- rather by than an equal- or lower-status interviewer. This is fundamentally a response of the sympathetic nervous system to the social anxiety induced by interacting with someone who is of higher social status.

In sum, Wilkinson focuses his explanatory hypothesis on social anxiety. He links social anxiety to shame, depression and violence, and emphasizes that social anxiety has its roots in perceptions of inferiority, unattractiveness, failure or rejection. This helps explain why health is so closely related to lack of friends, low social status, violence and poor early emotional attachment, all of which are associated with similar patterns of raised basal cortisol levels and attenuated responses to experimental stressors. He concludes, therefore, that social anxiety is a very plausible central source of the chronic anxiety that depresses health standards and feeds into the socioeconomic gradient in health. As he puts it, 'the most important psychosocial determinant of population health is the levels of the various forms of social anxiety in the population, and these in turn are determined by income distribution, early childhood and social networks' (Wilkinson, 1999, p. 60). Thus, social anxiety is suggested as an explanation for the links between health and friendship, health and early emotional development, health and the direct psychosocial effects of low social status, the patterning of violence and health in relation to inequality, and health and social cohesion (Wilkinson, 1999, p. 61).

While Wilkinson's approach is perhaps the best known, I will review several other hypotheses in the remainder of this section.

Kaplan

George Kaplan has shown that US states with greater inequality have higher rates of violence, more disability, more people without health insurance, less investment in education and literacy, and poorer educational outcomes, all of which he calls 'structural' characteristics. Moreover, the socioenvironmental characters of population areas are importantly related to the mortality rates, *independent* of the characters of individuals. In addition, personal and socioeconomic risk factors cluster together in areas of low income and high mortality. In a thorough local study of Alameda County, California, Kaplan examined parts of the pathways linking social class and mortality. His basic claim is that health inequality is correlated to social instability, which is in turn correlated to the lack of investment in 'structural' characteristics, such as education, proximity of healthful food outlets, pharmacies, accessibility of transportation, etc.

Kaplan criticizes the usual approaches to uncovering the biological and physiological pathways that allow social class to 'get under the skin', claiming that they fail to examine the larger social contexts. (For example, more smoking is correlated with higher fibrinogen, although the researchers don't explain why.) The most fundamental flaw that he observes with

conventional approaches is that they see socioeconomic status (SES) as an individual-level trait. Approaching SES this way ignores 'patterned sets of exposures, opportunities and resources that differ by social class level,' all of which can make a difference to health outcome (Kaplan, 1996, p. 508). In his studies, Kaplan includes ecological as well as individual variables, for example, in his Alameda County study, 'residence in a poverty area' turned out to be a key determinant of health (Kaplan, 1996, p. 509).

Kelly, Hertzman and Daniels

On Clyde Hertzman's theory, the socioeconomic gradient in health status discussed in the previous section cuts across a wide range of disease processes and is capable of replicating itself on new disease processes as they emerge in society. In order to understand the gradient, we need to understand what makes human organisms become generally vulnerable or resilient to disease over time. According to Hertzman, 'The hypothesis that best fits current evidence is that the gradient is an ''emergent property'' of the interaction between the developmental status of people and the material and psychosocial conditions they encounter over their life course' (Hertzman, 1999, p. 85).

Hertzman focuses mainly on child development: socioeconomic differences in the quality of early life experiences contribute to subsequent gradients in health status through socioeconomic differences in brain sculpting and the conditioning of host defense systems that depend on communication with the developing brain. The contribution to the gradient in health is theorized to occur through a combination of latent effects, pathway effects and cumulative disadvantage.

In work carried out with Shona Kelly and Mark Daniels, Hertzman's approach to explaining the correlations between socioeconomic variables and health is to treat life as a cumulative process. According to their view, life experiences, especially early childhood brain development, condition individual biological responses, especially resilience and vulnerability to disease. According to Kelly, Hertzman and their co-workers, the most plausible biological connection is the central nervous system, which 'talks to' the immune, hormone and clotting systems, all of which can be involved in disease processes (Kelly *et al*., 1997, p. 438). In addition, chronic stress leads to subtle, long-term changes in endocrine, hemostatic, and immune system function. These authors are able to draw on the extensive knowledge regarding socioeconomic gradients in health status, the biology of stress, and the connections between consciousness and host defense mechanisms.

However, they note, there is no scientific consensus 'that the conditions of life actually do embed themselves in human biology over the lifecycle,' or, even if they do, that this is a 'significant determinant of health in the populations of high-income countries' (Kelly *et al*., 1997, p. 438). In fact, this has never been subjected to rigorous empirical scrutiny, for a good reason. It would require lifelong longitudinal studies of large representative population samples, involving both extensive questionnaire responses and biological sampling at frequent intervals (however, see the following section).

Lynch

In addressing the question of how income inequality is linked to population health, Muntaner and Lynch (1999) identified two strands of causation, thus combining the approaches of Kaplan and Wilkinson. First, they claim that income inequality is associated with a set of social processes and economic policies that systematically under-invest in physical and social infrastructure (e.g. education). Secondly, large disparities in income distribution may have direct consequences on people's perceptions of their relative place in the social environment, which leads to behavioral and cognitive states that influence health.

Kawachi

Ichiro Kawachi and co-workers have pursued a hypothesis that centers on social cohesion and trust. They claim that the growing gap between the rich and the poor has led to declining levels of social cohesion and trust, or disinvestment in 'social capital,' i.e. features of social organization such as civic participation, norms of reciprocity, and trust in others. Social capital is understood as civic engagement and levels of mutual trust among community members, and civic engagement is the extent to which citizens involve themselves in their communities, as most often measured by either membership in groups and associations. Social capital is thus a 'community level' ('ecologic') variable whose counterpart at the individual level is measured by a person's social networks. There is a large literature linking social networks to health outcomes at the individual level, but studies of social capital have so far only focused on performance of civic institutions, which does not really get at the flavor of Kawachi's variable.

In a 1997 study, Kawachi and co-workers (Kawachi *et al*., 1997, p. 1492) reported on a test of three linked hypotheses as follows:

(1) 'That state variations in income inequality predict the extent of investment in social capital'.

(2) 'That the degree of investment in social capital predicts state variations in total and cause-specific mortality'.

(3) 'That there is little residual direct association between state income inequality and mortality after investment in social capital has been controlled'.

The results were that income inequality was strongly associated with lack of social trust, and that states with high levels of social mistrust had higher age-adjusted rates of total mortality (level of social trust explained 18% of variance in total mortality, under their regression). Lower levels of social trust were associated with higher rates of most major causes of death, including coronary heart disease, malignant neoplasms, cerebrovascular disease, unintentional injury, and infant mortality.

On the other hand, per capita group membership was strongly inversely correlated with all-cause mortality. Level of group membership was also a predictor of coronary heart disease, malignant neoplasms, and infant mortality.

When Kawachi and co-workers carried out a path analysis, it indicated that the primary effect of income inequality on mortality is mediated by social capital (as measured by level of perceived fairness). Income inequality exerts a large indirect effect on overall mortality through the social capital variable. As income inequality increases, so does the level of social mistrust, which is in turn associated with increased mortality rates.

They concluded that income inequality was directly and strongly related to the postulated causal factor (disinvestment in social capital), but when the causal factor was controlled, there was little residual direct association between the instrumental variable and the outcome (Kawachi *et al.*, 1997, p. 1496).

Wilkinson indicates that he considers social cohesiveness to be an epiphenomenon. The evidence shows that where income differences are greater, violence tends to be more common, people are less likely to trust each other, and social relations are less cohesive. However, the impression that social cohesion is beneficial to health may be less a result of its direct effects, and more of 'a marker for the underlying psychological pain of low social status'. He believes that the biological causal pathways are 'Likely to center on the influence that the quality of social relations has on neuroendocrine pathways' (Wilkinson, 1999, p. 48).

Prospects for research

We are left with many questions still unanswered. What is it about social status and social integration that makes them so important to health? What are the main sources of chronic anxiety, and what are their effects on health? (This is an especially promising question, since we already have a good idea about why stress affects health (Sapolsky, 1998).) What is the association between income inequality and homicide? (Homicide can account for half the variation in mortality rates between states.) How does inequality affect emotional development in early life?

Here is one primary challenge. If the biological embedding hypothesis is correct, and somehow the socioeconomic system is being read into the biology of the body, then it should be possible to show that differences in socioeconomic status and living conditions *precede* the emergence of systematic social class differences in biological variables. Kelly *et al*. (1997), as well as some of the others, have made a testable prediction – the results should show that central nervous system-mediated host defense pathways function differently in people who have more income, better beginnings, better jobs, more social supports, etc. Plus, the temporal relations between socioeconomic, living conditions, and measures of host defense must make sense.

In order to test this, Kelly *et al*. (1997) point out that we need a set of biological markers thought to be sensitive to long-term systematic differences in socioeconomic status and living conditions, and these markers must be feasible to measure in large population surveys, so their role in the biological embedding process can be evaluated on a population-based, person-specific basis.

As mentioned above, such investigations might require a vast longitudinal study. We have birth cohort studies from the UK (1958) and the US, which can already be overlapped with longitudinal studies from working age and old age to simulate the entire life cycle. (These are not complete, but can be pieced together.)

Such longitudinal studies could show how social class factors influence health throughout the life cycle, and motivate investigations into the *biological pathways* linking class and health, e.g. the National Population Health Survey in Canada, begun in 1994.

However, biological measures are needed, and relevant ones. Hertzman and his colleagues have suggested a small group of biologically relevant tests. The idea is to obtain information about the processes by which socioeconomic and psychosocial factors embed themselves in human health. These include biological measures of the status of the psychoneuroimmunology/psychoneuroendrocrinology pathways. In their review article of 1997,

Hertzman and co-workers set out criteria to evaluate potential physiological markers of chronic stress. Recognizing that population health surveys involved a massive number of samples, with some care towards timing and delivery of such samples, they recommend studying the following: glycosylated proteins, especially glycosylated hemoglobin and advanced glycosylation end-products, immune function, particularly antibody response to vaccines (they rule out any test requiring fresh, large volumes of blood), hemostasis, especially coagulation and fibrinolysis systems, and fibrinogen. They also mention peripheral benzodiazepine receptors and waist–hip ratio as possible measures (Kelly *et al*., 1997, pp. 441–454).

Conclusion

There is already enough evidence available to conclude that phenomena above the level of the individual organism can have a serious and lasting impact upon health. Research programs that focus exclusively on molecular-level understandings of the workings of the human body will be unable to contribute to improving these aspects of population health.

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QUESTIONS AND DISCUSSION

Alex Rosenberg: There must be some obvious defect in this explanation, so let me try it out on you. The first component is that inequality is the result of an incentive structure that makes some people work much harder than other people. The second is that harder work *ceteris paribus* produces higher mortality and morbidity, and the third is that higher morbidity at lower socioeconomic status plus contagion leads to higher morbidity and mortality at higher socioeconomic status – end of story.

Elizabeth Lloyd: No, these are all non-contagion related medial situations. I mean, these are all countries in which contagion is not a significant medical factor.

Alex Rosenberg: All right, but now the first two would, by themselves, explain the character both of the relationships between the gradients and the steepness of the morbidity and mortality histograms.

Elizabeth Lloyd: Oh, a common cause. Well, I'd be more inclined to accept something that had a certain economic structure at its center except that these same results have been shown across 159 different countries and several countries in the former USSR.

Alex Rosenberg: But there are still incentive effects in those countries. It is just the pay-offs that are different. You have to work hard to climb the ladder in the Communist Party, as opposed to working hard in climbing the corporate ladder.

Elizabeth Lloyd: Maybe I misunderstood, but the claim that these guys are making is precisely that it is the reflection of differential socioeconomic status that creates the stress in the society that makes people sick. Is that not the explanation you just gave?

Alex Rosenberg: No, the explanation I just gave is that the harder you work, the more likely you are to show morbidity and mortality. And a society which has a stronger incentive structure, for example, a capitalist society as opposed to a highly egalitarian society, is likely therefore to result in individuals working harder and showing greater . . .'

Elizabeth Lloyd: Well it is not a good incentive if it is going to kill you, is it?

Alex Rosenberg: We'll have time in the round table to continue this discussion. John, do you want to talk?

John Dupré: Yes, I suppose, partly my reaction is a little similar to Alex's in the sense that the first thing that surprised me more than anything else was your surprise at these results. And I guess the reason I'm surprised is that in the course of your talk, about 10 different hypotheses occurred to me, most of which you discussed. As far as the pathogens are concerned, surely we don't know which major diseases have some pathogenic component in them, and that could be more important you suggest. It seemed to me that as you went through, you mentioned a whole lot of things and you said of them that ethos doesn't explain a whole lot of the difference. Another thing that Alex suggested was that it is very difficult to get causal direction; a lot of the things, particularly social cohesion, might well be a cause of these inegalitarian societies, as well as mentioned, half of these hypotheses reflecting my general intuition that these are generally more dysfunctional societies with less social cohesion, a lot more violent. And of course the murder rate – the violence causes stress. One knows, in fact, rich people aren't usually victims of violence but we all know lots of rich people whose lives are made miserable by the stress that the fear of violence causes to them, and so on, and so on. It just seems the likely explanation is dozens of explanations, dozens of things that are dysfunctional in these societies that all contribute at least a little bit to a higher mortality rate.

Elizabeth Lloyd: One thing that was very difficult for me in sorting through this literature was deciding why these people thought they disagreed with each other so much, about what the explanatory hypotheses were. Now it is true that they did have different explanatory emphases in their theories. One of them, one that kills me the most, quite frankly, is the guys who go out and measure and get a response, because that is what I want to see (laugh)! Then I have some numbers that I can look at and I can see and compare with other numbers. And the thing is they do have lots of numbers already – it is just that with psychoneuroimmunology having progressed so much just in the last 5 years, the kind of information would provide genuinely new data.

John Dupré: It doesn't sound that anything you said goes strongly against the hypotheses that they are all right . . .

Elizabeth Lloyd: I would say nothing I said goes against the hypothesis that they are all right.

John Dupré: You add them all together, and there is not so much of a problem.

Elizabeth Lloyd: Right.

Robert Williams: Can I make two points? One – nobody has ever suggested that the population of England works harder than any other population. Everybody always says exactly the opposite. Certainly academics all through Europe. I don't think working hard can be put opposite the British problem. The second is, when you draw straight lines, this is more serious, as you have to look at the asymptotes as well as at the gradients. Now the question is, can you then show us anything about asymptotes, so let's just see what actually happened in a population. In Finland, they've undergone a very considerable experiment on these lines. They've increased the life expectation quite considerably in a very simple way. And so I'd love to know where Finland lies in these studies before, let's say, about 15 years ago and today, because I think what has happened is the whole line has been just lifted up and I don't believe that the socioeconomic status, the slope of it, I can hardly believe that this is changed much, although it has become a much more successful society.

Elizabeth Lloyd: According to the theory, what matters to these guys, the phenomena that these guys are looking at, is not the gross national product, but what the gradient is.

Robert Williams: Yes, but where does the line intersect the axes? Where is the intercept, because if you plot intercepts, do you get any result at all about mortality? It would be very strange if you didn't.

Elizabeth Lloyd: Well, Finland has gone up in expected age, and the Russians have gone down. Some of the studies that I was reading in preparation for this talk were on the former Czech Republic and on other areas behind the Iron Curtain, where the mortality rate has skyrocketed since 1989 through all sources of death, all causes of death, and that is very interesting. In these cases, the line went from being very flat with a little flip-up at the end to being extremely steep, and you had a dramatic fall of life expectancy. That is actually a beautiful confirmation of what these guys had been predicting was actually the case. So I don't know about the Finland case, but for the other cases it's clear.

Chapter 6

'Who's Afraid of Reductionism?' 'I Am!'

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Introduction

For more than thirty-five years, I've been studying evolution – originally the evolution of cancer (Shostak and Tammariello, 1969; Shostak, 1981), and more recently, the evolution of tissues (Shostak, 1993; Shostak and Kolluri, 1995). During this time, I have encountered reductionism, sometimes as a prod and frequently as an obstacle. I have learned, thereby, to appreciate the difficulties that reductionism presents for studying evolution. Thus, when Daniel Dennett, the philosopher of evolution and consciousness, asks in his perennially popular, *Darwin's Dangerous Idea*, 'Who's Afraid of Reductionism?' (Dennett, 1995, p. 80) I'm compelled to answer 'I am!' and explain why.

Of course, one could hardly have lived through the second half of the Twentieth century without marveling at the accomplishments of reductionism – there would be no biotech industry or Human Genome Project without it. Nevertheless, a considerable part of what interests biologists – between the beginning and end of evolution – is not necessarily congenial to reductionist approaches. Reductionism prescribes that we take what we know and apply it to the past as long as the evidence produces no contradictions, and we use what we have learned about events and processes on a small scale to understand events and processes on a large scale unless overwhelmed by incongruities. Thus, instead, of acknowledging that what we know of the present cannot be applied *ipso facto* to the remote past, to the Prephanerozoic or Archean, reductionists extrapolate from data for extant species to unknown ancestors. In addition, instead

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of pondering how species are related to larger taxa, reductionists elide differences and assume sameness (Shostak, 1999). Thus, some biologists, mathematicians, philosophers and psychologists have brought reductionism into the mainstream of evolutionary thought.

What is reductionism, anyway? Dennett tells his reader that ' ''reductionism'' has no fixed meaning' (Dennett, 1995, p. 80), but he defines 'bland' reductionism as something 'No sane scientist disputes' (Dennett, 1995, p. 81) while 'good reductionism ... is simply the commitment to non-question-begging science without any cheating by embracing mysteries or miracles at the outset' (Dennett, 1995, p. 82).

I have difficulties with both 'bland' and 'good' reductionism. Instead of 'bland' meaning 'insipid' or 'matter-of-fact', Dennett's 'bland' seems more like something one curls one's lip over. Dennett seems to be saying that a scientist who is not a reductionist must be insane, lacking scientific credentials, or both! Similarly, Dennett's 'good reductionism' is an indictment of nonreductionist thinking, accusing it of 'question-begging', 'cheating', and 'embracing mysteries' or 'miracles'.

Possibly there is a middle course between reductionism and its nonreductionist alternative. John Maynard Smith (1998, p. 41), for example, looks (in vain, it would seem) for a compromise between approaches that are 'local, reductionist and dependent on notions of information, regulation and control' on one side and those that are 'global, holistic and dynamic' on the other. I certainly do not propose to mimic Dennett's posturing ('There is no reason to be compromising', Dennett, 1995, p. 85) or his 'fighting words'. Rather, I take my lead from another philosopher, Georges Canguilhem, who tells his reader (Canguilhem, 1988, p. 89), 'Truth must submit itself to criticism and possible refutation or there is no science'. Thus, I propose examining reductionism, not as a generalization, but in terms of a specific concept, and not by a standard that 'No sane scientist disputes,' but by three standards for scientific discourse that allow room for controversy: (1) an hypothesis (law or theory) must be transparent (precise, having no shaded meaning, and carry no hidden inferences); (2) it must be testable (capable of generating or adjusting to alternatives); (3) it must 'do no harm' (neither impeding development nor stifling the flow of knowledge).

The specific concept I examine here is Darwin's singularly reductive statement (Darwin [1859] 1968, p. 398), 'the inevitable result is that the modified descendants proceeding from one progenitor become broken up into groups subordinate to groups'. With this statement, Darwin defined the 'natural' structure of life as one determined by genealogy. He thus changed forever how organisms were classified and how their classification was understood. Known today as *monophyly*, this cornerstone of Darwinism

supports a vast superstructure, from molecular phylogeny and cladistics to the annotation of protein sequences in databases. The question is, 'How does monophyly, as an example of reductionist statements, stack up against my three standards for scientific discourse?'.

Is monophyly transparent?

How does one 'see' the transparency of an idea? One approach is through historical analysis: to examine the 'faces' of an idea in its past in order to determine if its current 'face' is 'fresh' or covered over by cultural 'makeup'. Thus, I have examined the historical roots of monophyly in order to determine if its contemporary statement can be trusted to 'say what it means and mean what it says?'.

The monadic roots of monophyly

Conceptually, the idea of monophyly begins with crediting life to a class of things called 'living'. The proposition that life is an attribute shared by living things can be traced back to Aristotle (344–220 BC), but it was extended from animals to plants under the doctrine of organicism, that life was the manifestation of activity made possible by the state of autonomous organization in a system. 'Life' acquired its modern, inclusiveness in Western thought during the European Renaissance when life's microscopic wonders were first revealed. Speculation on life then flowered with classical analogies between macrocosms and microcosms.

In the Seventeenth century, when living things were first analyzed for their design qualities, life itself, or the vital properties of living things, were attributed to universal, elemental units. Gottried Wilhelm Freiherr von Leibniz (1646–1716) abandoned homogeneous atoms in favor of a hierarchy of monads, at the apex of which was the first principle or living force (Leibniz, [1714] 1974). Leibniz's monad had a soul and was self-generating, but it was not material, although in aggregate it was the link between form and matter, much as gravity was the link between force and matter. Toward the end of the Eighteenth century, however, Immanuel Kant (1724–1894) transformed the monad as principle into the monad as thing by merging the Leibnizian monad with Leonhard Euhler's (1707–83) physical, point atom. Thereafter, in all of their many guises, biological monads became instruments for unifying or annihilating the duality of physical and biological laws of nature, of spanning the divide between the natural philosophy of the universe and of life.

Nature philosophers were conspicuously influenced by the monad and routinely developed their concepts of life around these irreducible units.

Determinists, for example, placed the monad into a homunculus or into a principle which could be monotonously enclosed (the doctrine of *emboîtement*) to explain all manner of heredity and individual development. Rigid determinists at the time generally declined to study monads as things, however, preferring instead to study their hypothetical properties in the ascertainable qualities of living beings. Indeed, the Eighteenth century preformationist Charles Bonnet's (1720–1793) theory for the origin of form did not require a material basis and approached contemporary notions of coded informational transfer.

On the other hand, the cells which Caspar Friedrich Wolff (1738–1794) all but discovered in the chick embryo were rejected by determinists as lacking qualities required of monads.[1] Following the early Eighteenth century:

> *When microscopists began to look at the tissues of living forms they already had in their minds a view of matter as an aggregate of more or less uniform microscopic components. It is therefore understandable that when they saw everywhere agglomerations of more or less spherical halations, they concluded that these optical illusions were the fundamental subunits of animate matter, and when they actually saw cells they had no idea what they were (Harris, 1999, p. 3).*

Tissues filled the breach and became the first, successful materialist monads, the elements that bonded together and combined their properties in organs. Tissues were studied by early histologists without the necessity of looking through a microscope, and Marie Francois Xavier Bichat (1771–1802), arguably the parent of histology (see Foucault, 1970), identified dozens of tissues by purely chemical means. Biology was also finding its medical 'legs' at the time, and Bichat 'derived the principle of a genuinely etiological or causal pathology, the basis for a monist nosology that he used to challenge all essentialist and pluralist nosologies' (Canguilhem, 1988, p. 56).

Microscopists were not entirely idle, however, and after Giovanni Battista Amici (1786–1863) introduced achromatic lenses in France in 1827, the cell theory was not far behind. Henri Dutrochet (1776–1847) had already proposed that animal and plant tissues were constituted of cells, a view reiterated by many, notably Jan Evangelista Purkynê (1787–1869), Johannes Müller (1801–1858), and Jacob Henle (1809–1885). Félix Dujardin

[1] Ironically, in the first half of the Twentieth century, molecular biologists rejected nucleic acids as a genetic material, since they seemed entirely too simple, compared to proteins, to play roles in both heredity and development.

(1801–1860) had already described cellular contents, and Robert Brown (1773–1853) the nucleus. Christian Gottfried Ehrenberg (1795–1876) had described binary fission in infusorians, and Robert Remak (1815–1865) had described it in the animal body, demolishing, at the same time, notions of the intracellular origin of normal cells proposed by Matthias Schleiden (1804–1881), and the extracellular origin of normal cells proposed by Theodor Schwann (1810–1882), as well as the origin of tumors by an extracellular cytoblastem.

Rudolf Virchow (1821–1902) proceeded to replace tissues with cells as the dominant materialist monads of life and disease. According to his cell doctrine, all cells, and hence all life, came from cells: 'No developed tissue can be traced back either to any large or small simple element, unless it be to a cell' (quoted from Libby, 1922, p. 267). (The phrase, '*Omnis cellula e cellula*', however, frequently attributed to Virchow, seems to have been first used as an epigraph by François Raspail (1794–1878) (Harris, 1999, p. 33)).

Versions of the cell as monad flourished in Central Europe, nurtured equally by Romantics and microscopic anatomists, until monadism reached its apotheosis in the doctrine of 'monism' advanced by Ernst Haeckel. In the late Nineteenth century, Haeckel, following Christian Gottfried Ehrenberg, christened the unicellular bacteria and protists 'Monera' and declared that these cells gave rise to all other forms of life by branching evolution. Moreover, Haeckel asserted that the course of organismal development paralleled the evolution of a species. Thus, the fertilized egg, the 'cytula', was the stem cell for the organism and equivalent to the monera which was the trunk of all further revolutionary branching. Haeckel's fusion of evolution with development, known as the biogenetic[2] law ('*Ontogenesis is a brief and rapid recapitulation of phylogenesis*, determined by the physiological function of heredity (generation) and adaptation (maintenance) (Haeckel [1901] 1992, p. 81), was enormously influential, and for nearly half a century, biologists struggled to understand how cells both created and remembered branching patterns of organismal development and branching patterns of specific evolution.

Monads since Darwin

Charles Darwin was not particularly concerned with cells, although he was well aware of their role in development and was in communication with Haeckel, having even entertained him at Down. Darwin built his

[2] 'Genetic' used by Haeckel, as in 'genetic relationship' (Haeckel, 1901, p. 70), is short for genealogical.

own evolutionary edifice upon a rock of gemmules, monads of a different cast. He adopted these irreducible elements of heredity and development reluctantly, however, not so much because he believed in them but because he could think of 'no good reason why animals *should* recapitulate their evolutionary history' (Maynard Smith, 1998, p. 15), and genes had not yet been invented.

Darwin was aware, nevertheless, that monadism of some form was necessary to sell Darwinism to his English and American cousins in science (see Desmond and Moore, 1994). Monadic unity of life won over religious colleagues (e.g. Asa Gray) who might otherwise have found Darwinism too materialist to be acceptable, while the idea of a single unit at the origin of life was sufficiently mechanistic to retain the support of agnostic colleagues (e.g. Thomas Huxley). A single origin of life was, thus, at peace with life's unity, the work of a deity, and the creation of God. Many forms of life evolved simply as the outflow from the original one (or 'One', as the case may be).

What made evolution flow might also have proved contentious had Darwin not also oiled his way around problems of mechanism. Darwin's sixth edition of *Origin* ultimately accommodated evolution to Lamarck's principle of psychic anamnesis and the inheritance of acquired characteristics, the laws of nature as prescribed by a deity, and God's eternal wisdom. Darwin only hoped that natural selection would be seen to play some part somewhere along the way of 'descent with modification'.

In the early Twentieth century, monadism was reinvented as Mendelian factors, or particulate hereditary factors, and, after an initial period of uncertainty (the heyday of mutationism and biometric analysis) and jockeying for position, the American, Thomas Hunt Morgan (1866–1945) and colleagues reworked hereditary particles into chromosomes and finally into genes. The gene theory fed into and gave a tremendous boost to the eugenics movement, the science of improving races or breeds, and English eugenicists soon worked out a reliable (if only stochastic) mechanism for evolution through shifting pools of genes. At the same time, the operation of universal laws of heredity provided the theoretical foundations for the 'new evolutionary synthesis', also known as neoDarwinism. Thus, Mendelian factors, in the guise of genes, were fused to evolution in much the same way that Haeckel earlier welded cells to evolution.

In the Twentieth century, monadism gradually acquired the flavor of modern monophylism. In the first half of the century, genes gradually replaced cells as the center of monadic thinking, and in the second half of the century, DNA was installed alongside genes, and biology entered its contemporary, DNA/gene-centered period. The DNA/gene concept has not

only been successful at spawning the biotech industry with all its useful and profitable products, but in launching evolutionary studies into new orbits.

Cladistics, the method of studying evolutionary scenarios from variation in character sets (traits or attributes) of organisms, was reconstructed for studying evolutionary scenarios from variation in molecular sequences. In its contemporary incarnation, however, the subject/object of cladistics is inverted. Instead of studying the evolution of organisms through their molecules, molecular cladists study the evolution of molecules through their organisms. Monads and monophyly, thus, merge in the molecule: monads are reduced to sequences of nucleotides in DNA, and monophyly is reduced to patterns of change in nucleotide sequences.

Conclusion

Returning now to my question, 'Is monophyly transparent?', the answer is 'No!'. Monophyly carries a baggage of history that, unless unpacked, mystifies and obscures understanding of evolutionary processes. Indeed, the doctrine of life's unity, its emergence from a single source, and its diffusion through living things is virtually the same today as it was 300 years ago. Many transformations took place (monads were reified as tissues, cells, genes and DNA), and, at each transformation, old relationships acquired new forms (Virchow fused monads with cells, Haeckel turned monera into the cytula, Morgan turned Mendelian factors into genes, and Watson and Crick turned genes into sequences in DNA). What pealing off all of these layers of transformations and forms reveals is that today's DNA is the Seventeenth century monad. They are both programs for life's 'coming-into-being' – the power of life before the being of life.

Analogies and metaphors change with the times, but dominant ideas are not that easily rooted out. In the Seventeenth century, questions about how the monad was acquired and how it dispensed its powers were answered with invisible entities. These entities were understandable during the first flowering of microscopy when 'the lower limits of visibility were not necessarily the lower limits of life . . . Since the soul [after all] was invisible by definition, preformed units [monads] could also be invisible' (Shostak, 1998, p. 43). In the late Twentieth century, our tolerance for metaphysics is diminished, and questions about how the DNA/gene works were answered with mechanistic analogies (telephone networks, tape recorders, computers, hardware, software, etc.) and problems with how the DNA/gene influences development are solved with material metaphors ('a program,' 'a blueprint,' or 'a recipe'). At some level, all biologists must know that molecules do not reproduce, that they do not evolve, that DNA is neither a ticking clock

nor a super-computer, and that thinking in terms of these analogies and metaphors is confining. However, as long as biologists are thinking in these reductive terms, they are sharing concepts with their Seventeenth century ancestors.

Does monophyly meet the standard of testability?

The standard of testability (vulnerability to negation in the framework of a working hypothesis in the hypothetico-deductive mode or of simultaneous adjustment in the framework of Bayesian modeling) is probably the toughest standard demanded in science. Ideas as old as the monad are not necessarily tested and validated by repeated corroboration. Indeed, they may be untested and powered by inertia. Ideas which are testable are those for which there are alternatives; otherwise ideas are either unnecessary or untestable. Since Dennett has already asserted that reductionism permits no alternative, monophyly as such would have to be untestable, but, before condemning it to the rank of scientific dogma, let me cite two cases in which monophyly was tested as the alternative to a different (polyphylic) hypothesis.

Monophyly as working hypothesis

Monophyly was recently tested on the species level as the alternative to a clear (polyphylic) choice. Specifically, monophylic relationships among extant species belonging to the same putative genus of the parasitic red algal genus *Asterocolax* were tested by comparisons of nuclear ribosomal repeat regions (actually the ITS region) from the parasites, their hosts and similar nonhosts. The results militated against a monophylic relationship, however, leading the investigators to conclude that the parasites generally originated independently, each from its own host (the genus is polyphylic, which is to say, not a genus at all according to taxonomic canon) (Goff *et al*., 1997).

Monophyly does not fare well either when tested as an alternative explanation for the emergence of early life forms, including noncellular life forms (i.e. viruses).[3] For instance, the idea of a monophylic origin of nucleated, or eukaryotic, cells has been more or less broadly rejected and

[3] Similarly, the case for monophyly is hard to sustain for the origin of multicomponent (segmented) RNA viruses (positive single stranded RNA viruses, e.g. tobravirus, cucumovirus and bromovirus) and plant bipartite DNA viruses (single stranded DNA viruses, e.g. geminivirus) where coinfection ('two for one') is required for the production of new virions (see Summary in Shostak, 1999).

abandoned by the weight of empirical evidence favoring their (polyphylic) origin through combining cells.

Lynn Margulis originally elaborated her serial endosymbiosis theory (or SET) for the origin of eukaryotic cells[4] as a theory for the origin of cell organelles known as mitochondria and chloroplasts. She suggested that these arose from endosymbiotic bacteria and had changed through coevolution with their host cell. According to Margulis and others, mitochondria were purple (nonsulfur) bacteria and chloroplasts were bluegreen bacteria living in permanent, mutually dependent, physical relationships with the remainder of the nucleated cells. These relationships were so successful that mitochondria and chloroplasts are virtually the dominant bacterial species, however modified, on Earth.

The most compelling evidence for a bacterial origin of mitochondria and chloroplasts is similarity in the sequence data for bacterial DNA, mitochondrial DNA (mtDNA) and chloroplast DNA (cpDNA). Recently, the successful sequencing of the DNA (complete genome) of *Rickettsia prowazekii* (Andersson *et al*., 1998), the agent of louse-borne typhus in human beings, has capped speculation that the rickettsial subdivision of purple bacteria is virtually a sibling ('sister') group of mitochondria. As expected, genomic size is both reduced and tailored by *Ri. prowazekii*'s parasitic life styles – the 834 complete open reading frames (ORFs), or protein-encoding genes, of *Ri. prowazekii* is scarcely 20 % of the ORFs of *Escherichia coli*, a free-living (enterobacterium) purple bacterium. Nevertheless, *Ri. prowazekii*'s ORFs still represent 10 times more genes than those in the most bacterial-like mtDNA (that of *Reclinomonas americana* (Lang *et al*., 1997), and *Ri. prowazekii* also has physically more DNA than *Re. americana* (1 111 523 base pairs (bp) in *Ri. prowazekii*, compared with 69 034 bp in *Re americana* mtDNA), a remarkably large part of which excess (24 %) is attributed to noncoding DNA. Thus, DNA in mitochondria, and I might add, chloroplasts, seems to have been drastically 'down-sized' following the exile to nucleated cell cytoplasm.

How did mitochondria and chloroplasts become fixed – fixtures – in nucleated cells? The answer would seem to be, at least in part, through this 'down-sizing'. Mitochondrial and chloroplast genes did not disappear, however, so much as they moved to the nucleus of their host cell (reviewed by Gillham, 1994).

This process of gene transfer, called lateral gene transfer (LGT), does not seem to have stopped at the borders of cellular organelles and nucleus, either. LGT may explain incongruous patterns of inheritance for some

[4] For other alternatives, see Cavalier-Smith (1992) and Martin and Müller (1998).

essential proteins, including the aminoacyl-tRNA synthetases, and the chaperonins responsible for protein folding (Lerous and Hartl, 2000), and, according to Doolittle (1999) and others (Yang *et al*., 1985; Lang *et al*., 1997; Andersson *et al*., 1998), LGT crosses the borders of domains (Altschul and Koonin, 1998; Nelson *et al*., 1999) kingdoms (Crawford and Milkman, 1991; Lamour *et al*., 1994; Tateno *et al*., 1995.), phyla, and classes (Lawrence and Ochman, 1997, 1998).

In the case of eukaryotes, LGT accounts for the movement of genes (*P* elements) between *Drosophila* species via a mite intermediate (Charlesworth and Langley, 1991; Houck *et al*., 1991; Cummings, 1994; Syvanen, 1994). This is not to say that LGT has replaced gene movement by well known vertical paths (sexual reproduction). Indeed, Doolittle (1999, p. 2127) warns:

> *LGT is not expected to be common among or play the same role in the evolution of multicellular plants and animals, especially those with sequestered germ lines, and there simply is no extensive data on LGT in unicellular eukaryotes.*

Nevertheless, Carl Woese (1998), the parent of the three domains concept of life and of the 'universal tree of life' has now adopted broader bases for ancient life than the thin lines and point nodes of cladistic trees. Possibly one should not be too surprised, since other biologists are also finding 'worm holes' in the 'tree of life' (e.g. Martin, 1996; Benson, 1997; Keeling, 1998; Gibson and Wagner, 2000), and, after all, Periannan Senapathy (1994) showed on statistical grounds that DNA probably had multiple origins.

Monophyly as paradigm

Not all scientific statements are testable hypotheses, laws or theories. For example, scientific paradigms, by one definition (Masterman, 1970; Horgan, 1996), are organizing principles which encompass much of the work of 'ordinary science,' in the language of Thomas Kuhn (1970) but are not necessarily testable. 'Ordinary science' is not the source of 'revolutionary science' (except, possibly when it breaks down) and is not 'hypothesis driven' so much as driven by the requirement to 'fill in the holes' opened in a field by the scientific paradigm.

Monophyly, thus, might be a scientific paradigm. Indeed, Dennett seems to have a paradigm in mind when he tells his reader:

> *The power of the theory of natural selection is not the power to prove exactly how (pre)history was but only the power to prove how it could have been, given what we know about how things are (Dennett, 1995, p. 319).*

What would legitimize monophyly as a paradigm?

Several answers to this question come to mind, most conspicuously, 'If it makes work, its a paradigm!'. Any perusal of current evolutionary literature (Shostak, 1999) based on extant species and modern molecules shows that monophyly makes work, and, in the words of the philosopher and culture critic, Éric Alliez (1991, p. 76), 'ADMIT IT: our situation is difficult because it works too well, because it's going too fast.' Monophylism is thus legitimized by this fundamental requirement of paradigms.

Paradigms are also closely shaven by Ockham's razor. The principle that what is simplest is best may legitimize a paradigm, and monophyly is as simple as it gets. However, Ockham's razor may cut too finely when the simplest explanation is inadequate. As illustrated above, SET and LGT are not simple, but they are supported by evidence. Indeed, a monophylic explanation for the data supporting SET and LGT would have to be rejected by Ockham's razor as 'unnecessarily complicated'.

Paradigms are also legitimized by common sense, but suggesting that a species should arise from a common ancestor because all members of the species arise from fertilized eggs is clearly stretching. Paradigms should also be 'tidy', and monophyly is most certainly easier to program than its (polyphylic) alternatives, as testified by the plethora of canned alignment and phylogenetic-treeing programs based on monophylic assumptions. The appearance of objectivity and of mathematical rigor implied by the use of these programs might be illusory, however, if biologists are unaware of assumptions made in configuring the underlying algorithms (e.g. Steele *et al*., 1998[5]).

Finally, paradigms frequently have the look of a sensible refuge in a chaotic sea of competing ideas. Monophyly is portrayed in precisely this way even if several alternative refuges are lurking on the horizon. For example, Carl Woese's alternative, which he calls the 'genetic annealing model' (Woese,

[5] Steele *et al*. (1998, p. 220) make the case this way – 'Thus all of this computer-based model demonstrating the ''the power of natural selection'' depends ultimately on Dawkins setting *all* the selection criteria and the sequential (algorithmic) rules for the desired result of his selection program'.

1998), acknowledges a wide role for LGT, especially in the early evolution of living forms. In addition, polyphylism offers a range of complex alternatives to monophylism.

What's harmed by monophyly?

Monophyly, in and of itself, of course, 'does no harm', but those who advocate it do! Above all, they do not encourage and may go so far as to stifle work on polyphylic alternatives. Suffice it to say, that distinguished monophylists, as members of editorial boards, including an executive editor and an editor-in-chief, have stooped so low as to summarily exclude from their journals papers submitted on polyphylic themes. Recently, when I asked a prominent monophylist why a polyphylic alternative to the concept of *Bauplane* was not even mentioned in his recent book, I was told, 'There is no alternative!'.

Advocates of polyphylism have indeed been harmed professionally by the attitudes and actions of monophylists. Moreover, the study of evolution has been harmed. Evolution, like weather and climate, should be studied by modeling – Bayesian modeling with multiple, simultaneous hypotheses – but because the study of polyphylic alternatives is stifled, modeling evolution is set back and all but killed.

My intention here is not to recall 'horror tales from the crypt', the extremes to which reductionists may threaten, malign, sensor, and censure scientists pursuing nonreductive alternatives to monophyly. Rather, I will show how polyphylism can flesh out evolutionary skeletons and prepare the way for modeling evolution itself.

'Strange bedfellows'

Polyphylism does not propose merely multiple origins of living forms – that would constitute a simple multiple of monophyly. Rather, polyphylism proposes that multiple living things, protoliving things (transposons), and noncellular living things (viruses) all take part in evolution, and their ways of interacting can be through combining, fragmenting, or both (see Shostak, 1999). Furthermore, polyphylism assumes that more than organisms evolve, and a study of evolution must include a study of organismic relationships.

Some of the 'strange bedfellows' one finds in natural relationships presumably reflect a multiplicity of interactions. Lichens, for example, consist of fungal units and either algal or cyanobacteria in a symbiotic (possibly a master/slave) relationship. In endosymbiotic relationships, compound organisms are constituted by algae (e.g. the zoochlorella of green hydra, and

the zooxanthella of marine ciliates and invertebrates) or bacteria (in the case of insects) living within an animal's cells. The symbiotic partners do not share their genomes, however, and endosymbionts, such as hydra's zoochlorella, retain cell walls and are not transferred within eggs. Rather, they are acquired by offspring from the detritus of parents (horizontal inheritance) or even nonparents (diagonal inheritance). Some endosymbiotic bacteria, on the other hand, such as those of aphids, are transmitted through eggs.

Organisms capitalize on their relationships in a variety of ways, from birds and bees pollinating plants to mollusks taking up cnidocysts from prey. Parasitism is another type of relationship with ancient roots. Ordinarily defined as a $-/+$ relationship in which one member of a pair, the host, suffers a loss of fitness, while the other member, the parasite, benefits, parasitism may be better understood as a successful relationship in which the benefit/cost ratio reverses itself at the parasite's departure from its host. At that time, the parasite, rather than the host, pays an energetic premium.

Origins of parasitism

Parasitism is a broad category of dependency relationships among organisms, stretching between closely related to unrelated host and parasite pairs. One would anticipate, therefore, an equally broad range of evolutionary scenarios leading to parasitism. Even where the parasite and host are closely related, the evolutionary distance may be quite great. For example, facultative 'autoparasitoids' among aphelinid wasps, in which male eggs are selectively laid on conspecific female larvae (thereby biasing the sex ratio toward males), are presumably highly evolved and far from the origins of parasitism (Williams and Polszek, 1996). Other cases of closely related parasites and hosts, however, suggest how parasitism may be rooted in genealogically preadaptation.[6]

Imagine that a cell produced originally by an imperfect cell division gives rise through vegetative growth to an imperfect organism; this fragment of the original organism, incapable of life on its own, may, nevertheless, survive and reproduce as a parasite on its parent. The parent, while not propagating its complete genome, preserves, nevertheless, part of its genome by aiding the parasite, and the subsequent spread of the parasite to new hosts (i.e. establishing alloparasitic relationships) offers the parent an opportunity to spread some of its genes to otherwise inaccessible territories.

[6] A dubious, but not uninteresting case can be made for mammalian herpesviruses, 'large' double-stranded DNA viruses, which might have evolved from their mammalian hosts. Their nonstructural (enzymatic and control) viral proteins are similar to those of nonviral host proteins (McGeoch and Davidson, 1995), although recombination might also explain these similarities.

Several specific cases fit this scenario, from agastoparasitism in insects (bees and dulotic ants), and adelphoparasitism in plants, algae and fungi, to two of the most profoundly reduced animal parasites, the dicyemids (Mesozoa, *Dicyema orientale*) and the myxozoan (Myxozoa, *Henneguya, Myxobolus*, and *Myxidium*). Dicyemids are typically parasites of the renal sacs of squid and octopus – mollusks. Dicyemids are small, cigar-shaped organisms consisting of a central, core cell surrounded by anciliated 'epithelium' of 10–40 cells. Ordinarily considered 'primitive' and placed among the diploblasts (Radiata – Cnidaria, Ctenophora, Placozoa, and sponges), dicyemid's 18S-ribosomal DNA, and its Hox-gene, *DoxC* (specifically the 'spiralian peptide', also called the Lox5 peptide), 'argue that dicyemids are members of the Lophotrochozoa and are related to phyla such as platyhelminths, molluscs [*sic*], nemerteans, brachiopods and annelids' (Kobayashi *et al*., 1999, p. 762). Because these similarities extend to multiple, unrelated genes they are unlikely to have resulted from LGT. Rather, the similarities suggest 'that dicyemids are secondarily simplified from higher protostome animals [and] represent one of the most extreme cases of secondary reduction of body-plan complexity' (Kobayashi *et al*., 1999, p. 762).

Reduction would seem to be even greater in Myxozoa (Myzosporea and Actinosporea), indeed, reaching its cellular limits. Myxozoans are ordinarily considered unicellular or oligonuclear (oligocellular) protozoans (protoctistans). They are obligate parasites and have radiated widely, with hosts primarily oligochaete worms and marine fish. Sequences of 18S (16S-like) rDNA from five species of myxozoans (Myzosporea, *Henneguya* sp. 1 and 2; *Myxobolus* sp. 1 and 2; *Myxidium* sp. 1) and two rDNA sequences from *Myxidium lieberkuehni* suggested, however, a close ('sister') relationship with the bilateral (triploblastic) metazoans (Smothers *et al*., 1994; Schlegel *et al*., 1996), while the analysis of full-length 18S rDNA from representatives of the same three genera of myxozoans provided 'robust evidence in support of the inclusion of the myxozoans within the phylum Cnidaria' (Siddal *et al*., 1995, p. 966).

According to Siddal *et al*. (1995), the greatest similarity in 18S rDNA was between myxozoans and the cnidarian *Polypodium hydriforme* (Narcomedusae), the notorious spoiler of fine sturgeon caviar, whose parasitic life cycle parallels the myxozoan life cycle. The Narcomedusae are an order or suborder of Hydrozoa and, according to Hyman (1940) and later Petersen (1979), lie at the base of the hydrozoan radiation. In the majority of narcomedusae, eggs develop as parasites on their mother, and planula larvae escape the mother to become parasites of other jellyfish. Thus, were the Myxozoa to have evolved from narcomedusans, they would have been parasites to begin with.

Agasto- and adelphoparasitism may be ongoing, but the dicyemids and Myxozoa would seem to have originated at some remote time. Possibly, they originated before mitosis (precise, chromosomal partitioning) was performed routinely with precision – at a time when cells were routinely produced with imprecision. Today, cells generally destroy themselves if their DNA is damaged beyond 'the point of no return', that is, when errors cannot be 'fixed'. The path to cell death found in modern eukaryotic cells and known as apoptosis is set in motion by 'tumor suppressor genes' and initiator caspase activation. At an earlier time, however, incomplete cells might not have destroyed themselves, simply because the cascades leading to cell death had not yet been invented. After all, even some cells in modern organisms do not destroy themselves upon accumulating serious DNA damage. These cells – parasites of a sort – are the source of tumors and cancers.

The origins of tissues in Cnidaria

Normal tissues also have a relationship with each other and with the organism as a whole resembling a parasite/host relationship. Tissues are, after all, dependent on the 'host' and cannot survive on their own, except with the help of tissue culture or deep freeze. Certainly, like parasites, tissues seem to have 'gotten around' as demonstrated by similarities in the sequence of control genes, from those determining the running period of circadian rhythms to those directing embryonic development (maternal-effect genes controlling pattern formation, zygotic-effect genes organizing gastrulation, HOX genes influencing regional identity, and segmentation genes governing segmental differentiation). Is it possible, therefore, that what were once cells living in adelphoparasitic relationships became tissues living in permanently integrated relationships within the organs of modern organisms?

The case in point is the phylum Cnidaria. Named for its cnidocytes, or nettle cells (cnidocytes actually produce more than 30 varieties of cnidocysts, although usually only one or two and no more than seven are found in a species), cnidarians are also characterized by the presence of two tissues, i.e. epithelial and amoeboid. The epithelial tissue forms the inner and outer cell layers of the body wall (ectoderm or epidermis and endoderm or gastrodermis), separated by a largely acellular mesoglea. Amoeboid cells lie interspersed among the epithelial cells and differentiate into all specialized cells, i.e. cnidocytes, nerves, numerous gland cells, and sex cells. Cells of the two tissue are readily distinguished in maceration preparations where the amoeboid cells are represented largely by cnidoblasts containing partially

differentiated cnidocysts and present in small nests of 2–8 cells. The formation of nests of interconnected cells is reminiscent of early stages of egg and spermatozoan formation in other animals, but is otherwise unique.

In 1993, and again in 1995, I discussed the possibility of the epithelia and amoeboid tissues arising from separate organisms (Shostak, 1993; Shostak and Kolluri, 1995). The epithelia of cnidarians, I suggested, originated from an 'epithelial animal', a multicellular, epithelial organism resembling the extant Placozoa, namely *Tricoplaxa*. A placozoan is a ball of ciliated epithelium capable of flattening into a plate – hence its name; the plate is 2–3 mm in diameter. Placozoans probably live by scavenging, sliding over a food item and digesting it via activities of ventral epithelial cells. A 'kind of mesenchyme' occupies the space between the epithelia, but no internal organs are present, and investigators have found no nervous system of any kind. *Tricoplaxa* has dorsoventrality, and its epithelia are polarized around their basement membrane, but the organism has no anterior/posterior axis or right and left sides (Grell and Ruthman, 1991).

I also suggested in 1993 and 1995 that amoeboid cells originated from amoeboid cells containing their own variety of cnidocysts, although I had no idea whether these were related to extant Myxospora, Microsporidia, or predatory dinoflagellates. For example, the predatory dinoflagellate, *Polykrikos schwartzii*, has a cnidocyst attached to an extrusion apparatus that is similar to cnidarian cnidocysts (Westfall *et al*., 1983). Likewise, various myxosporean spores contain cnidarian-like cnidocysts (Lom, 1990; Siddal *et al*., 1995), and cnidocysts (polar capsules) of the myxosporidia *Henneguya psorospermica* and maturing spore of *Henneguya adiposa* (Perkins, 1991), resemble microbasic mastigophores, for example, of the cnidarian Cubozoan (Lesh-Laurie and Suchy, 1991), and nematocysts from the anemone *Actinia equina* (Fautin and Mariscal, 1991).

I did not know, at the time I made these suggestions, about the possibility that myxozoans might have originated from Cnidaria. However, if this possibility is confirmed, I would suggest a more complicated scenario for the origin of cnidocysts than the one I proposed originally, namely, that myxozoans or a similar adelphoparasite of cnidarians 'reannealed' with a protocnidarian epithelial animal after a sojourn to other hosts where the 'cnidocyst' was 'improved' by coevolution.

My hypothesis otherwise remains what it was in 1993 – the epithelial component originated from an epithelial animal and the amoeboid component originated from an amoeboid animal equipped with a protocnidocysts, and possibly already living as an intracellular parasite on the epithelial animal during some stage of its life cycle. One or another device for cell fusion would have to be invoked to explain how an amoeba and an epithelium

could stabilize their relationship. For example, cell fusion might have been facilitated by a 'syncytial' virus (e.g. cytomegalovirus) or fusion might have occurred in the course of parasitism, as it does in adelphoparasites of red algae (Goff and Coleman, 1995). Possibly, the protocnidocyst acted as a device for introducing a paraplast as it does in extant myxozoans. Following the formation of a heterokaryon, nuclear fusion might have been effected in any of several ways, e.g. LGT, introgression or syngamy, possibly made easier by a close genealogical relationship.

Today, as a result of success in producing chimeric animals and 'knock-out' mice, problems of integrating foreign, but closely related, cells into a 'host' organism do not seem as insurmountable as they did a mere decade ago. Chimeric animals and 'knock-out' mice are prepared by adding inner cell mass cells or embryonic stem cells to blastocysts. Following embryo transfer, development takes place in pre-natal foster mothers. Chimeric mice incorporate the transplanted cells into a variety of tissues, which may include the germ line – eggs and spermatozoa. Once incorporated in the germ line, descendants of the transplanted cells can reproduce *ad infinitum* by the usual methods of sexual reproduction. Possibly something similar took place for the integration of the amoeboid and epithelial ancestors of modern cnidarians.

This hypothesis would seem testable in a number of ways, one of which I am working on currently. Basically, since epithelial tissue and muscle fibers are present in Placozoa and in the epithelial component of Cnidaria, the specific proteins of epithelia and muscle should show more similarities to each other than to nerve which is absent in Placozoa and derived from amoeboid cells in Cnidaria. My students and I are attempting to test this hypothesis on a broad scale (not confined to Cnidaria) by looking at similarities among tissue-specific proteins in general. The question is 'Do sequences in proteins identified with epithelia and muscle show more similarities with each other than they do with sequences of specific proteins for other tissues?'.

What others are saying

Inevitably, the study of evolution will take a modeling approach, and discussions such as those above, on 'strange bedfellows', parasitism and tissues, will point to and illuminate the types of relationships and evolutionary mechanisms that should (and must) contribute to the broader study of evolution. Of course, I am not alone among biologists in advocating such an approach, but my most important allies in the struggle to study the complexity of evolution are philosophers, particularly the biophilosophers and the philosophers of becoming who sometimes 'wear the same hat'.

Since the Nineteenth century, these philosophers have struggled to rescue time from a dimension on a simple, linear scale and install time as a multidimensional variable in a complex way of thinking about life. The biophilosophers have been drawn to evolution as a place to resolve the fundamental conundrum of time – How does it affect life? The biophilosopher Georges Canguilhem, for one, tells his reader:

> *[T]he* Origin of Species *proposed a radically new idea, conceiving of time not as a power but as a factor whose effect could be perceived directly in distinct but complementary forms: fossils, embryos, and rudimentary organs. The fossil was petrified time; the embryo, operative time; the rudimentary organ, retarded time. Together these bits of evidence constituted the archives of biological history . . . .*

Philosophers of becoming

I have selected four philosophers of becoming and a psychiatrist to represent this field, namely Friedrich Nietzsche (1844–1900), Henri Bergson (1859–1941), the team of Gilles Deleuze (1925–1995) (philosopher), Félix Guattari (1930–) (psychiatrist), and Keith Ansell Pearson (1960–). Their work shares an understanding of becoming as time's message written across life and rejects the linear schemes presupposed in phylogenetic treeing, although they probably would not have agreed on any model for nongenealogical evolution.

Nietzsche is well known as a critic of Darwinism, but the essence of his critique is rarely examined. Indeed, Nietzsche's 'becoming' is close to evolution, not an historical evolution or historicism to be sure, but an active evolution. This activism is suggested by the 'taskmaker who once bade himself, and not in vain: ''Become what you are!'' ' (Nietzsche, [1885] 1969, p. 252 also Nietzsche, 1989). For Nietzsche, science required 'antidotes to the stifling of life by the historical, by the malady of history' (Nietzsche, [1874] 1983, p. 121).[7] One must remember, however, that Nietzsche also told his reader:

> Science . . . *hates forgetting, which is the death of knowledge, and seeks to abolish all limitations of horizon and launch mankind upon*

[7] Keith Ansell Pearson (1997, p. 107) is critical of Nietzsche's antiDarwinism, explaining that 'in upholding his 'contra Darwin' position, [Nietzsche] is fatally propelled back into that hangman's metaphysics – of intentionality, of teleological purposiveness – that he was so keen to deconstruct and overcome'.

> *an infinite and unbounded sea of light whose light is knowledge of all becoming (Nietzsche, [1874] 1983, p. 120).*

Nietzsche was followed by Bergson, who, like Nietzsche, is frequently accused of having fallen victim to vitalism. This characterization is partial, however, as Bergson explains, '[T]he ''vital principle'' may indeed not explain much, but it is at least a sort of label affixed to our ignorance, so as to remind us of this occasionally . . . . while mechanisms invite us to ignore that ignorance' (Bergson, [1911] 1988, p. 42). Rather than advancing a vital principle, Bergson is critical of it, telling us:

> *In short, the theory of final causes does not go far enough when it confines itself to ascribing some intelligence to nature, and it goes too far when it supposes a pre-existence of the future in the present in the form of idea. And the second theory, which sins by excess, is the outcome of the first, which sins by defect (Bergson, [1911] 1988, p. 362).*

For Bergson, 'becoming' offers access to life by shifting the burden of analysis to 'duration.' He tells the reader, 'The more duration marks the living being with its imprint, the more obviously the organism differs from a mere mechanism, over which duration glides without penetrating' (Bergson, [1911] 1988, p. 37). What duration illustrates is that a lifetime is not a thing. If anything, it is not even many things. It is not a process either. It is not even a mélange of processes. 'Real duration is that in which each form flows out of previous forms, while adding to them something new and is explained by them as much as it explains them . . .' (Bergson, [1911] 1988, p. 362). 'Duration,' thus, is a 'becoming' that endures. This nonconglomate and noncollection, this tendency to act which defies description and tendency to be which defies narration is 'becoming'. Beyond that, 'Becoming is infinitely varied' (Bergson, [1911] 1988, p. 304).

For Deleuze and Guattari, 'becoming' is not an evolution. Rather, becoming is 'creative evolution', to borrow the title of Bergson's book. It is 'born in History, and falls back into it, but is not of it' (Deleuze and Guattari, [1991] 1994, p. 296):

> *[B]ecoming is neither an imitation nor an experienced sympathy, nor even an imaginary identification. It is not resemblance, although there is resemblance. But it is only a produced resemblance. Rather, becoming is an extreme contiguity within a coupling of two sensations without resemblance or, on the contrary, in the*

> *distance of a light that captures both of them in a single reflection (Deleuze and Guattari [1991] 1994, p. 173).*

Finally, Ansell Pearson, virtually a biologist in philosopher's clothing, finds the critique of the philosophers of becoming congenial to his own point of view on mechanism and causal determinism. He tells his reader:

> *'[B]ecoming' remains the great monstrous unthought in mechanistic and thermodynamical conceptions and calculations of the energy of the universe .... To use the language of the contemporary science of complexity, the eternal return is a thought of non-linear becoming in which the stress is on non-equilibrium and positive feedback as the conditions of possibility for a truly 'creative' and complex (involuted) mapping of 'evolution ...' (Ansell Pearson, 1997, p. 62).*

And showing his critical understanding of both biology and philosophy, Ansell Pearson (1997, p. 134) continues:

> *When viewed in terms of symbiosis a clear establishment of distinct kingdoms is rendered problematic and what becomes important is a 'machinic' phylogenetic becoming. Symbiosis also challenges the notion of informationally closed systems, and corresponds to the function of the idea of the 'rhizome' in the work of Deleuze and Guattari, in which evolution is removed from the limits imposed by filiation (Ansell Pearson, 1997, p. 134).*

Getting back to Dennett

A complex analysis of time, thus, links the biological and philosophical studies of evolution. Dennett might indeed have made a contribution to these studies if, as a philosopher, he had examined the work of the biophilosophers and the philosophers of becoming. Regrettably, he did not undertake a critique of Nietzsche, Bergson, Deleuze, Guattari and Ansell Pearson in *Darwin's Dangerous Idea*. Instead, he put on the hat of biologist and attempted to drive a wedge between biologists and philosophers.

Dennett above all is not unaware of his agenda. Elsewhere, in his explanation of the 'tactic' he calls 'intentional stance,' he tells the reader:

> *This is a tactic of interpreting an entity by adopting the presupposition that it is an approximation of the ideal of an optimally designed (i.e. rational) self-regarding agent. No attempt is made to*

> *confirm or disconfirm this presupposition, nor is it necessary to try to specify, in advance of specific analyses, wherein consists rationality. Rather, the presupposition provides leverage for generating specific predictions of behavior, via defeasible* [sic] *hypotheses about the content of the control states of the entity (Dennett, 1998, p. 360).*

Dennett's philosophy, thus, descends to ideology:

> *Ideology is an epistemological concept with a polemical function, applied to systems of representation that express themselves in the languages of politics, ethics, religion and metaphysics. These languages claim to express things as they are, whereas in reality they are means of protecting and defending a situation, that is, a particular structure of the relations between men and things (Canguilhem, 1988, p. 29).*

Also, as Canguilhem goes on to remind us (1988, p. 104), '[S]cientific discoveries in one field, if degraded into ideologies, can impede theoretical work in other fields'. In the final analysis, the reductionism I am afraid of is not *Darwin's Dangerous Idea*. The reductionism is Dennett's dangerous idea.

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QUESTIONS AND DISCUSSION

Robert Richards: I have two complaints, also two historical observations. First, that Darwin's first hypotheses was a polyphyletic hypothesis, namely that there are different archetypes that come up independently of one another, and even that hypothesis is preserved in the Origin, and he says,

but by analogy perhaps there is only one source of life, so he was willing to consider, in fact, did consider for most of his theorizing, a kind of polyphyletic view, that is one historical observation. The other historical observation is that perhaps the greatest polyphyletic evolutionist of the nineteenth century was Ernst Haeckel, and he thought that there was a polyphyletic origin for the different species of men as well as at the roots of the tree of life. So, both monophyletic views and polyphyletic views have a kind of almost common origin in evolutionary theorizing from the beginning, and I suspect that they both carry, in your terms, a lot of theoretical baggage, which we've seen, so those are the historical remarks. The objection, in the form of a question, but I'll forget the question, is that you seem to think that analogy and metaphor are obscuring kinds of moves, but I think most people would say that things like models in science are in fact analogies, and I did hear you say, I believe, that, in the case of lichens, they often have a slave–master relationship. Just one final objection which is this, that you suggested that monophyly hypotheses were in some sense not testable but in fact you've offered compelling evidence against them, which means in fact they are testable. So, two objections . . .

Stan Shostak: I have no objection to your objection. As a matter of fact, I don't believe you've really objected. As for Darwin, I think that he understood very well that he had to use monophyly to sell cultural selection, that monophyly was the crisp way of bringing Asa Gray and the American cousins who found natural selection rather materialist without a single origin, and also to bring in the agnostics who could accept a single original Eden, and evolutionary flow out of it without having to bite the bullet. So, we're talking about two different things, the selling of evolution and the . . .

Robert Richards: Well, this is an historical question, about which there may be some dispute, but there is evidence for it and we can talk about that later.

Stan Shostak: . . . as for Haeckel, he coined the Monera, not because he was polyphyletical. I thought you might have brought up Cuvier. Cuvier took a hammer to the *scala natura*.

Robert Richards: There are different kinds of Monera, that produce the different . . .

Stan Shostak: No, Monera is the trunk, 1866.

Robert Richards: If you look at the *Generelle Morphologie der Organismen*, which is the 1866 book, as he says the roots for Protista, for plants, and for animals have different foundations.

Stan Shostak: What was the other objection?

Stan Shostak: Just one moment, about metaphor and analogy. I think those are the diagnostic characteristics of reductionism. As soon as you find metaphor and analogy-this morning we heard the word 'machine', the cell machine, and I'm sure you didn't intend it in any way to be reductionist, but that's how you know it's there.

Robert Richards: But models are in fact analogies.

Stan Shostak: No, I have much more respect for models than to call them analogies. Models are serious business. You allow a model to work and figure out the parts of the model. It is not a matter of taking the truck apart. You drive your truck up and it suddenly stops. Reductionist – Well, I ran out of gas. Put some gas into the tank, truck starts again, you drive off, you don't care whether that's the real explanation, but it works. Your computer breaks down, you have a crash, you can't put gas in the tank, you reboot. That's the model. Where reductionism doesn't work, you begin with modelling.

Ken Schaffner: On the model front. Trying to think through the implications of your argument for the supermodels that are the thrust of a lot of the Human Genome Project and I'm thinking of yeast, of worm, of flies, that are used to look for strongly conserved sequences, one can then use to extrapolate to the rest of life, including humans. I'm not sure exactly where your thesis will take us with respect to that, but it seems to me it's a premise of billions of dollars of research programs per year and there may be some interesting implications. I was wondering if you could maybe elaborate a little bit on the implications for model organism studies.

Stan Shostak: Well, I brought up LGT (lateral gene transfer). I think we'll probably find many more possibilities for moving genomes around. I think of Don Williamson's concept of embryo transfer. I think hybridization is far more widespread and far more important than any of us are willing to admit, even hybridization among extant species. My guess is, of course, that at a time before there were individuals, before there was sex, that hybridization, or what we might call hybridization today, was rampant, and that genes moved freely between what were unrelated lines of organisms.

Ken Schaffner: So the genes moved relatively freely. What are the implications for looking for sorts of common mechanisms? I could see it going either way. If the genes are moving freely and these are selected because they are very successful in the organisms which incorporate them, then you may have a rather small number of frozen accidents which are found all over the tree of life, of the bush of life.

Stan Shostak: I agree. What's the difficulty with that?

Ken Schaffner: I'm just trying to look at the implications for whether or not we're likely to find usefully, the analyses we do of these strongly conserved genes which we think are strongly conserved.

Stan Shostak: Yes, I think the language of strongly conserved genes is really the wrong language. It's not where the model brings us. My guess is that back-mutations perhaps have to be introduced here as a corrective, but moving around, genes moving between organisms is probably the explanation for much of what goes by the name of conservative genes.

Sohotra Sarkar: What I hear from you and find very interesting is the fact that once we come to investigate things at the molecular level a certain neo-Darwinian interpretation of evolution is not going to work. And this is not the first development that has suggested that. The first one that suggested it was initially the neutrality selectionism debate. Then there was the whole issue of directional mutations, epigenetic inheritance, and now we're getting lateral gene transfer and things like that, and our view of evolution has to become much more sophisticated that it is now. What I don't see is what this has to do at all with any of the issues connected with reductionism. I mean I'm not clear what you meant by reductionism, and why you thought that anything you say challenges the usual reductionist view that we take which is that we are going to find explanations and interesting things at the molecular level. In fact, most of the evidence you are presenting seems really to be good evidence because we went to the molecular level.

Stan Shostak: I'm certainly not against the molecular level. The question this morning was 'what do you mean by understanding?'. And I think it depends on where are you pitching the question. If the question is pitched at the molecular level, then there can be some sort of understanding at that level. It's moving between levels that I think is problematic. What you must understand is that in the field, trying to publish papers that are non-reductionist is very difficult. There are journals that are dedicated to reductionist research that won't consider publishing papers that deviate from the canon. There are editors of journals who simply send you back a one-liner – 'this is not suitable for this journal' – even though it's an evolutionary or developmental journal. And friends of mine are just unable to publish. So I'm talking about the real problems of being a professional biologist and getting your work out. Reductionism bites and it hurts.

Sohotra Sarkar: I agree that when you're presenting results that go against the dominant orthodox view, that difficulties of this sort occur and

we are to worry about it, but what I'm still not getting at is why you are using the term reductionism to describe this. I mean why not use neo-Darwinism. What you are criticizing really is neo-Darwinism. Why not use that? Why is it reductionism?

Stan Shostak: Well this is the word that Daniel Dennett uses. He defines bland reductionism as something no sane scientist disputes, and I dispute it. He defines good reductionism as simply the commitment to non-questioning science without any cheating, erasing, mysteries, or miracles at the outset. Anyone who takes a non-reductionist posture is thus invoking miracles!

Sohotra Sarkar: I never thought I would ever be in a position to defend Dennett, particularly *Darwin's Dangerous Idea* book, but I do think you are being unfair to him. I mean, what he did mean by bland reductionism primarily is some kind of physicalism that nobody is going to deny, and that's all he meant by that. And then what you are presenting here as definitions are statements he makes, and those are not things that he calls definitions.

Stan Shostak: I'm sorry he does. And furthermore, let me give you another quotation from him. He talks 'this is elsewhere in his Consciousness', about a tactic. He calls it an intentional stance. And this is what he advocates – this is a tactic of interpreting an entity by adopting a presupposition that it is an approximation of the ideal of an optimally designed, rational, self-regarding agent. No attempt is made to confirm or disconfirm this pre-proposition. Nor is it necessary to try to specify in advance of specific analyses wherein consists rationality. Rather presupposition provides leverage for generating specific predictions of behavior via defensible hypotheses about the content of the control-states of the entity. That's reductionism. That's where he clobbers people who think differently.

Jim Griesemer: One question was when you talked about the Myxozoa as a sister group to the Bilateria. Doesn't that depend on an assumption of monophyly in order to talk about sister taxa. My motivation for asking it is out of sympathy for your view. But to think that monophyly can be a false hypothesis that leads us to a better understanding of the non-monophyletic relationships among taxa, although we still use hypotheses of monophyly to structure our descriptions. The other question is, when you talked about algae as endosymbionts of hydra, you said they were compound organisms. But isn't that by analogy to the idea of an organism?

Stan Shostak: As I said, we have an understanding at various levels. We use the term 'levels of organization' and 'levels of complexity' or what have you, and I don't have a quarrel with data at any level whatsoever. My intention was to increase the complexity of the ideas, to ask, to

consider – the part that I left out was a discussion of Deleuze and Guatrari and Bergson and Nietzsche, all of that came below what the others are saying. So I wanted to bring in time, but I only actually got to talk about relationships. . . These are the complex relationships: I started with cancer and would up with tissues, and I'm asking a question about how those relationships became and how they became sustained. So, if parasites evolved the way I've described, and tissues evolved from parasites, there's no way to account for that evolution in terms of monophyly.

Round Table Discussion 1: Chair – Alex Rosenberg

Alex Rosenberg: I would like to use the chairman's prerogative and raise a question for those of our participants who have spoken already. Partly it's because there's been some expression of urgency that we get a characterization or a definition, or at least a working account, of what is meant by reductionism in the context of this conference so that we can at least start from the same point. It is a term that has had many different characterizations over the course of the past 50 years or so, and I think that several people will be talking about it tomorrow as well. I know I will. Let me put a question to those of our speakers who have already attacked reductionism. A very simple kind of a question that may enable us to make more concrete the debate among us. Newtonian mechanics is said to provide a reductive account, a reductive explanation of say, Kepler's laws of planetary motion. We know perfectly well that when it comes to dealing with the interaction between three bodies, Newtonian mechanics cannot provide a calculation of the interaction of the three bodies insofar as it affects the position and momentum of the three bodies, and therefore we have to resort to approximation techniques. My question for the speakers who have already given us their talks is simply this – Does the fact that in the case of Newtonian mechanics we must resort to approximation methods and can't calculate the actual position and momentum of the three bodies suggest that we cannot, or do not have a complete reductive explanation of the motion of the planets? With that as a, perhaps, common problematic, let me throw the floor open to those of you who wish to raise any question you like about the talks so far today. I'm sorry, Lisa . . .

Elizabeth Lloyd: Well, no, I had a specific idea of reductionism in my talk which actually didn't address the Newtonian question, but rather sees reductionism as an approach or an attempt to explain phenomena in terms of certain types of entities and their properties at these levels. A reductionist

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program or research program or approach is successful if it explains the phenomena it's trying to explain in terms of entities and properties at a lower level. So, in that sense, it would be successfully reduced to that level. The claim in my case being, although health seems to be a very personal and individual thing, it seems if these people are even half-way right that it's not possible to explain the phenomena in terms of entities and their properties at the level of the individual but rather you need to take into account societal level properties, which are not in any sense reducible to lower levels of explanation. So I would say, reduction, or reductionism that I had in mind really had to do with explanation in terms of entities and their properties at a particular level. I don't know if this is helpful for others who are working.

Speaker: Yours is a classic example of the kind of argument for holism that we found in the social sciences since Durkheim. Durkheim's argument, for example, for the social suicide rates being independent of any psychological considerations is very similar in structure to the kind of epidemiological data you provided us with today and the attempt to exclude non-social factors or individual psychological or individual physiological factors as explainers of these regularities. I'm inclined to say that there are at least two kinds of reductionism that have been bones of contention in both philosophy and the methodology of science. One is, reductionism as the criticism of the attempt to explain phenomena by neglecting or ignoring certain variables, and an inter-theoretical relation. And these are two quite district meanings of the term 'reductionism'.

John Dupré: Just to elaborate here for a moment on what Lisa is saying. One idea that relates to what a number of people have said today is that reductionism is a prohibition on downward causation, where by downward causation, I think Donald Campbell may first have introduced the term. I mean the idea that one explains the behaviour of something by citing a system of which it is part as the primary explainer. So, of course, reductionism in the second of your senses was I think characteristically the idea that you explain the behaviour of something by talking about its parts, by talking about the behaviour of its parts. Now I think there's an intermediate level, which is your first sense, which is same level, and which may or may not be reductive in assuming monocausality. But, then I say that they both mean anybody who is a reductionist is likely to want to deny the possibility of downward causation. But a number of speakers today spoke about the importance of relationship, and I think that the way relationship specifically connects with that conception is that by citing relationship as ineliminable, one is gesturing towards what people have meant by downward causation, by the idea that you have to have a structure

involving a number of things to understand what the thing you're interested in, your target of explanation, is doing.

Claude Debru: My point is not a comment on reductionism, but a comment on the movement of the planets. We know since Poincaré that the movement of the planets is chaotic, which means that it would be predictable if we would have the knowledge of the initial conditions of the system. But in the ignorance of this data of the initial conditions, it remains unpredictable. So I think this qualifies some ideas, perhaps. I don't know how it fits into the framework about reductionism – because you mentioned the movement of the planets.

Alex Rosenberg: My inclination is to say that it doesn't because most reductionists are perfectly happy to accept chaotic phenomena as an epistemic limit on predictability and not a limit on either on the understandability of a system or on the degree of its determinism, whether upward in its causal determinism or not.

Michel Morange: I didn't get the sense of downward causation. What is really downward or upward causation?

John Dupré: I guess the idea of upward causation is what I think philosophers have tended to think of as the classic form of reductionism, that you'd . . .

Alex Rosenberg: For example, you'd explain the behaviour of gas by reference to the behaviour of constituent molecules in accordance with Newtonian principles.

John Dupré: Or you'd explain human behaviour in terms of the interactions of brain cells. The opposite, downward causation, would be, for example, to say that the behaviour of a person causes their brain cells to move in a certain way. Lisa's example today, I take to be, as she just summarised it, precisely a claim to downward causation. That is to say that the social phenomena actually act causally on the individual, and, of course, to deny what is a very common thesis in the philosophy of social phenomena, which is methodological individualism, which says, and many people, social scientists and philosophers have said – you have to be able to explain social phenomena by looking at the behaviour of individuals. And that's the reductionist view as opposed to the downward causation view, which is an anti-reductionist view. And I think that's certainly one of the standard ways philosophers have understood the debate.

David Hull: Another example would be species selection, for upward versus downward. Are there characteristics of whole species which influence the behaviour of individual organisms, rather than the other way around? (Audible 'No' from someone). Yeah. There's a lot of people who say there is no species selection. This is an example of where the debate is.

Speaker: Don't we really have to have both processes? I mean in physics it's common – its called retroaction. One cause, one effect, the effect causes another effect, which becomes the next cause to the process. Everything is evolving this way.

Alex Rosenberg: What we do in the sense of feedback and cyclical phenomena are not examples of downward causation on the reductionist's view. In fact, they are ways of explaining away the appearance of downward causation. We have to quite clearly distinguish both feedback, 'feed-forward' and various kinds of cyclical causal processes from upward or downward causal processes. Mereological determinism is one label for upward causation, that the whole is not greater than the sum of its parts, that there are no really emergent properties, and that the phenomena of the whole are to be explained by decomposition into the behaviour of the individual constituents. By contrast with a claim favouring downward causation, according to which the behaviour of the whole cannot be explained by decomposition, and indeed moreover, the behaviour of the components can only be explained by reference to causal properties of the whole.

Terrance Brown: People seem to be using the words 'cause' and 'explanation' as if they had some almost synonymous meaning. My question is – Are explanation and cause the same, or are there explanations that are not causal?

Alex Rosenberg: That's a critical question because there are at least some defenders of emergentism and anti-reductionism who have distinguished sharply between causation as an ontological phenomena and explanation as epistemological and say that though physicalism is true, that is, we are nothing but matter and motion, nevertheless, the best explanations of our behaviour will not be physical. Bob?

Robert Richards: I just wanted to get on Lisa's case for a moment about downward causation. Isn't it, in your account, at least I thought you indicated, that a common element in all the efforts at explaining these anomalous phenomena concerning health had to do with the production of anxiety in the people who were suffering in various ways. But if you think about this, it is both a question and an objection, but if you think about the ways in which they gibe the account of how anxiety operates on the individual, presumably – it's my job, doesn't pay me enough, I work too hard, and so forth – these are very local and individual situations. And it is not, I would take it, the characteristic of a society at large that has the impact on a particular person, it is the people around that particular person. So it strikes me that these group phenomena that were described, can be reduced to the activities of individuals on one another and that as the production of illness in these particular cases.

Elizabeth Lloyd: I was most interested in just presenting the lay of the land in terms of mechanisms that had been offered for explaining these phenomena and just giving a description of the phenomena. The reason that I have been emphasising the irreducibility aspect of it was that it's not the mechanisms that themselves are irreducible in every single case. One assumes, I assume, that there is a specific family, a specific context, a specific job, a specific set of biological exposures that are causal, in fact. What seems to not be reducible to that level is in fact the gradient. It's the gradient itself, and a gradient can only be something that exists across a group or a society.

Robert Richards: But unless you assume the gradient is doing the causing, as opposed to just a description of the situation. If it's actually supposed to be doing the causing, I would agree, but I don't think anyone thinks the gradient itself is doing the causing.

Alex Rosenberg: Durkheim does, in 'Suicide'.

Robert Richards: Fortunately, he is no longer with us.

Elizabeth Lloyd: No, in fact, a lot of these mechanisms that are being introduced actually are ways of saying that the gradient does the causing.

Robert Richards: I would think that to be a pseudo-account. Gradients don't do anything except lie on a page.

Elizabeth Lloyd: That you cannot give a full explanation of what's happening in the group without giving an account of the gradient, and, in fact, the difference in socioeconomic gradients – I wouldn't prefer to call them causal myself but that they are descriptors of the situation that you cannot take them away from the explanation and understand it in the same way. I said one explains the phenomena in terms of what types of entities and their properties and so I take that to be a standard definition of a reductionist or anti-reductionist position.

Robert Richards: I don't see how a gradient *per se* has any causal impact.

Robert Williams: In the course of reductionism, what you try to do and it's perfectly fair to use the gradient in this sense, is you try to study a phenomenon and relate it to some property. Now, how far you can go with that depends on the level you're trying to reach. In this case, it's perfectly fair to say that a certain observation is a function of an observable gradient. In the same way it's perfectly fair to say in thermodynamics, although we don't understand the nature of liquids really, we understand it has something to do with the co-operative nature of the whole system. And I cannot relate it to the property of a single molecule. And this is the trouble – this is where you get the co-operative impact on a particular measurable. That is then, if it's the co-operatively that does it. In fact, it's not strictly reducible all the way to individual units, but you may reduce it to a certain level. And in

thermodynamics you choose to reduce it to thermodynamics, and you don't necessarily try to go all the way down to the molecular level. It's where you choose to stop.

Robert Richards: Yes, it's where you choose to stop but I guess in this case I would say that it's a placeholder for a kind of explanation that we know would be the more appropriate form of explanation.

Michel Morange: The definition of levels is essential. It's simple, for instance, in the case of social versus individual explanations of behaviours, but when you look at living beings, what exactly is the molecular level? I'm not sure that it's so easy to tell what is the molecular level, because in fact you have different levels which are all called 'molecular'. So the difficulty with living beings, and the program of reductionism is to explain what is meant by a level, and what kind of levels exist in living beings, or at least what kind of levels we consider in living beings.

Alex Rosenberg: I think that in fact that's an empirical problem and what the levels are will be relative to what the available successful theories are.

Armando Aranda: I have a general question. Is it currently valid to think that behind any kind of correlation there is an implication for a causal relationship? Considering the data that we saw for these gradients, and these lines, because ... going even to a simpler level than that ... it's very common, for example, in medicine that you start establishing correlations between a germ and a pattern of disease and then you think that there is a causal relationship. But there is already evidence, historical evidence, that some of these correlations were interesting, they pointed out towards something, but they were not strictly speaking showing a direct causal relationship.

Alex Rosenberg: We all recognise, I think, that correlation is not causation and is at most a symptom for either a causal relation, or for joint causes, or joint effects of a common cause, and the inference from correlation to causation is always an inductive one.

Armando Aranda: So, sorry, is it because in relation to what Dupré has said that I presume that downward causation can be based on something stronger and deeper than correlations?

Alex Rosenberg: Probably not, because correlations are all we ever have to go on, no matter how simple the causal hypotheses that we advance are.

Stan Shostak: All this talk about top-down and bottom-up reminds me of an ecological chain which is usually called top-down ecology, but we resist the chain, we pull at the chain, and it becomes a food web. I think I'm hearing here the scientists are saying 'hey', let's stretch this thing out, along various axes, and not get bogged down in what the philosophers will want us to do in terms of causal chains, because we see complexity along many

more axes. So stop trying to push us back into your top-down, bottom-up, whatever. We're breaking out. I hope so.

Robert Williams: Because it may not be clear to you what I'm trying to say, just take physicochemical phase diagrams. I wish to say that you may want to try to reduce biological systems to some sort of functionality, which is similar to the way we try to reduce when we're stuck with co-operative phenomena in physical sciences as in phase diagrams. I don't think we've got the right terms or description for the biological sciences to make this type of reduction in terms of functions which are relevant to systems far from equilibrium. What we do in physical chemistry is to take composition against free energy and we may get a continuous curve in an equilibrium phase diagram when A and B completely mix with one another. Or we can get a curve with maxima and minima where species appear. And species usually appear, the lower the temperature and the more the cooling. All gases mix completely, and when you move into liquids, substance mix partially, and then in solids you gradually get more and more species appearing. And that's the way chemistry has evolved in the universe. Now let's take biology. It isn't a matter of mixing in a static system – it's a matter of mixing with flows. And where flow differs from a static system is that flow has a set of vectors. And the question is – is there a corresponding equation to the equilibrium, $\Delta G = \Delta H - T\Delta S$ for vectors? Vectors are the means for carrying information. So if you have a function which, like Shannon did for information, it may be an entropy limitation on information, like he described it, which is really the entropy of the vectors. So what is this term? This term represents a constraint on the entropy of the vectors. And that causes what is known in mathematics and physics as the barriers. So you look at the barriers and ask yourself the nature of the barriers. Now the barrier functions can either be square waves for the simplest case, which would be like a capillary tube, in which you have a control over all the vectors as the liquid flows down it. Or, it can be a sort of gently reclining thing, where the vectors are wobbling about quite a bit. The more you develop a feedback evolution structure, the more you'll develop control over the wobbly flow. Now the question is – is there a similar principle to the fact that entropy increases in the universe, and can it be made equivalent to it in some sort of way? And can we start to think in biology, not in terms of what DNA does when it moves between organisms, which is what you were thinking, but can we think of the way flows become compatible with one another, and therefore you can transfer one sort of flow into another as a restriction. Some flows will mix and some won't and therefore you get speculation, not a continuity. And so I think we should look for a different sort of functionality from the ones we've

looked for so far, and that would be a form of reductionism for me. It's a start to go to some numerical analysis of the system in functional terms which are common to different parts of the system. But it doesn't get down to molecules and it never will. In essence, we need functional analysis of organisation, not of order.

John Dupré: I just wanted to respond to what I was trying to say with top-down, bottom-up. This is not a debate, as I see it, with some philosophers saying causation is top-down, some saying it's bottom-up. At least to me, the point of talking about top-down causation is to deny an extremely strong, an extremely restrictive view that an enormous number of philosophers have, which they derive from what may seem like a kind of band physicalism, and which leads them to deny that ultimately it's legitimate to appeal to any complex object in giving an ultimate explanation. And it seems to me insofar as there are ultimate explanations or best explanations, they will appeal to a group of entries drawn quite catholically from anywhere up the scale of the hierarchy of complexity. It seems to me that what I've heard in all the talks today from scientists is precisely that kind of claim. So I don't think it's trying to remove a set of shackles rather than to impose an alternative one, or to force people to choose between one and another.

Sohotra Sarkar: Going back to what John said, and earlier to Lisa's talk, there are two issues that have to be separated. The first one is that, when you're giving an explanation, the context determines when the explanation is good or not, when you're satisfied with how far you've gone. In the social case that Lisa was talking about, even in a particular context a second issue will arise, which is, when you're appealing to properties of the system, are the properties in principle not explainable by what happens at the individual level? I'll give you an example of a situation where I think properties like this arise. When you have something that is frequency dependent. In Lisa's income distribution, if the shape of the distribution matters in the explanation, then you have a case where methodological individualism is being denied, from my point of view at least. But if it's really a place holder, as Bob was saying, that is, for temporarily giving an explanation in terms of particular income levels and stress, and let's say that for whatever reason you're happy that this is the correct explanation, nothing more needs to be said, then it's not yet reductionist, but you leave yourself open to the fact that the causes of stress itself are going to be other individuals doing other things and so you have not really given an in-principle reason to doubt that methodological individualism can take care of the situation.

Marc Van Regenmortel: It may be appropriate to distinguish between reductive explanations, the cornerstone of reduction, and the possibility of achieving understanding by reduction rather than in a holistic or contextual

manner. The classical approach has been to use mechanistic and linear causation for the purpose of explanation but I think that it is now generally accepted that biological systems are too complex to be explained only by the nature of their individual components. Non-additivity and co-operativity between factors does not allow one to account for the behaviour of complex systems in terms of mechanistic, linear causality. Network causation is a more useful concept but it may be preferable to abandon the idea of causes altogether and to replace them by the innumerable 'factors' that influence a particular system. A great many factors influence cellular activity at a given time, but when you change these parameters, you unwittingly change many others because of internal co-operative interactions. As a result, you cannot explain what happens simply by looking at the role of one individual component. Available mathematical tools are mainly of a linear type and these cannot be used to describe complex systems that obey non-linear models. I think much of the non-additive, interactive systems in biology cannot be understood in terms of single causal factors taken out of their context.

Elizabeth Lloyd: Going back to what Sohotra and also Marc was saying, and actually going back to what Bob was saying, the fact that you've got these gradients is actually not explained yet. It may be that it will be explained through some common-sensical, normal way that is actually in terms of entities at the individual level and their properties. It has not been explained that way, it has no promise of being explained that way, they've been working on it for quite a while, and everything about it basically screams that it's an emergent property that is based on the actual slope of the gradient of the socioeconomic status. So I don't see any reason to actually balk at pursuing a higher-level type of explanation. I mean I see the difficulty as saying – well given that we usually want to pursue reductionist research methods, I'm just looking at ways to proceed which will be useful for testing alternative hypotheses about what is causing this sort of thing. There is one 'in-principle' claim, which is that an socioeconomic status gradient which is a group of property that . . .

Marc Van Regenmortel: The question is – is that a cause, and can you invoke a casual mechanism?

Elizabeth Lloyd: I am not claiming that it is a cause, and I never claimed that it was a cause. These people are not claiming that it is a cause. The problem is that there is nothing at the individual level that can even come close to explaining the results that they have. And that's the puzzle.

Marc Van Regenmortel: But what is your definition of an explanation? I mean . . . what is an acceptable explanation?

Alex Rosenberg: What would an acceptable explanation of the phenomena be, if not one in terms of the individual psychological states of the subject?

Elizabeth Lloyd: An explanation that, for example, said why it was that living in a society with a steep socioeconomic gradient was correlated with the kind of death and mortality rates that we're showing, and why living in a society with a much shallower gradient was correlated with a much lower death rate.

Alex Rosenberg: But what would satisfactorily show either of those things?

Robert Williams: You have to show the corpus of psychology, that such a thing exists?

Elizabeth Lloyd: Well that is one of the hypotheses. And I find the hypothesis quite congenial, but there are a number of hypotheses that have been presented. I don't think that any one of them is in the bag yet, is the point. I suppose that the main point of it was really to point out Al Tarov's diagram is even close to being right, and the genes and biology have that tiny little piece of the pie, and the rest of it is explained by societal and social factors, in terms of the death and the disease rate of your population in your country. I would think that would be of interest, and I think that would be of interest for the people looking to pour money into a medical project.

Eugene Dowdle: I'm not sure that explains, it rather correlates with social effects . . . You used the word 'explained' by social effects. It seems they're just correlated with social effects. Is that not right?

Elizabeth Lloyd: I used the word 'correlated' with social effects.

Eugene Dowdle: No, I am sorry you used the word, you said 'explained'. Looking at the pie, you actually said 'explained', by social factors and that it warranted the expenditure of money to investigate that explanation. I think it's actually a correlation.

Elizabeth Lloyd: Well if there's a correlation, and the correlations look like that, I think that's enough to put your money into it too. So I don't think that it makes any difference.

Eugene Dowdle: Well, it is not an explanation.

Elizabeth Lloyd: Well look. I hold a pragmatic view of explanation, which means that I think that whether you have explained it or not depends on what the question is.

Eugene Dowdle: You know, there was a study showing that carcinoma of the pancreas was associated with drinking coffee. A very strong correlation. Then it turned out that people who drink lots of coffee smoke while they're

drinking coffee. And the correlation with cigarette smoking was a lot tighter than the correlation with coffee.

Elizabeth Lloyd: I understand the difference between correlation and cause.

Eugene Dowdle: So now you know that I think that here, we might find a much tighter correlation with a gradient than social effects. You think it's possible?

Elizabeth Lloyd: Without putting the money into it, we are never going to find out. I mean if all the money is going into genetics you're never going to find that out.

Jim Griesemer: Let me end with a question. We've been talking about societies or groups perhaps not being acceptable loci of causation, but since much of the sense of the meeting so far has been that organisms are complex, why do we accept organisms as causes?

Chapter 7

Reductionism in an Historical Science

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Reductionism is a metaphysical thesis, a claim about explanations, and a research program. The metaphysical thesis reductionists advance (and antireductionists accept) is that all facts, including all biological facts, are fixed by the physical and chemical facts; there are no non-physical events, states or processes, and so biological events, states and processes are 'nothing but' physical ones. The research program can be framed as a methodological prescription which follows from the claim about explanations. Antireductionism does not dispute reductionism's metaphysical claim, but rejects the explanatory claim and so the methodological moral. To a first approximation what reductionists and antireductionists disagree about is whether explanations in functional biology can be or need to be explained by or completed or perhaps replaced by explanations in terms of molecular biology.[1] In addition, this disagreement over the adequacy of explanations in functional biology drives a significant methodological disagreement with consequence for the research program of biology.

The reason is simple. If the aim of science is explanation and explanations in functional biology are adequate, complete, and correct, then the methodological prescription that we must search for molecular completions, corrections, or foundations of these functional explanations in molecular processes, will be unwarranted. Consequently, molecular biology need not be the inevitable foundation for every compartment of functional biology. If the aim of science is explanation, and functional explanations are either false or incomplete, and molecular explanations either (more) correct or (more) complete, then biology must act on the methodological prescription

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that we should seek macromolecular explanations. If at its explanatory base, all biology is molecular biology, then all biologists, or at least all those who seek complete and correct explanations, will have eventually to be molecular biologists.[2]

Biologists are unlikely to be interested in philosophical disputes about the nature of explanation. Regrettably, they will have to be, if they wish to decide intelligently about whether to embrace a reductionist or nonreductionist methodology. For the dispute between reductionists and antireductionists turns very largely on the nature of scientific explanation. If there is no consensus on the nature of explanation, there will be no way to adjudicate the dispute between reductionism and antireductionism.

Matters used to be clearer, as a bit of the history of philosophy of biology will show.

What was reductionism?

For the record, let us recall how philosophers supposed reduction was to proceed, and some of the qualification added to the original model in order to bring it into contact with the history of science. Reduction is an intertheoretical relation between theories. In the Anglo-Saxon *locus classicus*, Ernest Nagel's *Structure of Science* (1961), reduction is characterized by the deductive derivation of the laws of the reduced theory from the laws of the reducing theory. The deductive derivation requires that the reduced theory shares meanings with the terms of the reducing theory. Although often stated explicitly, this second requirement is actually redundant as valid deductive derivation presupposes univocality of the language in which the theories are expressed. However, as exponents of reduction noted, the most difficult and creative part of a reduction is establishing these connections of meaning, i.e. formulating 'bridge principles', 'bilateral reduction sentences' and 'co-ordinating definitions'. Thus, it was worth stating the second requirement explicitly.

In posing the question above, I use the past tense advisedly. For reductionism, as a doctrine received from the logical positivists and their post-positivist empiricist successors, is a dead letter, at least in biology. An account of why this is so for physical science is relegated to a footnote.[3] To the general philosophical difficulties which the post-positivist account of reduction faced, biology provided further distinct obstacles. To begin with, as Hull (1974) first noted, the required 'bridge principles' between the concept of a gene as it figures in population biology and as it figures in molecular biology could not be effected. In addition, all of the ways philosophers contrived to preserve the truth of the claim that the gene is nothing but a

(set of) string(s) of nucleic acid bases, could not provide the systematic link between these two 'types' required by a reduction. There is of course no trouble identifying 'tokens' of the population biologist's genes with 'tokens' of the molecular biologist's genes. However, token-identities won't suffice for reduction, even if they are enough for physicalism to be true.

The second problem facing reductionism in biology is the absence of laws, either at the level of the reducing theory or the reduced theory. If there aren't any laws in either theory, there is no scope for reduction at all. Understanding the reason that there are no laws anywhere in biology is not only essential for understanding why post-positivist reductions are impossible, but equally essential to understanding the problems of antireductionism and to framing any alternative notion of either thesis.

That there are no laws in biology is now widely recognized among philosophers of biology, although some philosophers have responded to this realization by redefining the concept of 'law' so that some biological general statements may continue to be so-called (Sober, 1993; Lange, 1995).

The absence of laws in biology reflects some fundamental and ineliminable facts about the biological realm and the scientific study of that realm. To begin with, individuation of types in biology is almost always via causal role, and in particular via function. For instance, to call something a wing, or a fin, or a gene, is to identify it in terms of its function. However, biological functions are naturally selected effects. That is, the Larry Wright (Wright, 1976) analysis of function as etiological is correct in broad outline. In addition, natural selection for adaptations – i.e. environmentally appropriate effects – is blind to differences in physical structure that have the same or roughly similar effects.

Natural selection 'chooses' variants by *some of their effects*, those which fortuitously enhance survival and reproduction. When natural selection encourages variants to become packaged together into larger units, the adaptations become functions. Selection for adaptation and function kicks in at a relatively low level in the organization of matter. As soon as molecules develop the disposition chemically, thermodynamically or catalytically to encourage the production of more tokens of their own kind, natural selection comes into force. To employ vocabulary due to Dawkins (1983) and Hull (1989), at this point in the aggregation of matter, replicators and interactors (or vehicles) first appear. As a result of purely physical processes, some molecules become replicators – template or catalyze or otherwise encourage the production of copies of themselves, and these molecules interact with the environment so that changes in them – mutations – will result in changes in their rates of replication in their environments. Among such replicating and interacting molecules, there are frequently to be

found multiple *physically distinct* structures with some (nearly) identical rates of replication, different combinations of different types of atoms and molecules, that are about equally likely to foster the appearance of more tokens of the types they instantiate. This structural diversity explains why no simple identification of molecular genes with the genes of population genetics of the sort post-positivist reduction requires is possible. More generally, the reason there are no laws in biology is thus the same reason there are no bridge principles of the sort post-positivist reduction requires (one might have expected this consequence – bridge principles are supposed to be laws).

It is the nature of any mechanism that selects for effects, that *it cannot discriminate between differing structures with identical effects*. In addition, functional equivalence combined with structural difference will always increase as physical combinations become larger and more physically differentiated from one another. Moreover, perfect functional *equivalence* isn't necessary. Mere functional similarity will do. Since selection for function is blind to differences in structure, there will be no laws in any science which, like biology, individuates kinds by selected effects, that is by functions. A law in functional biology will have to link a functional kind either with an other functional kind, for example, 'all butterfly wings have eyespots' or a structural kind, 'all eyespots are composed of proteins'. However, neither of these statements can be a strict law, because of the blindness of natural selection (which forms functional kinds) to structure (which will therefore heterogeneously realize functional kinds). The details of this argument are relegated to a footnote.[4]

Any science in which kinds are individuated by causal role will have few if any exceptionless laws. However, of course, many will argue that neither biology nor reduction requires strict laws. Non-strict, *ceteris paribus* laws will suffice. However, there are no non-strict laws in biology either. The reason is that what makes for the allegedly *ceteris paribus* claims of physics does not obtain in biology. In physics, there is a finite (indeed small) number of forces – mechanical, electromagnetic, thermodynamic, etc. – that all work together to produce actual outcomes we seek to explain. To the extent a text-book generalization of mechanics, like $F = gm_1m_2/d^2$, is silent on these other forces, it is not a completely true description of physical processes, but rather a *ceteris paribus* law. There may perhaps be what Cartwright (1983) calls 'super-laws', which include the finite number of forces actually operative in nature. These will in effect be strict laws. However, in biology the role of natural selection does not limit the number of interfering forces that would turn a *ceteris paribus* law into a 'super' or strict law. The reason is to be found in the role of the environment

in setting adaptational or design problems for evolving lineages to solve. At a relatively early stage in evolution, these design problems take on the reflexive character of what Dawkins and others have called 'arms races', dynamic strategic competitions in which every move generates a counter-move so that conditions are never constant and *ceteris* is never *paribus*.

Ever since Darwin's focus on artificial selection it has been recognized that in the evolution of some species, other species constitute the selective force channeling their genetic changes. The interaction of predator and prey manifest the same relationship. Since the importance of frequency-dependent selection became apparent, it has been recognized that an interbreeding population can be an environmental force influencing its own evolutionary course. Competition for limited resources is endemic to the biosphere. Any variation in a gene, individual, line of descent or species which enhances fitness in such a relentlessly competitive environment will be selected for. Any response to such a variation within the genetic repertoire of the competitor gene, individual, lineage, or species, will, in turn, be selected for by the spread of the first variation, and *so on*. One system's new solution to a design problem is another system's new design problem. If the 'space' of adaptational 'moves' and counter-moves is very large, and the time available for trying out these stratagems is long enough, every regularity in biology about functional kinds will be falsified (or turned into a stipulation) eventually.

What this means, of course, is that any functional generalization in biology will be a *ceteris paribus* generalization in which, over evolutionary time scales, the number of exceptions will mount until its subject becomes extinct. Take a simple example, such as 'butterflies have eyespots'. The explanation for why they do is that such eyespots distract birds from the butterflies' more vulnerable and more nutritious parts and provide camouflage where they give the appearance of the eyes of owls (which prey on birds). This strategy for survival can be expected in the long run to put a premium on the development of ocular adaptations among birds, say the power to discriminate owl eyes from eyespots, which foil this stratagem for the butterfly. This, in turn, will lead either to the extinction of eyespot butterflies or the development of still another adaptation to reduce predation by birds, say the development of an unappetizing taste, or shift in color to the markings of another butterfly which already tastes 'bad' to birds. In turn, this stratagem will lead to a counter-stroke by the bird lineage. The fantastic variety of adaptational stratagems uncovered by biologists suggests that there is a vast space of available adaptive strategies among competing species, and that large regions of it are already occupied. The upshot is that to the extent that general laws must be timeless truths to which empirical

generalizations approximate as we fill in their *ceteris paribus* clauses, no such laws are attainable in biology because we can never fill in these clauses.

Notice this result obtains as much for molecular biology as it does for functional biology. Because the kinds of molecular biology are also functional, even at the level of the biochemical, natural selection's persistent exploration of adaptational space makes for lawlessness at the level of macromolecules as well. Consider three examples of generalizations in molecular biology once held to be strict laws and now found to have exceptions: (i) all enzymes are proteins, (ii) hereditary information is carried only by nucleic acids, and (iii) the central dogma of molecular genetics, DNA is transcribed to RNA and RNA is translated to protein. It turns out that RNA catalyzes its own self-splicing, that prions (the proteins responsible for 'Mad Cow Disease') carry hereditary information, and the retroviruses carry their own hereditary material in RNA and transcribe it to DNA. These exceptions to the relevant generalizations emerged through the operation of natural selection – finding strategies in adaptational space that advantage one or another unit of selection in the face of stratagems employed by others.

If there are no laws in biology, then biological theories cannot be related to one another in ways that satisfy the post-positivist conception of reduction. For the bridge principles that this formulation of reduction requires are laws, and the derivations they consists of require laws. Without recourse to laws, reductionism must be rejected or reformulated.

What was antireductionism?

If antireductionism were merely the denial that post-positivist reduction obtains among theories in biology, it would be obviously true (in part, for the reasons outlined in Note 2). However, antireductionism is not merely a negative claim. It is the thesis that (a) there are generalizations at the level of functional biology, (b) these generalizations are explanatory, (c) there are no further generalizations outside of functional biology which explain the generalizations of functional biology, and (d) there are no further generalizations outside functional biology which explain better, more completely, or more fully, what the generalizations of functional biology explain.

All four components of antireductionism are daunted by at least some of the same problems that vex reductionism: the lack of laws in functional biology and the problems in facing a nomic subsumption-account of explanation. If there are no laws and/or explanation is not a matter of subsumption, then antireductionism is false too. However, besides the

false presuppositions antireductionism may share with reductionism, it has distinct problems of its own.

In order to see the distinctive problems for antireductionism, consider a paradigm of putative irreducible functional explanation advanced by antireductionists.

The explanadum is as follows:

(G) Genes on different chromosomes, or sufficiently far apart on the same chromosome, assort independently.

The antireductionist proffers an explanans for (G), which we shall call (PS):

(PS) Consider the following kind of process, a *PS*-process (for *pairing* and *separation*). There are some basic entities that come in pairs. For each pair, there is a correspondence relation between the parts of one member of the pair and the parts of the other member. At the first stage of the process, the entities are placed in an *arena*. While they are in the arena, they can exchange segments, so that the parts of one member of a pair are replaced by the corresponding parts of the other members, and conversely. After exactly one round of exchanges, one and only one member of each pair is drawn from the arena and placed in the *winners box*.

In any PS-process, the chances that small segments which belong to members of different pairs or which are sufficiently far apart on members of the same pair will be found in the winners box are independent of one another. (G) holds because the distribution of chromosomes to games at meiosis is a PS-process.

This I submit is a full explanation of (G), and an explanation that prescinds entirely from the stuff that genes are made of (Kitcher, 1999, pp. 199–200).

Leave aside for the moment the claim that (PS) is a full explanation of (G), and consider why, according to the antireductionist, no molecular explanation of (PS) is possible.

The reason is basically the same story we learned above about why the kinds of functional biology cannot be identified with those of molecular biology. Because the same functional role can be realized by a diversity of structures, and because natural selection encourages this diversity, the full macromolecular explanation for (PS) or for (G) will have to advert to a range of physical systems that realize independent assortment in many different ways. These different ways will be an unmanageable disjunction of alternatives so great that we will not be able to recognize what they

have in common, if indeed they do have something in common beyond the fact that each of them will generate (G). Even though we all agree that (G) is obtained in virtue only of macromolecular facts, nevertheless, we can see that because of their number and heterogeneity these facts will not explain (PS), still less supplant (PS)'s explanation of (G), or for that matter supplant (G)'s explanation of particular cases of genetic recombination. This is supposed to vindicate the antireductionism's theses that functional explanations are complete and that functional generalizations cannot be explained by non-functional ones, or replaced by them.

However, this argument leaves several hostages to fortune. Begin with (G). If the argument of the previous section is right, (G) is not a law at all, but the report of a conjunction of particular facts about a spatiotemporally restricted kind, 'chromosomes', of which there are only a finite number extant over a limited time-period at one spatio-temporal region (the Earth). Accordingly, (G) is not something which we can expect to be reduced to the laws of a more fundamental theory, and the failure to do so constitutes no argument against reductionism classically conceived, nor is the absence or impossibility of such a reduction much of an argument *for* antireductionism.

The antireductionist may counter that regardless of whether (G) is a generalization, it has explanatory power and therefore is a fit test-case for reduction. This, however, raises the real problem which daunts antireductionism. The latter requires an account of explanation to vindicate its claims. Biologists certainly do accord explanatory power to (G). However, how does (G) explain? In addition, the same questions are raised by the other components of the antireductionist's claims. Thus, what certifies (PS) – the account of the PS-processes given above – as explanatory, and what prevents the vast disjunction of macromolecular accounts of the underlying mechanism of meiosis from explaining (PS), or for that matter from explaining (G) and indeed whatever it is that (G) explains?

There is one tempting answer, which I shall label, 'explanatory Protagorianism', the thesis that 'some human or other is the measure of all putative explanations, of those which do explain and those which do not'. Thus, consider the question of why a macromolecular explanation of (PS) is not on the cards? One answer is presumably that it is beyond the cognitive powers of any human contemplating the vast disjunction of differing macromolecular processes each of which gives rise to meiosis, to recognize that conjoined they constitute an explanation of (PS). Or similarly, it is beyond the competence of biologists to recognize how each of these macromolecular processes give rise to (G). This is explanatory Protagorianism. That the disjunction of this set of macromolecular processes implements PS-processes and thus brings about (PS) and (G) does not seem to be at issue.

Only someone who denied the thesis of physicalism – that the physical facts fix all the biological facts – could deny the causal relevance of this vast motley of disparate macromolecular processes to the existence of (PS) and the truth of (G).

In fact, there is something that the vast disjunction of macromolecular realizations of (PS) have in common that would enable the conjunction of them to fully explain (PS) to someone with a good enough memory for details. Each was selected for because each implements a PS-process and PS-processes are adaptive in the local environment of the Earth from about the onset of the sexually reproducing species to their extinction. Since selection for implementing PS-processes is blind to differences in macromolecular structures with the same or similar effects, there may turn out to be nothing else completely common and peculiar to all macromolecular implementations of meiosis besides their being selected for implementing PS-processes. However, this will be a reason to deny that the conjunction of all these macromolecular implementations explain (PS) and/or (G), only on a Protagorian theory of explanation.

Antireductionists who adopt what is called an erotetic account of explanation, in preference to a unification account, a causal account or the traditional D–N account of explanation, will feel the attractions of explanatory Protagorianism. For the erotetic account of explanations treats them as answers to 'why questions' posed about a particular occurrence or state of affairs, which are adequate, i.e. explanatory, to the degree they are appropriate to the background information of those who pose the 'why question' and to the degree that the putative explanation excludes competing occurrences or states of affairs from obtaining. Since it may be that we never know enough for a macromolecular answer to the question of why does (G) obtain, no macromolecular explanation of why (G) obtains will be possible. Similarly, we may never know enough for a macromolecular explanation of (PS) to be an answer to our question 'Why do PS processes occur?'. However, this seems a hollow victory for antireductionism, even if we grant the tendentious claim that we will never know enough for such explanations to succeed. What is worse, it relegates antireductionism to the status of a claim about biologists, not about biology. Such philosophical limitations on our epistemic powers have been repeatedly breeched in the history of science.

Antireductionists wedded to alternative, non-erotetic accounts of explanation, cannot adopt the gambit of a Protagorian theory of explanation in any case. They will need a different argument for the claim that neither (G) nor (PS) can be explained by its macromolecular supervenience base, and for the claim that (PS) does explain (G), and (G) does explain individual cases of recombination. One argument such antireductionists might offer for the

former claim rests on a metaphysical thesis: that there are no disjunctive properties or that if there are, such properties have no causal powers. Here is how the argument might proceed. The vast motley of alternative macromolecular mechanisms that realize (PS) have nothing in common. There is no property – and in particular no property with the causal power to bring about the truth of (G) which they have in common. Physicalism (which all antireductionists party to this debate embrace) assures us that whenever PS obtains, some physical process, call it P_i, obtains. Thus we can construct the identity (or at least the bi-conditional) that:

$$(R)PS = P_1, \text{ v } P_2 \text{v} \ldots \text{v } P_i, \text{ v} \ldots \text{v } P_m$$

where m is the number, a very large number, of all the ways that macromolecular processes can realize PS-processes.

The Protagorian theory of explanation tells us that (R) is not explanatory roughly because it's too long a sentence for people to keep in their heads. A causal theory of explanation might rule out R as explaining PS on the ground that the disjunction, $P_1, \text{ v } P_2 \text{v} \ldots \text{v } P_i, \text{ v} \ldots \text{v } P_m$, is not the *full* cause. This might be either because it was incomplete – there is always the possibility of still another macromolecular realization of PS arising, or because disjunctive properties just aren't causes, have no causal powers, or perhaps aren't really properties at all. A unificationist-theory of explanation (or for that matter a D–N account) might hold that since the disjunction cannot be completed, it will not effect deductive unifications or systematizations. Thus (PS) and (G) are the best and most complete explanations biology can aspire to. Antireductionist versions of all three theories, the causal, the unificationist, and the Protagorian, need the disjunction in (R) to remain uncompleted in order to head-off a reductionist explanation of (PS) and/or (G).

Consider the first alternative, that (R) is not complete, either because some disjuncts haven't occurred yet or perhaps that there is an indefinite number of possible macromolecular implementations for (PS). This, in fact, seems to me to be true, just by virtue of the fact that natural selection is continually searching the space of alternative adaptations and counter-adaptations, and that threats to the integrity and effectiveness of meiosis might in the future result in new macromolecular implementations of (PS) being selected for. However, this is no concession to antireductionism. It is part of an argument that neither (PS) nor (G) report an explanatory generalization, that they are in fact temporarily true claims about local conditions on the Earth.

On the second alternative, (R) can be completed in principle, perhaps because there are only a finite number of ways of realizing a PS-process.

However, the disjunction is not a causal or a real property at all. Therefore, it cannot figure in an explanation of either (PS) or (G). There are several problems with such an argument. First, the disjuncts in the disjunction of P_1, v P_2v . . . v P_i, v . . . v P_m, do seem to have at least one or perhaps even two relevant properties in common: each was selected for implementing (PS) and causally brings about the truth of (G). Secondly, we need to distinguish predicates in languages from properties in objects. It might well be that in the language employed to express biological theory, the only predicate we employ which is true of every P_i is a disjunctive one, but it does not follow that the property picked out by the disjunctive predicate is a disjunctive one. Philosophy long ago learned to distinguish things from the terms we hit upon to describe them.

Arguing against the causal efficacy of some disjunctive properties, Sober has held that 'disjunctive properties will appear to be causally efficacious only to the degree that their disjuncts strike us as subsuming similar sorts of possible causal processes' (Sober, 1984, p. 94). Suppose we drop out the qualifications 'will appear to be' and 'strike us' as unsuited to a question about whether disjunctive properties really are causally efficacious as opposed to seeming 'to us' to be causally efficacious. If we adopt this principle, the question at issue becomes one of whether the disjunction of P_1, v P_2v . . . v P_i, v . . . v P_m subsumes similar sorts of causal processes, to which the answer seems to be that the disjunction shares in common the features of having been selected for resulting in the same outcome, i.e. PS-processes. Thus, the disjunctive predicate names a causal property, a natural kind. Antireductionists are hard pressed to deny the truth and the explanatory power of (R).

Besides its problems in undermining putative macromolecular explanations of (PS), (G) and what (G) explains, antireductionism faces some problems in substantiating its claims that (PS) explains (G) and (G) explains individual cases of genetic recombination. The problems, of course, stem from the fact that neither (PS) nor (G) are laws, and therefore an account is owing of how statements like these can explain. This, in fact, is a problem that any revision of a thesis of reductionism must come to grips with as well. So, perhaps we should turn to this problem directly, and then reformulate and reassess both reductionism and antireductionism as explanatory theses in its light.

Biology is history (all the way down)

The upshot is not simply that there are no laws, *ergo* neither reductionism nor antireductionism about laws is tenable in biology. The entire character

of biology as a discipline reflects the considerations which make laws impossible. Functional kinds have etiologies that reflect natural selection operating on local conditions, and natural selection is constantly changing local conditions. This makes biology an essentially historical discipline. Any reformulation of the thesis of reductionism or of antireductionism will have to reflect this fact about the discipline if it is to have a ghost of a chance of illuminating the structure of biology or motivating a research program.

Evolution is a mechanism – blind variation and natural selection – that can operate everywhere and always throughout the universe. It obtains whenever tokens of matter have become complex enough to foster their own replication and variation so that selection for effects can take hold. Recent experiments in chemical synthesis suggest that this may not be an uncommon phenomenon.[5] Macromolecules are the initial replicators and also the initial interactors or vehicles (although they are eventually selected for 'building' larger interactors or vehicles – chromosomes, cells, tissues, organs, bodies, etc.).

However, we express the mechanism of natural selection, its general principles operate without exception everywhere replicators and their vehicles appear. The principles of the theory of natural selection are the only real laws in biology. Beyond the bare theory of natural selection itself, the rest of biology is a set of subdisciplines, historically conditioned by the operation of natural selection on local circumstances during the history of the Earth. The functional individuation of biological kinds reflects the vagaries and vicissitudes of natural selection, since biological kinds are the result of selection over variation in order to solve design problems set by the environment. Possible solutions to the same problem are multiple and one biological system's solution sets a competing biological system's next design problem. Therefore, each system's environment varies over time in a way that makes all putative biological 'generalizations' about these systems into historically limited descriptions of local patterns. Any subdiscipline of biology – from paleontology to developmental biology, to population biology, to physiology, or molecular biology – can uncover at best historically conditioned patterns, owing to the fact that (a) its kind of vocabulary picks out items generated by a historical process, and (b) its 'generalizations' will always be overtaken by evolutionary events. Some of these 'generalizations' will describe long-term and widespread historical patterns, such as the ubiquity of nucleic acid as the hereditary material. Others will be local and transitory, such as the description of the primary sequence of the latest AZT-resistant mutation of the AIDS virus.

The apparent generalizations of functional biology are really spatiotemporally restricted statements about trends and the co-occurrence of finite

sets of events, states and processes. Beyond those laws which Darwin uncovered, there are no other generalizations about biological systems to be uncovered, at least none to be had that connect kinds under biological, i.e. functional, descriptions.

Biological explanation is historical explanation, in which the implicit laws are the principles of natural selection. This will be true even in molecular biology. To cite a favorite example of mine,[6] the explanation of why DNA contains thymine, while messenger mRNA transfers tRNA, and ribosomal rRNA contains uracil, is a thorough going historical one. Long ago on Earth, DNA won the selective race for best available solution to the problem of high-fidelity information storage: Meanwhile, RNA was selected for low-cost information transmission and protein synthesis. Uracil is cheaper to synthesize than thymine, because the latter has a methyl group that uracil lacks. Cytosine spontaneously deaminates to uracil. DNA with uracil produced by deamination results in a point mutation in the conjugate DNA strand on replication since cytosine pairs with guanine, while uracil and thymine both pair with adenine. A repair mechanism evolutionarily available to DNA removes uracils and replaces them with cytosines to prevent this point mutation. The methyl group on thymine molecules in DNA blocks the operation of these repair mechanisms when it attempts to remove thymines. Employing this relatively costly molecule was a cheaper and/or more attainable adaptation than DNA evolving a repair mechanism that could distinguish uracils which are not the result of cytosine deamination from those which are the result of deamination. Thus, it was selected for. Meanwhile, the spontaneous deamination of cytosine to uracil on one out of hundreds or thousands of RNA molecules engaged in protein synthesis will disable it, but result only in a negligible reduction in the production of the protein it would otherwise build. Ergo, natural selection for economic RNA transcription resulted in RNAs employing uracil instead of thymine. Notice how the explanation works: First, we have two 'generalizations': DNA contains thymine, while RNA contains uracil. They are not laws but in fact statements about local conditions on the Earth. After all, DNA can be synthesized with uracil in it and RNA can be synthesized with thymine; secondly, the explanation for each appeals to natural selection for solving a design problem set by the environment. Thirdly, tRNA, mRNA, and the various rRNAs are functional kinds, and they have their function as a result of selection over variation. Finally, we can expect that in nature's relentless search for adaptations and counteradaptations, the retroviruses, in which hereditary information is carried by RNA, may come to have their RNAs composed of thymine instead of uracil, if and when it becomes disadvantageous for retroviruses to maximize their rates of mutation. At this

point, of course, the original generalizations will, like other descriptions of historical patterns, cease to obtain, but we will have an evolutionary explanation for why they do so, and we will be able to retain our original explanation for why these generalizations obtained about the composition of DNA and RNA during the period and in the places where they did so. In these respects, explanation in molecular biology is completely typical of explanation at all higher levels of biological organization. It advances historical explanation-sketches in which the principles of the theory of natural selection figure as implicit laws.

Reductionism in an historical science

In biology, neither reductionism nor antireductionism can be theses about the explanation of laws, except perhaps about the explanation of the laws of natural selection. I say 'perhaps' because there may be parties to this dispute that will not grant nomological status to any principles of the theory of natural selection, and so cannot dispute whether there are any laws of this theory to be explained by more fundamental ones (see, for example, Brandon, 1990). It is not obvious among philosophers of biology that there are such laws of natural selection. However, I have assumed as much above. Moreover, I have assumed that the laws of natural selection obtain just by virtue of chemical and physical regularities, since all it takes for replicators and interactors to be possible is that these physical laws obtain. Reductionists should welcome the addition of laws of natural selection to the explanatory store of a reductionistic approach to biology. On the other hand, it would be an easy vindication of antireductionism if such laws were not themselves accepted as physical principles explainable without remainder as the result of physical processes. For, as we have seen, every part of biology relies on natural selection to give content its functional individuation. If generalizations of natural selection are irreducible, so is all, not just some, of biology, including all of molecular biology – the part of biology to which it is proposed by reductionists to reduce the rest of biology to physical science.

If reductionism is to be given a chance of being right, we must give it natural selection as at least a component of the reduction base of biology in physical science.

Reductionism will have to be a thesis about the explanation of historical facts, some more general than others, but all of them ultimately the contingent results of general laws of natural selection operating on boundary conditions. Reductionism needs to claim that the only way to explain one historical fact is by appeal to other historical facts, plus some

laws or other. If there are no laws in biology beyond the principles of the theory of natural selection, then the explanation of one historical fact by appeal to another will have to appeal to these laws and if necessary to other laws drawn from physical science. This might be viewed as a vindication of some form of reductionism, understood as the claim that explanations of biological phenomena are ultimately to be given by appeal to the operation of non-biological laws drawn from physical science. However, it will be a hollow vindication of reductionism. There must be more to reductionism that the claim that evolutionary explanation is physical explanation.

To see what more there must be to reductionism, recall the distinction between two different kinds of explanatory tasks in biology, i.e. the distinction between proximate and ultimate explanation due to Mayr (1981). Thus, the question as to why do butterflies have eyespots may be the request for an adaptationalist explanation that accords a function in camouflage, for instance, to the eyespot on butterfly wings, or it may be the request for an explanation of why at a certain point in development eyespots appear on individual butterfly wings and remain there throughout their individual lives. The former explanation is an ultimate one, while the latter is a proximate one. Reductionism must be a thesis about both sorts of explanation. In fact, I shall suggest that it is the radical thesis that ultimate explanations must give way to proximate ones and that these latter will be molecular explanations.

To expound its thesis about explanations, reductionism adduces another distinction among explanations. It is a distinction well known in the philosophy of history, a division of philosophy whose relevance to biology may now be apparent. The distinction is between what William Dray (1957) called 'how-possibly explanations' and 'why-necessary explanations'. A 'why-necessary explanation' effectively rebuts a presumption that the explanandum need not have happened, 'by showing in the light of certain considerations (perhaps laws as well as facts), it had to happen'. (Dray, 1957, p. 161). 'How-possible explanations' show how something could have happened, by adducing facts which show that there is after all no good reason for supposing it could not have happened. 'The essential feature of explaining how-possibly is . . . that it is given in the face of a certain sort of puzzlement' (Dray, 1957, p. 165). The appeal to puzzlement makes it clear that Dray was sympathetic to erotetic models of explanation. Indeed, he went on to say 'These two kinds [of explanation] are logically independent in the sense that they have different tasks to perform. They are answers to different questions' (Dray, 1957, p. 162). However, Dray recognized an important asymmetrical relationship between them:

> *It may be argued that although, in answer to a 'how-possibly' question, all that need be mentioned is the presence of some previously unsuspected necessary condition of what happened .... [N]evertheless, this does not amount to a full explanation of what happened. Insofar as the explanation stops short of indicating sufficient conditions, it will be said to be ... an incomplete explanation, which can only be completed by transforming it into an appropriate answer to the corresponding 'Why?'.*
>
> *... Having given a how-possibly answer it always makes sense to go on to demand a why-necessary one,* ***whereas this relationship does not hold in the opposite direction****. (Dray, 1957, p. 168, with emphasis added).*

Of course, Dray's concern was human history, but the claims carry over into natural history. They enable us to see how reductionism might be vindicated, among biologists at least, as an ultimate how-possibly explanation gives way to proximate why-necessary explanation. Let us see how.

Consider the ultimate explanation for eyespots in the species *Precis coenia*. Notice, to begin with, that there is no scope for explaining the law that butterflies have eyespots, or patterns that may include eyespots, scalloped color patterns, or edge-bands. There is no such law to be explained.[7] There are, however, historical facts to be explained.

The ultimate explanation has it that eyespots on butterfly and moth wings have been selected for over a long course of evolutionary history. On some butterflies these spots attract the attention and focus the attacks of predators on to parts of the butterfly less vulnerable to injury. Such spots are more likely to be torn off than more vulnerable parts of the body, and this loss does the moth or butterfly little damage, while allowing it to escape. On other butterflies, and especially moths, wings and eyespots have also been selected for taking the appearance of an owl's head, brows and eyes. Since the owl is a predator of those birds which consume butterflies and moths, this adaptation provides particularly effective camouflage.

Here, past events help to explain current events via implicit principles of natural selection. Such ultimate explanations have been famously criticized as 'just-so' stories, too easy to frame and too difficult to test (Gould and Lewontin, 1979). There is certainly something to this charge. Just because available data or even experience shows that eyespots are widespread does not guarantee that they are adaptive now. Even if they are adaptive now, this is by itself insufficient grounds to claim they were selected because they were the best available adaptation for camouflage, as opposed to some other function, or for that matter that they were not selected at all but

are mere 'spandrels', or traits riding piggy-back on some other means of predator avoidance or some other adaptive trait.

Reductionists will reply to this criticism that adaptationalist ultimate explanations of functional traits are 'how-possibly' explanations, and the 'just-so-story' charge laid against ultimate explanation on these grounds mistakes incompleteness (and perhaps fallibility) for untestability. The reductionist has no difficulty with the ultimate functional how-possibly explanation, as far as it goes. For its methodological role is partly one of showing how high fitness could, in principle, be the result of purely non-purposive processes, and partly, to set the research agenda which seeks to provide why-necessary explanations, which cash in the promissory notes offered by the how-possibly explanation. However, the reductionist shares with others suspicious of ultimate explanation a cognition of its severe limitations, i.e. its silence about crucial links in the causal chains to which it adverts.

The how-possibly explanation leaves unexplained several biologically pressing issues, ones which are implicit in most well-informed requests for an ultimate explanation. These are the question of what alternative adaptive strategies were available to various lineages of organisms, and which were not, and the further question of how the feedback from adaptedness of functional traits – like the eyespot – to their greater subsequent representation in descendants was actually effected. Silence on the causal details of how the feedback loops operate from fortuitous adaptedness of traits in one or more distantly past generations to improved adaptation and ultimately an approach to constrained locally optimal design, is the most disturbing lacuna in how-possibly explanations. Dissatisfaction with such explanations, as voiced by those suspicious of the theory of natural selection and those amazed by the degree of apparent optimality of natural design, as well as the religious, all stem from a widely shared pre-scientific commitment to complete causal chains, along with the denial of action at a distance, and of backward causation. Long before Darwin, or Paley for that matter, Spinoza diagnosed the problem of purposive or goal-directed explanation as that it 'reverses the order of nature', and makes the cause the effect. Natural selection replaces goal-directed processes. However, natural selection at the functional level is silent on the crucial links in the causal chain which convert the appearance of goal-directedness into the reality of efficient causation. Therefore, explanations that appeal to it sometimes appear to be purposive or give hostages to fortune, by leaving too many links in their causal chains unspecified. Darwin's search for a theory of heredity reflected his own recognition of this fact.

The charge that adaptational explanations are unfalsifiable or otherwise scientifically deficient reflects the persistent claim by advocates of the adequacy of ultimate explanations that their silence on these details is not problematic.

Only a macromolecular account of the process could answer these questions. Such an account would itself also be an adaptational explanation: it would identify strategies available for adaptation by identifying the genes (or other macromolecular replicators) which determine the characteristics of Lepidopteran's evolutionary ancestors, and which provide the only stock of phenotypes on which selection can operate to move along pathways to alternative predation-avoiding outcomes – leaf color camouflage, spot-camouflage, or other forms of Batesian mimicry, repellant taste to predators, Mullerian mimicry of bad-tasting species, etc. The reductionist's 'why-necessary explanation' would show how the extended phenotypes of these genes competed and how the genes which generated the eyespot eventually become predominant, i.e. are selected for. In other words, the reductionist holds that (a) every functional ultimate explanation is a how-possibly explanation, and (b) there is a genic and biochemical pathway selection process underlying the functional how-possibly explanation. As we shall see below, reduction turns the merely how-possible scenario of the functional ultimate explanation into a why-necessary proximate explanation of a historical pattern. Note that the reductionist's full explanation is still a historical explanation in which further historical facts – about genes and pathways – are added, and are connected together by the same principles of natural selection that are invoked by the ultimate functional how-possibly explanation. However, the links in the causal chain of natural selection are filled in to show how past adaptations were available for and shaped into today's functions.

Antireductionists will differ from reductionists, not on the facts, but on whether the initial explanation was merely an incomplete one or just a how-possibly explanation. Antireductionists will agree that the macromolecular genetic and biochemical pathways are causally necessary to the truth of the purely functional ultimate explanation. However, they don't complete an otherwise incomplete explanation. They are merely further 'facets of [the] situation that molecular research might illuminate' (Kitcher, 1999, p. 199). The original ultimate answer to the question as to why do butterflies have eyespots does provide a complete explanatory answer to a question. Accordingly, how-possibly explanations are perfectly acceptable ones, or else the ultimate explanation in question is something more than a mere how-possibly explanation.

Who is right here?

On an erotetic view, how-possibly and why-necessary explanations may be accepted as reflecting differing questions expressed by the same words. The reductionist may admit that there are contexts of inquiry in which how-possible answers to questions satisfy explanatory needs. However, the reductionist will insist that in the context of advanced biological inquiry, as opposed say to secondary-school biology instruction, for example, the how-possible question either does not arise, or having arisen in a past stage of inquiry, no longer does. How-possibly questions do not arise where the phenomena to be explained are not adaptations at all, for instance, constraints, or spandrels, and the only assurance that, in fact, how-possibly explanations make true claims is provided by a why-necessary explanation that cashes in their promissory notes by establishing the adaptive origins of the functional traits in molecular genetics. This will become clearer as we examine proximate explanation in biology.

Consider the proximate explanation from the developmental biology of butterfly wings and their eyespots. Suppose we observe the development of a particular butterfly wing, or for that matter suppose we observe the development of the wing in all of the butterflies of the buckeye species, *Precis coenia*. Almost all will show the same sequence of stages, beginning with a wing imaginal disk eventuating in a wing with such spots, and a few will show a sequence eventuating in an abnormal wing or one without the characteristic eyespot maladapted to the butterfly's environment. Rarely, one may show a novel wing or markings fortuitously more well adapted to the environment than the wings of the vast majority of members of its species. Let's consider only the first case. We notice in one buckeye caterpillar (or all but a handful) that during development an eyespot appears on the otherwise unmarked and uniform epithelium of the emerging butterfly wing. If we seek an explanation of the sequence in one butterfly, the general statement, that in all members of its species development results in the emergence of an eyespot on this part of the wing, is unhelpful. First, because examining enough butterflies in the species shows it is false. Secondly, even with an implicit *ceteris paribus* clause, or a probabilistic qualification, we know the 'generalization' simply describes a distributed historical fact about some organisms on this planet around the present time and for several million years in both directions. One historical fact cannot by itself explain another, especially not if its existence *entails* the existence of the fact to be explained. That all normal wings develop eyespots does not explain why one does. Most non-molecular generalizations in developmental biology are of this kind. That is, they may summarize sequences of events in organisms of a species, or for that matter in organisms of higher taxa than

species.[8] However, the reductionist will argue, they proximately explain nothing. They cannot, owning to their character as implicit descriptions of historically circumscribed events, states, conditions, processes or patterns.

How is the pattern of eyespot development in fact proximally explained? Having identified a series of genes which control wing development in *Drosophila*, biologists then discovered homologies between these genes and genes expressed in butterfly development, and that whereas in the fruit fly they control wing formation, in the butterfly they also control pigmentation. The details are complex but following out a few of them shows us something important about how proximate why-necessary explanation can cash in the promissory notes of how-possibly explanation and, in principle, reduce ultimate explanations to proximate ones.

In the fruit fly, the wing imaginal disk is first formed as a result of the expression of the gene *wingless* (so called because its deletion results in no wing imaginal disk and thus no wing) which acts a position signal to cells directing specialization into the wing disk structure. Subsequently, the homeotic selector gene *apterous* is switched on and produces apterous protein only in the dorsal compartment of the imaginal disk-control formation of the dorsal (top) side of the wing and activates two genes, i.e. *fringe* and *serrate*, which form the wing margin or edge. These effects were discovered by preventing dorsal expression of *apterous*, which results in the appearance of ventral (bottom) cells on the dorsal wing, with a margin between them and other (nonectopic) dorsal cells. Still another gene, *distal-less*, establishes the fruit fly's wing tip. Its expression in the center of the (flat) wing imaginal disk specifies the proximo-distal (closer to body/further from body) axis of wing development.[9]

Once these details were elucidated in *Drosophila*, it became possible to determine the expression of homologous genes in other species, in particular in *Precis coenia*. To begin with, nucleic acid sequencing showed that genes with substantially the same sequences were to be found in both species. In the butterfly, these homologous genes were shown to also organize and regulate the development of the wing, although in certain different ways. For instance, in the fruit fly, *wingless* organizes the pattern of wing margins between dorsal and ventral surfaces, restricts the expression of *apterous* to dorsal surfaces and partly controls the proximo-distal access where *distal-less* is expressed. In the butterfly, *wingless* is expressed in all of the peripheral cells in the imaginal disk which will not become parts of the wing, where it programs their death (Nijhout, 1994, p. 45). *Apterous* controls the development of ventral wing surfaces in both fruit flies and butterflies, but the cells in which it is expressed in the *Drosophila* imaginal

disk are opposite those in which the gene is expressed in *Precis* imaginal disks. As Nijhout describes the experimental results:

> *The most interesting patterns of expression are those of* Distal-less*. In* Drosophila*,* Distal-less *marks the embryonic premordium of imaginal disks and is also expressed in the portions of the larval disk that will form the most apical* [wing-tip] *structures .... In* Precis *larval disks,* Distal-less *marks the center of a presumptive eyespot in the wing color pattern. The cells at this center act as inducers or organizers for development of the eyespot: if these cells are killed, no eyespot develops. If they are excised, and transplanted elsewhere on the wing, they induce an eyespot to develop at an ectopic location around the site of implantation ... the pattern of* Distal-less *expression in* Precis *disks changes dramatically in the course of the last larval instar [stage of development]. It begins as broad wedge-shaped patterns centered between wing veins. These wedges gradually narrow to lines, and a small circular pattern of expression develops at the apex of each line ....*

What remains to be explained is why only a single circle of *Distal-less* expression eventually stabilizes on the larval wing disks (Nijhout, 1994, p. 45).

In effect, the research program in developmental molecular biology is to identify genes expressed in development, and then to undertake experiments – particularly ectopic gene-expression experiments – which explain the long-established observational 'regularities' reported in traditional developmental biology. The explanatia uncovered are always 'singular' boundary conditions insofar as the explananda are spatiotemporally limited patterns, to which there are always exceptions of many different kinds. The reductionistic program in developmental molecular biology is to first explain the wider patterns, and then explain the exceptions – 'defects of development' (if they are not already understood from the various ectopic and gene deletion experiments employed to formulate the why-necessary explanation for the major pattern).[10]

This program is by no means complete and the reductionist's why-necessary explanations are not yet in. However, they are obviously coming. In providing them, the reductionist also pays the promissory notes of the ultimate how-possibly explanations biologists proffer. Recall that the ultimate how-possibly explanation of the eyespot appeals to its predator-distraction and camouflage properties, but is silent on why this adaptation emerged instead of some other way of avoiding predation, and so is

vulnerable to question, and invulnerable to test. Developmental molecular biology can answer questions about adaptation by making its historical claims about lines of descent open to test.

The developmental molecular biologist, S. B. Carroll (and colleagues), who reported the beginnings of the proximal explanation sketched above, eventually turned their attention to elucidating the ultimate explanation. Carroll and co-workers write:

> *The eyespots on butterfly wings are a recently derived evolutionary novelty that arose in a subset of the Lepidoptera and play an important role in predator avoidance. The production of the eyespot pattern is controlled by a developmental organizer called the focus, which induces the surrounding cells to synthesize specific pigments. The evolution of the developmental mechanisms that establish focus was therefore the key to the origin of butterfly eyespots (Keys* et al *., 1999, p. 532).*

What Carroll's team discovered is that the genes and the entire regulatory pathway that integrates them and which control anterior/posterior wing development in the *Drosophila* (or its common ancestor with butterflies) have been recruited and modified to develop the eyespot focus. This discovery of the 'facility with which new developmental functions can evolve . . . within extant structures' (Keys *et al*., 1999, p. 534) would have been impossible without the successful why-necessary answer to the proximate question of developmental biology.

Besides the genes noted above, there is another, *Hedgehog* whose expression is of particular importance in the initial division of the *Drosophila* wing imaginal disk into anterior and posterior segments. As in the fruit fly, in *Precis* the *hedgehog* gene is expressed in all cells of the posterior compartment of the wing. but its rate of expression is even higher in the cells that surround the foci of the eyespot. In *Drosophila, Hedgehog*'s control over anterior/posterior differentiation appears to be the result of a feedback system at the anterior/posterior boundary involving four other gene products, and in particular one, *engrailed*, which represses another, *cubitus interruptus* (hereafter '*ci*' for short), in the fruit fly's posterior compartment. This same feedback look is to be found in the butterfly wing posterior compartment, except that here the *engrailed* gene's products do not repress *ci* expression in the anterior compartment of the wing. The expression of *engrailed*'s and *Ci*'s gene-products together result in the development of the focus of the eyespot. One piece of evidence that switching on the *Hedgehog-engrailed-ci* gene system produces the eyespot

comes from the discovery that in those few butterflies with eyespots in the anterior wing compartment, *engrailed* and *ci* are also expressed in the anterior compartment at the eyespot foci (but not elsewhere in the anterior compartment). 'Thus, the expression of the *Hedgehog* signaling pathway and *engrailed* is associated with the development of all eyespot foci and has become independent of the [anterior/posterior] restrictions [that are found in *Drosophila*]' (Keys *et al*., 1999, p. 534).

Further experiments and comparative analysis enabled Carroll and co-workers to elucidate the causal order of the changes in the *Hedgehog* pathway as it shifts from wing production in *Drosophila* (or its ancestor) to focus production in *Precis* eyespot development. 'The similarly between the induction of *engrailed* by *Hedgehog* at the [anterior/posterior] boundary [of both fruit fly and butterfly wings, where it produces the intervein tissue in wings] and in eyespot development suggests that during eyespot evolution, the *Hedgehog*-dependent regulatory circuit that establishes foci was recruited from the circuit that acts along the anterior/posterior boundary of the wing' (Keys *et al*., 1999, p. 534).

Of course, the full why-necessary proximate explanation for any particular butterfly's eyespots is not yet in, nor is the full why-necessary proximate explanation for the development of the *Drosophila's* (or its ancestor's) wing. However, once they are in, the transformation of the ultimate explanation of why butterflies have eyespots on their wings into a proximate explanation can begin. This fuller explanation will still rely on natural selection. However, it will be one in which the alternative available strategies are understood and the constraints specified, the time and place and nature of mutations narrowed, in which adaptations are unarguably identifiable properties of genes – their immediate or mediate gene products (in Dawkin's terms, their extended phenotypes), and in which the feedback loops and causal chains will be fully detailed, and the scope for doubt, skepticism, questions and methodological critique that ultimate explanations are open to, will be much reduced.

Methodological morals – reductionism and the return of the gene

At the outset, I claimed that reductionism is a methodological dictum that follows from biology's commitment to provide explanations. This claim can now be made more explicit, even against the background of an erotetic theory of what explanations are adequate and when. Everyone should agree that biology is obliged to provide why-necessary explanations for historical events and patterns of events. The latter-day reductionist holds that such why-necessary explanations can only be provided for by adverting

to the macromolecular states, processes, events and patterns that these non-molecular historical events and patterns supervene on. Any explanation that does not do so, cannot claim to be an adequate, complete why-necessary explanation.

The reductionist does not claim that biological research or the explanations it eventuates in can dispense with functional language or adaptationism. Much of the vocabulary of molecular biology is thoroughly functional. As I have noted, the reductionist needs the theory of natural selection to make out the case for reduction. Nor is reductionism the claim that all research in biology must be 'bottom-up' instead of 'top-down' research. Far from advocating the absurd notion that molecular biology can give us all of biology, the reductionist's thesis is that we need to identify the patterns at higher levels because they are the explananda that molecular biology provides the explanantia for. What the reductionist asserts is that functional biology's explanantia are always molecular biology's explananda – that molecular biology does not merely provide 'explanatory extensions' of functional biological explanations. It deepens and completes them, when it does not supplant them.

So, why isn't everyone a reductionist? Why indeed, is antireductionism the ruling orthodoxy among philosophers of biology and even among biologists? Because, in the words of one antireductionist, reductionism's alleged 'mistake consists in the loss of understanding through immersion in detail, with concomitant failure to represent generalities that are important to ''growth and form'' [invoking D'arcy Thompson's expression]' (Kitcher, 1999, p. 206). The reductionist rejects the claim that there is a loss of biological understanding in satisfying reductionism's demands on explanation, and denies that there are real generalities to be represented or explained. In biology, there is only natural history – the product of the laws of natural selection operating on macromolecular initial conditions.

Rejecting the claim that natural selection is always at bottom genic or some other sort of macromolecular selection, another antireductionist argues that reductionism adds nothing to the predictive power of functional biology:

> *A predictive theory needs to focus on fitness differences that can occur anywhere in the biological hierarchy. Multilevel selection theory [which denies reduction of selection to genic selection] offers a precise framework for identifying these differences [at the level of populations, groups, individuals, as well as genes] . . . and for measuring their relative strengths. Selfish gene theory requires all these same distinctions. But its central concept of genes as replicators offers no help. All the hard work is left for the . . . vehicles [populations, groups, individuals] (Sober and Wilson, 1998, pp. 93–94).*

Reductionism accepts that selection obtains at higher levels, and that for predictive purposes, a focus on these levels often suffices. However, the reductionist insists that the genes, and the proteins that they produce, do, in fact, offer irreplaceable 'help'. Sometimes, indeed for a long period in the natural history of the Earth, they were the only vehicles of selection, and they are still the 'bottleneck' through which selection among other vehicles is channeled. Without them, the causal credentials, and indeed the explanatory power of predictively useful claims in functional biology, are open to challenge, and with them, explanatory force is vouched safe, while predictive power may be increased.

In their article, 'The Return of the Gene', two antireductionists, Kitcher and Sterelny (1988), argue for a thesis they call 'pluralist genic selectionism' – the thesis that there is more than one maximally adequate representation of a selective process, and that for any given selective process, this set of maximally adequate representations will sometimes include a description in terms of individual selection, at other times kin selection, sometimes group selection, or even species selection. However, they argue, every set of (equally) maximally adequate representations for any one process will always include at least one representation attributing causal efficacy to genic properties (Kitcher and Sterelny, 1988; Hull and Ruse, 1998, p. 171). They distinguish this thesis from one they call hierarchical monist selectionism: the thesis that selection can operate independently at many different levels of organization – the gene, the individual, the group, the deme, etc., and 'that for each process there is one kind of adequate representation [not many, hence the monism], but that processes are diverse in the kinds of representations they demand [hence the hierarchy]' (Hull and Ruse, 1998, p. 173)

Antireductionism requires the truth of hierarchical monist selectionism. However, reductionists can accept pluralist genic selectionism. In order to see this, consider whether the adequacy of genic selection descriptions in every selective process is an accident, or has it an explanation? One explanation that Kitcher and Sterelny explicitly reject is the claim that genic selection is 'the (really) real causal story' (Hull and Ruse, 1998, p. 171) 'the virtue of the genic point of view, on the pluralist account is not that it alone gets the causal structure right, but that it is always available' (Hull and Ruse, 1998, p. 172) However, why is it always available? What seems like the right explanation of the universal appropriateness of the genic representation is not that it is the whole of the (really) real causal story in every case of selection, but that it is an indispensable *part* of the (really) real causal story in every case of selection. The only way to deny this is to claim that explanations of selective processes which do not advert to genes

are complete, adequate and correct. In addition, this is hierarchical monist selectionism, according to which the genes add nothing – all the work is done by the vehicles of selection.

Insofar as science seeks to complete this (really) real explanation for historical events and patterns on this planet, it needs to pursue a reductionistic research program. This is, biology can nowhere remain satisfied with how-possibly ultimate explanations, it must seek why-necessary proximate explanations, and it must seek these explanations in the interaction of macromolecules.

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Notes

[1]Let us distinguish between functional biology and molecular biology. Functional biology is the study of phenomena under their functional-kind-descriptions – for example, deme, organism, organ, tissue, cell, organelle and gene. Molecular biology is the study of certain classes of organic macromolecules. As I shall show below, this distinction is not entirely satisfactory, for many of the kinds identified in molecular biology are also individuated functionally. What makes a kind functional is that its instances are the products of an evolutionary etiology. Since natural selection operates at the macromolecular level, some of its kinds will be functional too. However, the functional/molecular distinction is a convenient one which reflects widespread beliefs about a real division in the life sciences.

[2]Some antireductionists might wish to saddle reductionism with the indefensible thesis that all biology is molecular biology, that molecular biology provides not only the explanans (what does the explaining), but also uncovers all the facts to be explained (the explanantia). This is not reductionism, for it affords no role to functional biology. It is some kind of eliminativism that no reductionist has ever advocated.

[3]Early on in discussions of reduction, Kenneth Schaffner (1967) observed that reduced theories are usually less accurate and less complete in various ways than reducing theories, and therefore incompatible with them in predictions and explanations. Accordingly, following Schaffner, the requirement was explicitly added that the reduced theory needs to be 'corrected' before its derivation from the reducing theory can be effected. This raised a problem which became non-trivial in the fall-out from Thomas Kuhn's *Structure of Scientific Revolutions* (1961), and Paul Feyerabend's *Reduction, Empiricism and Laws* (1964). It became evident in these works that 'correction' sometimes resulted in an entirely new theory, whose derivation from the reducing theory showed nothing about the relation between the original pair. Feyerabend's examples were Aristotelian mechanics, Newtonian mechanics, and Relativistic mechanics, whose respective crucial terms, 'impetus' and 'inertia', 'absolute mass' and 'relativistic mass' could not be connected in the way reduction required.

No one has ever succeeded in providing the distinction that reductionism required between 'corrections' and 'replacements'. Thus, it was difficult to distinguish reduction from replacement in the crucial cases that really interested students of reduction. This was a matter of importance because of reductionism's implicit account of scientific change as increasing approximation to more fundamental truths. It was also Schaffner who coined the

term 'layer-cake reduction' to reflect the notion that synchronically less fundamental theories are to be explained by reduction to more fundamental theories – at the basement level, some unification of quantum mechanics and the general theory of relativity, above these physical and organic chemistry, then molecular biology and functional biology, and at the higher levels psychology, economics and sociology. Synchronic reduction is supposed to be explanatory because on the account of explanation associated with reduction, the Deductive–Nomological [D–N] model, explanation was logical deduction, and the explanation of laws required the deduction of laws from other laws. Synchronic reduction is mereological explanation, in which the behavior of more composite items described in reduced theories is explained by derivation from the behavior of their components by the reducing theory. Thus, reduction is a form of explanation. Diachronic reduction usually involves the succession of more general theories which reduce less general ones, by showing them to be special cases which neglect some variables, fail to measure coefficients, or set parameters at restricted values. As the history of science proceeds from the less general theory to the more general, the mechanism of progress is the reduction of theories. But if there is no way to distinguish reduction from replacement, then the incommensurability of replacing theories makes both the progressive diachronic and synchronic accounts of inter-theoretical relations impossible ideals.

More fundamentally, reductionism as a thesis about inter-theoretical explanation was undermined by the eclipse of the Deductive–Nomological model. Once philosophers of science began to doubt whether deduction from laws was sufficient or necessary for explanation, the conclusion that inter-theoretical explanation need take the form of reduction was weakened.

Finally, reductionism is closely tied to the so-called syntactic approach to theories, an approach which treats theories as axiomatic systems expressed in natural or artificial languages. Indeed, 'closely tied' may be an understatement, since deduction is a syntactic affair, and is a necessary component of reduction. Once philosophers of science began to take the semantic approach to theories seriously, the very possibility of reduction became moot. For the semantic approach treats theories as families of models, and models as implicit definitions, about which the only empirical question is whether they are applicable to phenomena. For reduction to be obtained among models semantically characterized requires an entirely different conception of reduction, and whether such a conception would capture anything of interest about inter-theoretical relations is questionable.

[4]To see why there can be no strict laws in biology, consider the form of a generalization about all *F*s, where *F* is a functional term, like gene, or

wing, or belief, or clock, or prison, or money, or subsistence farming. The generalization will take the form $(x)(Fx \rightarrow Gx)$, a law about *F*s and *G*s. *Gx* will itself be either a structural predicate or a functional one. Either it will pick out *G*s by some physical attribute common to them, or *Gx* will pick out *G*s by descriptions of one of the causes or effects that everything in the extension of *Gx* possesses. However, there is no physical feature common to all items in the extension of *Fx*: the *Fx*s represent a physically heterogeneous class since its members have been selected for their effects. So *G* cannot be a structural predicate. Of course, some structural feature may be shared by all of the members of *F*. However, it will not be a biologically interesting one. Rather, it will be a property shared with many other things – like mass, or electrical resistance, properties which have little or no explanatory role with respect to the behavior of members of the extension of *Fx*. For example, the generalization that 'all mammals are composed of confined quarks' does relate a structural property – quark confinement – to a functional one – mammality – is exceptionlessly true but is not a law of biological interest.

The existence of a functional property different from *F* that all items in the extension of the functional predicate *Fx* share must be highly improbable. If *Fx* is a functional kind, then owing to the blindness of selection to structure the members of the extension of *Fx* are physically diverse. As such, any two *Fs* have non-identical (and usually quite different) sets of effects. Without a further effect common to the *F*s, selection for effects cannot produce another selected effect; it cannot uniformly select all members of *F* for some further adaptation. Thus, there is no further function kind for all *F*s to share in common.

Whether functional or structural, there will be no predicate *Gx* that is linked in a strict law to *Fx*.

[5]See, for example, Winter, (1996).

[6]First elaborated in Rosenberg (1985, Chapter 3).

[7]Perhaps the best explanation for why there is no law here is to be found in Lange (1995) (see also, Lange, 2000). Lange, however, employs his analysis to shows why biologists treat a statement of the form 'the S is (or has) T' as a law even though it is admittedly neither purely qualitative nor counterfactual supporting.

[8]Here is an example of typical generalizations in developmental biology, taken from Wolpert (1998, p. 320):

> *Both leg and wing discs (in* Drosophila*) are divided by a compartmental boundary that separates them into anterior and posterior developmental region. In the wing disk, a second compartment*

> *boundary between the dorsal and ventral regions develops during the second larval instar. When the wings form at metamorphosis, the future ventral surface folds under the dorsal surface in the distal region to form the double-layered insect wing.*

Despite its singular tone, this is a general claim about all (normal) *Drosophila* leg and wing imaginal disks. This is a purely descriptive account of events in a temporal process recurring in all (normal) *Drosophila* larva. This is given for purposes of proximate explanation of why a double layer of cells is formed in any one imaginal disk, to simply note that this happens in them all, or that it does so in order to eventually form the wing.

[9]The implicit naming convention for many genes is that a gene is named for the phenotypic result of its deletion or malfunction. Thus, *wingless* builds wings. Note that genes are individuated functionally and evolutionarily. *Wingless* is so called because of those of its effect which were selected by the environment to provide wings. Similarly, for *distal-less*.

[10]Is there an alternative to the reductionist's why-necessarily explanation in terms of the switching on and off of a variety of genes which control the emergence and activity of cells of certain types at the eyespots? Some antireductionists seek such an alternative in explanatory generalizations that cut across the diverse macromolecular programs that realize development. For example, Kitcher (1999) identifies certain mathematical models as regularities important to 'growth and form' (consciously echoing D'arcy Thompson) in development and which suggest a multilevel process, one in which levels above the macromolecular really are explanatory. In particular Kitcher cites the work of J. D. Murray (1989).

Murray elaborated a set of simultaneous differential equations reflecting relationships between the rates of diffusion of pigments on the skin and the surface areas of the skin. By varying the ratio of skin surface to diffusion rates, Murray's equations can generate patterns of spots, stripes, and other markings in a variety of mammals. As Kitcher has pointed out, (Kitcher, 1999, p. 204), Murray's system of equations together with some assumptions about the ratio of surface area to diffusion rates of pigments imply that there are no striped animals with spotted tails – an apparently well-established observational regularity. Although Kitcher does not mention it, Murray goes on to develop another system of differential equations for the relationship between the surface and the pigment which produces eyespots on butterfly wings. What is of interest in the present debate is Murray's assessment of the explanatory power of these mathematical models – sets of differential equations, together with restrictions on the ratios among their variables:

> *Here we shall describe and analyze a possible model mechanism for wing pattern proposed by Murray (1981). As in [mammalian coat color], a major feature of the model is the crucial dependence of the pattern on the geometry and scale of the wing when the pattern is laid down. Although the diversity of wing patterns might indicate that several mechanisms are required, among other things we shall show here how seemingly different patterns can be generated by the same mechanism (Murray, 1989, pp. 450–451).*

Murray concludes:

> *The simple model proposed in this section can clearly generate some of the major pattern elements observed in lepidopteran wings. As we keep reiterating in this book, it is not sufficient to say that such a mechanism is that which necessarily occurs .... From the material discussed in detail in [another chapter of Murray's book] we could also generate such patterns by appropriately manipulating a reaction diffusion system capable of diffusion driven pattern generation. What is required at this stage, if such a model is indeed that which operates, is an estimate of parameter values and how they might be varied under controlled experimental conditions (Murray, 1989, p. 465).*
>
> *... It is most likely that several independent mechanisms are operating, possibly at different stages, to produce diverse patterns on butterfly wings ...*
>
> *... Perhaps we should turn the pattern formation question around and ask–'What patterns cannot be formed by such simple mechanisms?'.*

Murray treats his sets of simultaneous equations not as generalizations with independent explanatory power, but as parts of a how-possibly explanation which needs to be cashed in by developments which convert it into a why-necessarily explanation or supplant it with such an explanation.

In the period after Murray first produced his models, molecular biology has provided more and more of the proximate why-necessary explanations that the reductionist demands for the historical facts about butterfly eyespots.

QUESTIONS AND DISCUSSION

Marc Van Regenmortal: Could you just explain what is erotetic theory?

Alex Rosenberg: Actually, a number of people have alluded to it already here. Erotetic theories of explanation, by contrast with, for example, a

deductive-nomological model of explanation, hold that whether an explanation is adequate or not is a function of the context of inquiry, the background presuppositions and information of the interlocutor who poses the question, and what will satisfy the interlocutor's question with respect to those particular presuppositions. So that depending on whether an explanation is sought for why the butterfly has eyespots by someone with a great deal of macromolecular information or with none, the varying explanations offered by way of answer to this question will be adequate. And a completely non-reductionist explanation will be adequate for one set of background assumptions and for another set a macromolecular explanation will be required. So there is no such thing as the correct, complete, and adequate explanation in biology. Explanatory adequacy is always relative to explanation and she might want to add more to what I've said.

Marc Van Regenmortel: Would you give us the etymology of erotetic?

Alex Rosenberg: Erotetic meaning from 'questioning'. Erotetic logic is the logic of questions. It's 'erotetic'. But erotetic logic is the logic of questions and erotetic models of explanation, advanced most prominently in the last 40 years or so by Bas Van Fraassen and to a lesser extent, Peter Achinstein. These models of explanation seek to solve the problems that were raised for the covering-law model, to dissolve the counter-examples by directing out attention to these contextual issues that arise in what the questioner is interested in. Perhaps the most famous example that is introduced to establish the relevance of such explanations is the square-peg–round-hole arguments of Putnam's. Hilary Putman argued, about thirty years ago, that the quantum electrodynamic explanation of why a square peg will not go into a round hole is less explanatory than simply pointing that it is square, and that its edges will protrude against the circumference of the round hole. Jim?

Jim Griesemer: I'm impressed, like you are, with Nijhout's butterfly work. But I'm wondering whether, particularly about the last step in the argument, his story supports your argument, because at the very last bit you talked about the evolutionary pathway from *Drosophila* genes to butterfly genes and argued that this is a proximal explanation.

Alex Rosenberg: I didn't deny that it was adaptive. I said it was proximate.

Jim Griesemer: Clearly. I'm with you there. But in order to make an ultimate explanation out of this, you appeal to the cladistic relationship of the taxa. And the assumptions that go into constructing the cladograms strike me as a 'how-possibly' explanation.

Alex Rosenberg: Because they are in principle impossible to complete?

Jim Griesemer: Because you have to make assumptions about the process of evolution to construct a genealogy out of cladistic data to argue that these

are sister taxa. So that kind of claim that goes into the reconstruction of the proximate pathway is dependent on those assumptions.

Alex Rosenberg: If it were the case that filling out the details of the proximate adaptational explanation in which the work is done by natural selection operating at the level of the gene or the macromolecule, if it were the case the filling out the details ultimately committed you to ultimate explanations where the causal chain could not be specified, and where you in principle could simply wave your hand and say 'this is the adaptive outcomer' without there being a causal mechanism connecting the environmental circumstances and the particular macromolecules interacting, then I'd think you'd be right. Then, at some point or other, biological explanation would inevitably be action-at-a-distance explanation.

Jim Griesemer: That is Sober's argument for parsimony that there are irreducible assumptions, process assumptions, that you have to put in to construct a cladogram in the first place. Unless he's wrong about that, I don't see that it supports your argument.

Alex Rosenberg: I wouldn't have thought that that was so bizarre even. I would have thought rather, as he argues in the 1984 paper, the argument is that there are irreplaceable generalisations at the level of function which we would miss if we focused exclusively on the interaction of macromolecules. That while we could possibly trace out the entire history behind the cladogram that we provide, in doing so we would still miss important generalisations about functional biology. That these generalisations not only cannot be explained by macromodular ones, but that in fact they explain macromodular ones. A nice example, a sort of classic example by antireductionism, is the explanation of, say, Mendelian laws of assortment by appeal to cell physiology, by appeal to meiosis, and the subsequent claim that no macromodular account of meiosis could improve on meiosis as the explanation for, say, the law of independent assortment. I think that's where the issue lies. But I grant you that if you're correct, that the program that I've attributed to the reductionist molecular biologists is going to fail, because at some point or other there will be ultimate explanations.

Claude Debru: I'm very much interested in the distinction you introduced in this discussion between how possible and necessarily. These ideas of possibility and necessity have obviously deep philosophical roots and the idea of possibility is extremely difficult anyway. My question would be the following one – Would you agree that when you ask the question of how possible, how possibly, you have to get an idea of all the possibilities which are involved before giving the answer? Then, do you think biologists have really the idea of all possibilities which are run at a certain level of biological evolution?

Alex Rosenberg: The answer is that for the ultimate explanation to work, you do not require the identification of all the alternative possibilities and the specification of why this among all the alternative possibilities was actually realised. The beauty, the attractiveness of ultimate explanations for biology and part of the claim for the difference between ultimate biological explanation and causal physical explanation resets on this very fact, that biological explanations are accepted as scenarios that could have led from initial condition to some consequent conditions. And my claim, the claim of the reductionist, is that ultimately, or in the end, the methodology of explaining why the particular route through a certain set of such possibilities was taken as opposed to an alternative route. And the reductionist goes on to say that the mistake of those who criticise ultimate explanation for either the left or the right, so to speak, for the Lewontin–Gould side, or the opposite pole, that the mistake made in claiming that such explanations are untestable or otherwise inadequate, is simply the mistake of treating an incomplete causal explanation for an unscientific one.

John Dupré: The metaphysics was not the focus of your talk.

Alex Rosenberg: Actually it was in a part of the paper that I didn't read.

John Dupré: Well, there's a very small part of the paper at the beginning that you did read. And right at the beginning you made a statement that is clearly false, and I'm sure you know is false, and it seems to me . . .

Alex Rosenberg: That antireductionists are physicalists.

John Dupré: Well it depends what you mean by 'physicalists'. What you said was that reductionists and antireductionists agree that biological events are nothing but physical, chemical events. Now I can suppose you might have just meant something like – biological events are composed of nothing but physical or chemical parts. Just as I might agree that Michelangelo's 'David' is composed of nothing but marble. But if you were to tell me that I believed it was nothing but a piece of marble I would disagree, just as I disagree with the statement you made, therefore at least refuting your claim as stated. And it seems to me it's very tendentious because to say that we all agree that biological events are nothing but physical and chemical events is to shift a kind of focus onto the antireductionist, to give the suggestion that we'd all wish we could be reductionists because given that we're just dealing with physical things (of course, we'd like to be unique), we actually don't believe in this metaphysical reductionism and therefore don't feel motivated to hope for or expect reductionist explanations. Of course, it might be nice to have one science for the whole world, but we don't believe it, not simply because we can't do it but because we don't think the metaphysics fits with it.

Alex Rosenberg: I plead guilty to this oversimplification of the intellectual landscape. And I plead guilty because with the exception of the present company, perhaps, it seems to me that in the philosophy of biology the consensus view is physicalist antireductionism. We're all physicalists now, but as a methodology reductionism won't work. Now, evidently you, among perhaps some others, reject physicalism.

John Dupré: Wait. But you are grabbing the term 'physicalism' for something that implies 'reductionism in principle' or something like that. I don't think that's by any means a consensus.

Alex Rosenberg: No. I think I'm using the word 'physicalism' to mean the claim that 'all the facts are physical facts'. That all the biological facts are specified by the physical facts. I'm using it simply to mean the supervenience of the biological and the physical, that if two worlds are physically identical, they'll be biologically identical. Now I think that may be problematic, but I do think that it's a fair assumption to foist on the current consensus in the philosophy of biology. If you deny physicalism, if you're some sort of a metaphysical pluralist, it's easy to be an antireductionist. In fact, antireductionism will follow from metaphysical pluralism. If there are kinds that are not physical, and these kinds have a causal role in biology, then it's obvious that the best biological theory will have to provide an account of these kinds and will not be physical and will therefore be a macromolecular theory. The intellectually interesting character of antireductionist physicalism is that it combines two of these that look very difficult to combine, physicalism and antireductionism. And it apparently does this so successfully that it is now the default consensus position in the philosophy of biology.

Steven Rose: I don't think that anyone would deny that genes have to be an indispensable part of any program of understanding biological processes. You've made a fundamental assumption in your argument, that somehow you transfer a 'how-possibly' into a 'how-necessary' approach by attributing causal and necessary power to strings of DNA. In fact, the relationship between a string of DNA nucleotides and a particular phenotype is multiple and not 'one-for-one'. Then the causal necessity which you're arguing falls, and you're left only with a 'how-possibly', that is, the genes provide one of the constraints on how an organism develops. It doesn't imply the only constraint.

Alex Rosenberg: Well, I guess I disagree, and the specification of my disagreement is that a macromolecular account is simply an account in terms of genes, it's an account in terms of both the genes and the environmental circumstances in which they operate the entire pathway – 'I use the term' where the pathway is to be described in biochemical terms. Now if there

are factors that are left out of the macromolecular account, whether genetic or otherwise, then there are factors that are non-physical. And if 'as I suspect' ultimately you're committed to an account of considerations, then there certainly is a fundamental disagreement in the way John and I were discussing, a metaphysical disagreement.

Steven Rose: I'll just say one thing. We have a problem in understanding and agreeing on what you mean by 'physical' in this particular context. But if, in fact, you insist on genes and environment, you also insist on development and therefore you insist upon history, and therefore you've reintroduced the problem which you've pretended to dissolve.

Alex Rosenberg: I hope not.

Chapter 8

Varieties of Reductionism: Derivation and Gene Selection

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As two recent collections (Bock and Goode, 1998; Gallagher and Appenseller, 1999) and a major book (Sarkar, 1998) indicate, reductionism in science is both a timely and a multifaceted topic. What is reductionism? What sorts of science count as reductionistic? What contrast is intended? Too often, 'reduction' simply means 'bad' or 'good', depending on which side of this divide one inhabits. The opponents of reduction tend to pick examples of especially bad science and term them 'reductionistic', when reductionists would reject these examples as well, while anti-reductionists view any example of good science as being automatically anti-reductionist, while reductionists would claim it as their own. In an effort to bring a bit of clarity to these issues, in this paper I set out six varieties of reductionism and expand on two of them (for an alternative classification, see Sarkar (1998)). The two sorts of reductionism that I discuss at some length are the reduction of Mendelian genetics to molecular biology and gene reductionism in evolutionary biology.

Most of these varieties of reductionism depend on scientific phenomena and scientific theories being organized in a hierarchy of levels. Just as the Periodic Table is the standard representation of the physical elements, the 'wedding-cake model' is the standard model of scientific disciplines (see Figure 8.1). According to this model, the lowest level is physics and chemistry. At one time the issue was whether or not chemistry could be reduced to physics. Instead of reduction, these two areas of science seem to have merged to form a single level. It is the lowest level because everything that exists has physical and chemical properties. Of these phenomena, a

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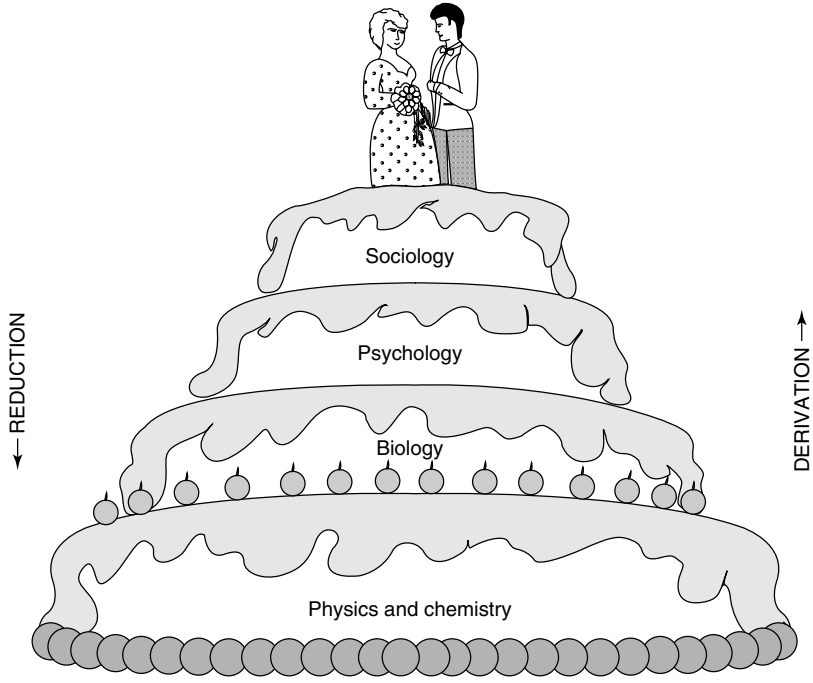

FIG. 8.1. Representation of the 'wedding-cake' model

vanishingly small percentage exhibit the properties of living creatures, the subject matter of biology. Among living creatures, some have psyches, the subject matter of psychology. Some of these creatures in turn form social groups. They are the subject matter of sociology.

In this context, reductionism is the view that entities and their properties (including relations) at the higher levels can be reduced to entities and their properties (including relations) at lower levels. The emphasis on relations is appropriate because anti-reductionist arguments tend to turn on the difficulty of handling complex relations. Handling numerous one-place predicates is hard enough. Handling numerous two-place predicates seems to be even more difficult. Sometimes these reductions take place within a single level, e.g. the reduction of thermodynamics to statistical mechanics. However, the most exciting reductions occur between one level and another, e.g. the reduction of psychological theories to neurophysiology.

According to Rose (1998, p. 10), this traditional wedding-cake hierarchy of levels is one source of the bias toward reductionism that permeates our understanding of science. It may well permeate our society and thus seem natural, but if this model is looked at somewhat more closely, it begins

to lose some of its attractiveness. For example, a strong correspondence exists between the levels recognized in this model and the organization of universities into academic departments. Has the structure of the world in which we live determined the organization of academic departments or has this academic structure been read into the world? In this connection, as someone who has spent most of his academic life in departments of philosophy, I need to register one complaint. The humanities are entirely omitted from this picture. We are not higher, lower or to the side. We are not even in the picture, as if we are not worth being reduced.

A second complaint concerns the assumption that these levels are strictly inclusive, as if levels are never skipped in reduction. Typically, only organisms that are reasonably smart can form social groups. Social organisms such as lions form prides, and lions clearly exhibit highly developed psychological properties. They may not be as smart as most people, but they are smart enough. However, what about ants, termites and honey bees? They form highly organized social groups even though they have only the most rudimentary nervous systems. One response is to side-step the issue by terming their social systems 'eusocial', but terminology to one side, naked mole rats are very bright mammals that exhibit a form of sociality that resembles that of their tiny brethren. Why is an organization social when exhibited by mammals but eusocial when exhibited by insects? In any case, it seems that at times sociality skips a level. It goes from the sociological to the biological level without stopping at the psychological level.

Computers provide another example of skipping a level in the traditional ordering of the sciences. Lots of people are fonder of computers than I am. They even claim that computers can think. Once again, people are reticent to admit that computers do anything that could possibly count as having psychological characteristics. Why? Because it means that the biological level is being skipped. Although computers might be able to reason, they do not come close to exhibiting any biological characteristics, e.g. no genes, selfish or otherwise, no sex drive, and no weakness for chocolate cake.

A common warning about intellectual pursuits is to watch out for that first step. Often it is a 'doozy'. With respect to reduction, the first step is the traditional hierarchy of levels running from sociology, through psychology and biology, to physics and chemistry. As firmly entrenched as it is, perhaps it needs to be re-examined and possibly replaced. If so, then the issue of reductionism becomes significantly recast.

Four varieties of reduction

One form of reductionism in science concerns advice about what to study and how. For example, a reductionist might recommend that we investigate

everything at the lowest level that is technologically feasible. This bit of advice comes in a weak and a strong form. The weak form urges us not to neglect the lowest levels. Sure, upper levels of organization are worth studying but don't forget the lower levels. The strong form is that the only level worth investigating is the lowest technologically feasible level. All else is a waste of time. For example, at the turn of the century, geneticists studied patterns of inheritance of such morphological traits as the color of seed coats in peas. At that time, Mendelian geneticists had no choice. They could not study genes as such because the only access that they had to genes was via patterns of hereditary transmission. Should geneticists have waited to study inheritance until they had access to the molecular level? I don't think so, nor does anyone else.

However, now we do have fairly direct access to genes, their molecular structure and their functioning. What now? Should we continue to run Mendelian breeding experiments or go directly to the molecular level? To be sure, so reductionists admit, Mendelian geneticists provided us with rough maps of the genomes of several hundred species of plants, animals and microbes, but their techniques are so laborious, time-consuming and limited that, increasingly, geneticists are turning to molecular genetics. Working out the genetics of sperm whales by traditional Mendelian studies is currently not feasible, nor is it ever likely to be. Molecular techniques can be used on any species, and these studies are becoming increasingly routine and inexpensive. In such situations, reductionists would urge everyone to go right to the molecular level.

A stronger reductionist position is that once explanations have been provided at a lower level of analysis, all higher-level explanations become otiose. We don't need them. They add nothing to our understanding. No one need learn Mendelian genetics nowadays. It is of historical interest only. Whether or not this claim is justified, flocks of biology majors in both undergraduate and graduate training are signing up for courses as if this reductionist claim were justified. In many cases, old-fashioned courses are not even being offered any more. If it does not come out of a Waring blender, it is not biology. At Northwestern University, biology majors do not confront anything that one might term 'biology' until their second year. Their first year is devoted entirely to chemistry and mathematics. Then, in their sophomore year they start a three-quarter sequence that is primarily molecular biology. Finally, in the last week of their second year they confront evolutionary theory. At Northwestern, at least, the Creationists have all but won (see Wilson (1994) for a discussion of what he terms 'The Molecular Wars' and Hagen's response (1999)).

The final two forms of reductionism are very different from all the preceding – and equally important. Reductionists urge that most, possibly all, of our grant money be spent on solving problems at the lowest levels possible. If all sorts of traditional biology departments in our universities must be done away with because of such funding decisions, so be it. Northwestern shut down its Department of Ecology and Evolutionary Biology a dozen or so years ago. Who needs comparative anatomy, embryology or evolutionary biology? These disciplines should go the way of tidology. I think that it is this latter position that really generates the emotional content of disputes over reduction. Money is a powerful motivator.

Finally, reductionism can refer to an attitude toward science, an attitude that I term the 'hup–two–three' school. Reductionists think that we can actually make progress in science. No problem is, in principle, impossible to solve. Perhaps we cannot solve it now, it looks too complicated, but if we only work harder, we can solve it. Anti-reductionists disagree. Some phenomena are simply too complicated to understand from a reductionistic perspective or by using reductionist methods. If these phenomena are to be understood at all, they will have to be understood from a more holistic perspective. In this connection, anti-reductionists view reductionists as philistines. Reductionists simply do not understand the scope, depth and complexity of the phenomena that they are investigating.

The appeal to complexity sounds suspiciously like the Creationists' God of the Gaps. According to Creationists such as Behe (1996), scientists will never explain certain phenomena, such as the human eye, bacteria flagella and phosphorous pumps without reference to a 'higher intelligence', an intelligence that sounds suspiciously like the Christian God of 'waste not, want not'. Holists also make an appeal to the inherent complexity of certain phenomena but, of course, without reference to God. So they claim, we will never be able to explain X, Y or Z from a purely reductionist perspective. As a quick glance at the history of science amply attests, this line of argumentation is a no-win strategy. 'Scientists will never explain X reductionistically'. X gets explained reductionistically. 'Well, scientists will never explain Y reductionistically'. Y gets explained reductionistically, and so on.

Charles Singer, in the first two editions of his *A History of Biology* (1931, 1950) claimed that no molecule could possibly do all the things that genes are supposed to do. In the third edition published in 1959, this claim was dropped. What had happened in the interim? Philistines who did not have a sufficiently sophisticated view of natural phenomena have done the impossible – once again. Philistines do not always succeed, most fail, but it seems that *only* Philistines ever succeed. Only Philistines are

incapable of appreciating how ineluctable certain natural phenomena are.[1] In the discussions following the papers delivered at the Phillipe Laudat conference, the complexity card was played over and over again. Thus far, I have briefly characterized four views that can be justifiably termed 'reductionist'. I now turn to two more examples and discuss them in greater detail – theory reduction and gene selectionism.

Theory reduction in genetics

Ernst Nagel (1961) set out the classic philosophical analysis of theory reduction. For the next two generations, philosophers of science took it as the standard explication that had to be attacked, defended or modified.[2] According to Nagel, higher-level theories are reduced to lower-level theories by deriving the basic principles of the higher level from those of the lower-level theories. Reduction runs in the opposite direction from inference (see Figure 8.1). This is the sense of 'reduction' that philosophers have worked on through the years. Just as thermodynamics can be reduced to statistical mechanics by deriving the basic principles of thermodynamics from the basic principles of statistical mechanics, Mendelian genetics can be reduced to molecular biology by deriving the basic principles of Mendelian genetics from those of molecular biology.

One virtue of the literature on reduction in genetics is that the biology has mattered. At times in the early years of the controversy, it threatened to degenerate into playing with empirically empty formalism, as if reduction is nothing more than an exercise in formal logic,[3] but these authors have recognized that reduction involves semantic as well as syntactic considerations. The conclusion of all this literature is that Mendelian genetics as it was formulated at the time, not to mention now, cannot be derived from molecular biology. At the level of Mendelian genetics, something like

[1] That I am using terms such as 'Philistine' and 'sophisticated' in ways to provoke the reader can be seen by the fact that on this usage Einstein was an unsophisticated Philistine. He was so unsophisticated that he was able to solve problems that generations of the best minds in the world had failed to solve. He retained this optimism for the rest of his life as he tried to provide a unified field theory, a quest that his more sophisticated contemporaries found foolish.

[2] See Schaffner (1967, 1974, 1993), Hull (1972, 1976, 1981), Kitcher (1984), Rosenberg (1985, 1997) and Fox Keller (1999).

[3] One bit of evidence that the participants in the controversy over reduction in genetics were not interested in formalism as such is the reaction of these philosophers to the work of Balzer and Dawe (1986). Their paper has disappeared without leaving a ripple. Later workers do not refute it but ignore it. Even though Schaffner is the most formalistically inclined of the philosophers who engaged in this dispute, even he gives Balzer and Dawe short shrift (Schaffner, 1993, p. 426). As Sarkar (1998, p. 29) remarks, 'One is left to wonder what all this formalism was developed in aid of'.

process laws can be found. At the level of molecular biology, however, all we find is mechanisms (Machamer *et al*., 2000). The trouble is that the relation between these two areas of investigation is 'many–many'. Any Mendelian regularity can be and is produced by a variety of molecular mechanisms, and any molecular mechanism can produce a variety of Mendelian regularities. Hence, reduction in the sense of theory reduction is impossible because the basic principles of Mendelian genetics in any of its formulations cannot be derived from molecular biology. Such derivations can be pulled off only if both theories are massively reworked with the sole purpose of producing such derivations. Thus far no biologists have seen the point of such revisions.[4]

Rosenberg (1997, p. 445) puts what he terms the consensus view among philosophers of biology today even more strongly than I have:

> *. . . there are in fact no laws of Mendelian genetics to be reduced to laws of molecular biology, and no distinctive laws in molecular biology to reduce laws of Mendelian genetics, that the kind terms of the two theories cannot be linked in general statements of manageable length that would systematically connect the two bodies of theory.*

Even so, as Rosenberg makes perfectly clear in this volume, he is hardly an anti-reductionist. It just so happens that Nagel-type analyses of reduction won't do. Without extensive 'finagling', Mendelian genetics cannot be derived from molecular biology. This conclusion should come as no surprise. The paradigm of theory reduction – the reduction of thermodynamics to statistical mechanics – cannot be brought off either. The general conclusion seems to be that theory reduction of the sort set out by philosophers may be in principle possible, but it is so difficult to carry out in practice and adds so little to our understanding that it is hardly worth doing (Allchin, 1999).

Gene selectionism

The final example of reduction that I discuss is also the most extreme – gene selectionism in evolutionary biology. All of the senses of reduction that I

[4] For an example of parallel claims about multiple realizability in psychology and its consequences, see Bechtel and Mundale (1999). As Van Regenmortel (1999) has remarked with respect to structure–function relations:

> *. . . a single chemical structure or protein fold can have a multiplicity of activities or functions, while a single activity can be generated by a variety of structures.*

have treated thus far have turned on the wedding-cake organization of science. In the context of evolutionary biology, a second system of levels can be discerned – levels of organization running most simply from genes and cells to organisms, and possibly entire species.[5] According to this organizational hierarchy, species are composed of organisms and nothing but organisms, organisms are composed of cells and nothing but cells, cells are composed of all sorts of molecular structures and nothing else, while genes are composed of molecules and nothing but molecules. One might go on to argue that molecules are composed of atoms and nothing but atoms, while atoms are composed of sub-atomic particles and nothing else.

This story is a bit too simple. An organism is nothing but its component parts and the relations among them. In addition, everything that is part of an organism must be included – all parts including fluids, colloids and the like. However, as Shostak asks in this volume, how about an organism's parasites? If you are going to reduce an organism to its parts, do you include parasites? Initially, the answer seems to be obviously, no, but many of the constituent parts of organisms began as parasites and gradually became part of the organism, e.g. chloroplasts. This distinction can be made at the organismic level – and it matters. Making the distinction between an organism and its parasites (or former parasites) and the rest of the organism at the molecular level is much more difficult. After all, molecules are molecules.

However, as problematic as relations between the levels in the organizational hierarchy may be, they can be ignored with respect to gene reductionism. A much more serious issue is at stake. Although Dawkins wrote *The Selfish Gene* (1976) as a popular work, it has generated a whole series of controversies among professional biologists. I think that one explanation for this unusual state of affairs is that Dawkins threatened to show that evolutionary biologists, like the proverbial emperor, wore no clothes. To be sure, evolutionary biologists commonly began each of their books or papers with reference to organisms and comments about how important organisms are, but they then immediately launched into discussions of gene frequencies and genetic fitness – and nothing else. As numerous evolutionary biologists have repeated through the years, evolution is nothing but changes in gene frequencies (or more accurately allele frequencies). Dawkins decided to take evolutionary biologists at their word. If evolution is nothing but changes in gene frequencies, then he would rework evolutionary theory so that it made references to nothing but changes in gene frequencies. No matter the causes at higher levels of organization, no matter how fascinating these causes are, eventually everything comes down to changes in gene frequencies.

[5] Sarkar (1998) distinguishes between abstract hierarchies and spatial hierarchies.

As might be expected, Dawkins has been characterized as an arch-reductionist, and he is. Reductionism, as it is usually presented, requires that you understand entities and processes at higher levels of organization in terms of nothing but their parts and interrelations – all their parts. Reduction as Dawkins construes it is so extreme because he proposes to ignore the vast majority of the parts of organisms and concentrate solely on genes. At times, opponents of genetic determinism seem to think that genes play no role whatsoever in living processes, as if we could do without genes and everything else would proceed as usual. Defenders of genetic determinism seem to go to the other extreme. Genes are all that matter. This is reductionism of the most extreme sort.

How could Dawkins have come up with such an extreme and counter-intuitive position? The source can be found in his analysis of selection. Dawkins (1976) did not introduce the notion of replicators, but he certainly popularized it. Some entities exhibit structures of the sort that deserves to be termed 'information'. Replication is the transmission of this information from one replicator to the next, copies producing copies. In biological evolution, so Dawkins argues, these replicators are genes. He also introduced a second process (environmental interaction) and corresponding entities (vehicles). As Dawkins sees it, the relation between replicators and vehicles is development. Replicators produce the vehicles in which they reside. Vehicles are clumsy robots, totally governed by the replicators that produce them.

Dawkins introduces the notion of a vehicle only to do away with it. First, he argues that we do not need vehicles as distinct entities. We can include environmental interaction by replacing organisms with phenotypic characters, and these phenotypes are then extended beyond the traditional boundaries of organisms. The web that a spider weaves is as much a part of its phenotype as are its spinnerets. This notion of phenotype can be extended to even include behavior. The species-typical song that a bird sings is also part of its extended phenotype. However, at bottom, whatever role phenotypic characters play in selection, the results must be recorded in the genotype. As fascinating as all the organic adaptations that result from selection may be, evolutionary biologists can ignore these idiosyncrasies when they are formulating evolutionary theory as a general theory. All you need are genes.

I think that Dawkins is right to subdivide selection into two subprocesses – replication and environmental interaction – but I think that the relation between these two processes needs to be made even more general than Dawkins succeeds in making them, and he is mistaken in demoting environmental interaction so severely. Development is one way in which

replication and environmental interaction can take place, but it is not the only way. All that is necessary is that environmental interaction causes replication to be differential, regardless of the nature of this cause. In addition, if Dawkins is serious about excluding environmental interaction from his analysis of selection, then selection cannot be distinguished from drift.

A long-standing controversy in evolutionary biology is the level or levels at which selection takes place. One advantage of subdividing selection into two subprocesses is that it allows this controversy to be treated more perspicuously. Replication is concentrated at the level of genetic material. It can occur at higher levels of organization only with considerable difficulty. Environmental interaction, to the contrary, can occur at all levels of the organizational hierarchy, including genes and possibly entire species. DNA includes information in its structure, but it also has phenotypic traits of its own, e.g. its helical structure. Species also exhibit characteristics of their own. For example, they can have highly convoluted peripheries. If a major mechanism for speciation turns on the presence of peripheral isolates, such species are likely to speciate much more frequently because of their convoluted peripheries. All that is needed in addition then to make species units of environmental interaction is that these convoluted peripheries be heritable. Hence, according to this analysis, there are units of replication (primarily genes) and units of environmental interaction (an extensive array of units), but there are no units of selection.

One of the peculiar features of the set of interrelated controversies between Dawkins, John Maynard Smith and Dan Dennett, on the one hand, and Steve Gould, Richard Lewontin and Steven Rose, on the other hand, concerns the role of adaptive scenarios in evolutionary biology. Dawkins and company claim that everything that is going on at higher levels of organization can be ignored. Everything of interest can be translated into changes in gene frequencies, and nothing but changes in gene frequencies. Yet, they fill their books with all sorts of fascinating adaptationist stories. How could sonar echolocation ever develop in bats? How could the cycling trait ever become established in certain tribes in Western Africa? Why all these higher-level stories if everything is reducible to genes? Why not skip right to the genetic level and ignore all these 'just-so' stories? One answer is that this aspect of evolution is far and away the most interesting part of evolutionary biology. Adaptations are what encouraged biologists to develop evolutionary theory in the first place. Another answer is that, for most of these scenarios, we do not know what is going on at the genetic level, at least not yet.

Gould and company, to the contrary, emphasize the importance of higher levels of organization for our understanding of the evolutionary process,

especially at the level of whole organisms. However, they also insist that in most cases adaptationist scenarios are largely nothing but unscientific 'just-so' stories. Something is desperately wrong. Dawkins says that all that really matters are genes and fills his books with stories about higher levels of organization, while Gould complains that Dawkins concentrates too narrowly on genes but then disparages attempts at explaining organismic adaptations.

Conclusion

Both reductionists and anti-reductionists present in-principle arguments for their favored position on the continuum between these two extremes, but few scientists find themselves firmly lodged at either extreme. The dispute is primarily over emphasis and for that reason even more difficult to evaluate. As far as I am concerned, I think that we should investigate phenomena at the levels that are currently feasible – *all* the levels. That means for a while that certain levels will not be investigated, but advances at one level (and not always a lower level) will sometimes open up another level for investigation, so that through time, the thrust of scientific investigation will wander from level to level in the organizational hierarchy. Nor is it the case that the lower-level explanations are always more useful than higher-level explanations. It all depends on what you want to do. Do you want to become the sort of person that other people find lovable or do you want to take a pill that makes you feel loved, regardless?

However, I also think that scientists working at the upper levels need to adopt a bit more of the 'hup–two–three' attitude of the reductionists: natural phenomena at the upper levels of organization can be explained. Scientists should be only selectively sophisticated. One of the great dangers in science is becoming so sophisticated that you can shoot down any new idea before anyone can develop it. Read the New York Review of Books if you must, but then come back down to do more plebian science. Too much sophistication can ruin otherwise excellent scientists.

My response to reductionists and anti-reductionists alike is 'If it is doable, then *do* it'. We have had enough hand waving on both sides. If Mendelian genetics is reducible to molecular biology, then do it – deduce the basic principles of Mendelian genetics from molecular premises. Stop gesturing toward possible reductions Actual accomplishments are always more convincing than in-principle arguments. If anti-reductionist holists, in their turn, want to be taken seriously, they best produce holist accomplishments of the magnitude being churned out by reductionists. If holistic explanations are so superior to those being provided by reductionists, then present such holist

explanations. Both Levins and Lewontin (1985) as well as Rose (1998) have acknowledged this challenge with respect to their holist, Marxist views. My plea to those scientists who are in power at any one time is not to kill off all those working at different levels from your own. Down the road you may need them.

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QUESTIONS AND DISCUSSION

Terrance Brown: Could we put back up the wedding cake? Because I think that, fundamentally it is a poor image of the way the sciences are related. I understand the idea of levels but it misrepresents the relations among the sciences. If we think of this from the point of view of how any knowledge is possible, what you see is that there is a mathematisation of nature. And so we have then to explain where mathematics comes from. Physics and chemistry reduce in a certain sense to mathematics, and mathematics, through logic, then reduces to sociology and psychology. So we need a bundt-cake model and not a wedding cake.

David Hull: My purpose for presenting the wedding-cake model is to indicate how inadequate it is. In my talk, I mentioned that the humanities are being left out of the wedding-cake model. Certainly mathematics is also being left out. I would like to see a model that is so structured that it includes more than just the empirical sciences, narrowly defined. But you are right. Mathematics is crucial to science, and it is omitted from the wedding cake model.

In addition, the wedding-cake model is metaphysical, not epistemological. G. G. Simpson argued that really biology and psychology are more fundamental than physics, but he meant epistemologically fundamental. According to Simpson, you must learn a variety of things before you can learn physics.

Finally, the organisation of the wedding cake suspiciously reflects the organisation of universities. Have we read the organisations of our universities into the world? Or possibly we have read the organisation of the world into the organisation of our universities. In any case, if we are going to talk sensibly about reduction, we have to rework the wedding cake picture. It is seriously misleading.

Steve Rose: I agree entirely about the reworking of the picture. The issue is whether (A) the levels are ontological versus epistemological, or (B) whether they are simply relating to different discourses about the universe. And one really has to rethink the easy way in which you use the word 'levels' in that context. But I just wanted to come back to your plea at the end for all of us to get together and to talk to one another, because I'm absolutely with you in all of your presentation. All I wanted to add is that despite continual pleas on my part at least, Richard Dawkins consistently refuses to discuss these issues with me and I suspect with other people. And

that's true also now, at least in the UK, of quite a considerable number of the new band of evolutionary psychologists who won't discuss those issues directly with us. It's a great pity, because I think it would help.

David Hull: The story that you tell from your own experience with socio-biology and later evolutionary psychology is commonplace in science. Science does not always supply a warm, supportive environmental for scientists. I wrote a very long book dealing with how the rise of cladistic analysis would kill it.

What causes this animosity among scientists? First and foremost, science is really hard. Most scientists put in the hours that used to be reserved for Victorian coal miners. One explanation for all these long hours of work is that scientists are fascinated by their subject matter. The time flies by. But they have other motivations as well. One of them is to get that 'son-of-a-bitch'! Someone responds to your work and totally misconstrues it. That will fire up your engines. You will work until the small hours of the morning to get that 'son-of-a-bitch'.

I'm an adaptationist, possibly too much of an adaptationist, but if something happens in science over and over again and the net result is scientific progress, then just possibly this behaviour, as unpleasant as it may be to those involved, may be doing some good. Objectivity through subjectivity may sound as mistaken as bombs for peace, but possibly not.

Stan Shostak: I came here to learn, and I learned from you that Dennett is not the darling of the philosophers. I'm glad of that. However, there is a larger audience, and there are other philosophers, none of whom seem to be represented here. I refer to my philosophers of becoming because of the absent dimension from everything that is being said – although you mentioned relationships, you haven't mentioned time, duration. So I thought I would use this moment to give you Ansell-mechanistic and thermodynamical conceptions and calculations of the energy of the universe. To use the language of the contemporary science of complexity, the eternal return is a thought of conditions of possibility for truly creative and complex involuted mapping of evolution. Now following. You don't seem to grasp that this is new territory that we want to enter and perhaps you could help us – but you shouldn't be trying to stop us.

David Hull: Let's see. Scientists lead philosophers, and Shostak is unhappy that we are not following closely enough and quickly enough. Who does the leading? Sometimes philosophers, sometimes scientists, but in general both groups are fairly independent of each other. What meetings like this one are for is to encourage philosophers and scientists to talk to each other. I'm not sure that in this context it is all that profitable to tell the other side that you are doing all the leading. Each side may think that they

are doing the leading, and let us just let it go at that. Some things are best left unsaid.

Armando Aranda: I'm asking you a question because I'm a molecular biologist, and I would like to know whether you have a theory about why fairly shallow tales such as those written by Dennett and Dawkins are so popular among molecular biologists – why they have such an important appeal. I'm really glad to find out that they are not particularly popular among philosophers, but nevertheless they are bestsellers.

David Hull: Why are the more popular versions of evolutionary theory so popular with the molecular biologists and their students? I've never thought of that question before. I suspect the reason is that, nowadays, biology majors are taught molecular biology almost exclusively. They are not taught much in the way of evolutionary biology and ecology. None too surprisingly, popular versions of these theories will attract them. Because they haven't been taught the hard stuff, they get the fun stuff and think that this is all there is. Evolutionary biologists do not like these popular versions because they know that lots of technical stuff is being blurred over. Molecular biologists aren't aware of these problems and find the popular stories really interesting.

Robert Williams: At your bottom level in that diagram you have physics and chemistry. The assumption that physics and chemistry is just molecular is a danger and therefore the fact that you've just identified physics and chemistry by molecular and not by the funny things that are in thermodynamics, which are co-operative events and therefore emergent from the molecules but not easily explicable in terms of the molecules, leaves you in a sort of world where you wonder what that bottom line means. And another thing about that bottom line – if you take a man like Penrose, who is a close colleague of mine, he would say that that line, 'physics and chemistry', is not yet fully identified. And because you can't fully identify it, if you go right to the very top and come to consciousness, when you discuss consciousness, he would say there is something missing in physics and chemistry and so it's not possible yet to explain in any way consciousness in terms of the bottom line. And what he would argue would be – that there is a different form of 'somewhere' in that world which is the real nature of consciousness. Now I'm not arguing that whatever you call it, you think that nothing is missing, or you think you know what you're talking about when you say everything is molecular.

David Hull: Related to the last issue that Williams raises, I must admit that I know no physics. I have no idea what is really going on down there at the lowest levels of organisation. I have to get my understanding from tertiary sources and hope they are right. But no one person can know everything.

I think that Williams' warning is good: there is lots still to be done at the higher levels of organisation but don't assume that the lowest level is complete. There are likely to be lots of changes at this lowest level, and these changes might end up totally reorganising the wedding-cake model.

Robert Williams: Right.

Robert Williams: We don't understand superconductivity of, say, methaloxides. Nobody understands what it's about. It has something to do with a co-operation phenomenon. Nobody knows what it is. Are there other things in the world that don't reduce downwards because we don't know what they might do? But they might not, and we don't know what they are. We have to be a bit careful, but we think the bottom is known. If we don't know the bottom, then that diagram means nothing because it could be there are things up there that don't belong down low. That's what Penrose would say.

Claude Debru: I would like to give arguments along the same lines as Professor Williams. Regarding statistical mechanics and thermodynamics, I was struck once by a remark which was made by a French mathematician, Rene Thom, who is rather well known, who said to me that the Boltzmann distribution, which is something very fundamental in these relationships between statistical mechanics and thermodynamics, is something mathematically not entirely rigorous. So perhaps the grounds are not entirely safe.

David Hull: An autobiographical aside. Ernst Nagal said that thermodynamics could be reduced to statistical mechanics, and Ken Schaffner published a paper which said that this is what is going on in genetics: classical Mendelian genetics is being reduced to molecular biology. So I said to myself 'Well I'm going to do for genetics what Nagel did for thermodynamics'. I worked, and I worked, and I worked and I could not derive anything from anything.

Alex Rosenberg: But Nagel wasn't able to derive anything either. The problems have not been solved.

David Hull: That's the kicker. When I was failing to derive the basic principles of Mendelian genetics from molecular biology, I thought that there was something wrong with me. I'm simply not smart enough to do it. Then later I discovered that Nagel had not been able to pull of his reduction in physics either, at least not without introducing a lot of finagling. The current opinion among philosophers is that Nagel-style reductions cannot be carried out in either instance without a significant amount of finagling. I don't know if 'finagle' is in your vocabulary, but it's a really good word.

Alex Rosenberg: Schaffner used the word 'incorrectly'.

Ken Schaffner: And that's right.

Alex Rosenberg: Schaffner pointed out that the problem is whether the correction produces a replacement or a reduction.

Robert Williams: You can only prove statistical mechanics if you can count. If you can't count the things, you can't do it. So you can't count the bits, and then it's only in principle I can do something if you can't do it.

David Hull: I get really tired of 'in-principle' tasks. I want to say 'okay, if it is in-principle possible to do it, then do it'.

Robert Williams: That's right. If it's in principle, do it. But . . .

Alex Rosenberg: But you know it has been done. The 'in-principle' has been converted in practice in certain areas, for example, our understanding of haemoglobin, of sickle-cells, of heterozygous superiority in this case, in fact all the way down to the . . . .

Ken Schaffner: I think we're getting out of hand.

Marc Van Regenmortel: Another question. David, you said we shouldn't be too unkind to reductionists, because they solve problems. That's fine, but surely we are sometimes unkind to them because we think they aren't explaining anything, or, you might say, they don't provide understanding. So isn't that still a good reason for being unhappy with reductionists. They might solve problems all right, but you can solve problems without actually understanding the system.

David Hull: And there is no beating success. Reduction has been very successful in certain areas.

Chapter 9

The Gene: Between Holism and Generalism

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I do not intend to pose the question of reductionism in an abstract way – is it possible to reduce complex systems such as organisms to their molecular components? – but in a more concrete, pragmatic way. First, I will briefly describe the forms of reductionism currently used by biologists. Then I will look at what recent studies have revealed about the nature of the molecular components present in living beings and the way they are organized. The main macromolecules that we need to consider are proteins. Nucleic acids (RNA or DNA) are only there to allow the synthesis of proteins at the appropriate time and place in the organism. I will describe the new rules of molecular organization which have led to the rejection of the simplistic reductionist vision held by some molecular biologists. I am convinced that the value of a reductionist approach in biology cannot be appreciated independently of the knowledge produced by this method. Finally, I will briefly discuss what the new techniques of post-genomics could bring to the reductionist approach used by today's biologists.

The existence of different 'levels' of molecular description

A study of the molecular descriptions provided by geneticists and molecular biologists reveals at least three different levels. The first can be illustrated by the schematic models of signal-transduction pathways. In such models, the precise shape of the different proteins, their atomic composition, is of no importance. Sometimes, only the name of the protein is given. What is important is the place of these proteins in the pathways, how they receive upstream signals and transfer them to downstream molecular components.

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The second level of molecular description is shown by the structure of RNA polymerase II, which was recently published by Roger Kornberg's group (Cramer *et al*., 2000). This enzyme plays a fundamental role in gene expression and describing its structure was a real 'tour-de force', as well as a major breakthrough. What this structure reveals is that RNA polymerase II grasps DNA as a pair of 'jaws' – this is the authors' term. There is also a pore in the protein complex which allows the entry of substrates for polymerization and the exit of the transcripts, as well as a 'clamp', which accounts for the great stability of the transcription complex. RNA polymerase is thus described as a molecular machine, whose active parts – what we might call mechanisms, because of their rigidity – do not correspond to atoms but to modules formed of thousands of atoms, of a complex assembly of α-helices and β-sheets.

Finally, the third level of molecular description can be illustrated by the complex formed between a transcription factor and the DNA molecule. In such a complex, the atoms involved in the interaction, the hydrogen bonds formed between the amino acids and the bases are shown, because this description, is necessary to explain the specificity of molecular recognition.

Through these examples, I wanted to illustrate the fact that the expression 'molecular description' can have at least three different meanings. These three levels of representation are not independent. For instance, the atoms and bonds that make up the 'jaws' of RNA polymerase II can be described, as well as RNA polymerase II can be integrated, with transcription factors and DNA, in the general picture of the preinitiation transcription complex. However, in order to answer a specific question, one particular level of description is always more significant, better adapted than others, with a greater explanatory value.

The end of the 'molecule-function'

Let us turn now to a different, but related question, i.e. the way that molecular components participate in the formation of complex structures and functions in the organisms. This question is not new. The relation between genes and characters was at the heart of the classical genetics, and was replaced by a dual relation in molecular biology: a precise link between gene and protein, a more problematic one between proteins and characters. In the early years of molecular biology, the relation between proteins and phenotypes remained largely abstract. It was only with the development of genetic engineering at the beginning of the 1980s that the situation became clearer. A range of studies performed over a twenty-year period provided more than a mere accumulation of results: they revealed the principles of organization of the macromolecular components in living cells. Some of

these principles had been previously outlined through the patient work of geneticists, while others were totally new and their discovery constituted a major surprise. I will describe these general principles, dissect their complexity and illustrate them by examples, mainly from developmental biology, which is probably one of the research fields that has contributed the most to this new vision of gene action (Duboule and Wilkins, 1998).

These principles of macromolecular organization replaced the naive vision of some of the early molecular biologists, who tried to reduce each complex structure and function of organisms directly to one (or a limited number of) proteins or other macromolecules. The best example of this simplistic reductionist approach was the efforts aiming in the sixties at discovering the 'molecules of memory' – molecules that allegedly encoded the memories or behaviors. Many articles and books[1] were devoted to this search, without any success.

Each time that the molecular components involved in a specific complex structure or function were characterized, those who thought it would be possible to summarize the complex process in one simple molecule, or explain this process merely in terms of the properties of these individual molecules, were severely disappointed. 'Molecular-functions' do not exist. For instance, the proteins involved in the internal clocks that control circadian rhythm are not in themselves rhythmic. The rhythm is generated at a higher level of organization by regulatory loops in which these proteins are active components (Dunlap, 1999). Similarly, the properties of the organizer – the structure in the early embryo which controls the early steps of embryogenesis – cannot be reduced to a single molecule as was initially thought (Cho *et al*., 1991), but is in fact a complex network of transcription factors and signalling molecules, which we still do not fully understand. These two examples show the limits of reductionism as revealed in recent studies. Complex processes cannot be explained by individual macromolecules, although the properties of these macromolecules are important to explain such processes. They also show that this simplistic reductionism has been replaced by the rules that control the assembly of the individual macromolecular components.

New principles of molecular organization

The importance of pathways and networks was revealed by the study of the mechanisms of action of hormones, as well as by numerous studies on the mechanisms of oncogenesis and development. Biology articles and books

[1] See, for instance, Gurowitz (1969), where various macromolecules, such as DNA, RNA and proteins, were successively considered as being the possible repository of memory.

are now full of diagrams showing these pathways and networks. Their complexity is astounding, not only because of the number of molecular components and the complex relations between them, but also because these pathways and networks are never the same from one cell to another, or from one tissue to another.

Not only do the macromolecular components which are the direct products of the genes participate in the formation of complex pathways and networks, they can also assemble to form macromolecular complexes and 'micromachines'. Some of these micromachines are now well known, such as ATPase, some parts of which turn like a rotor in the mitochondrial membrane to generate the energy of the cell, or the micromachines responsible for transcription or DNA replication. Some others are less known, but play critical roles, such as the complex that forms in the cell membrane and can induce the cell to commit 'suicide'.

The fact that molecular components are organized in pathways, networks and complexes used for different 'tasks' in the organism explains, at least partly, the existence of pleiotropy as shown in particular by gene inactivation studies.

Pleiotropy was not a new concept for geneticists. Morgan's group had shown that the mutation of a single gene can affect different unit-characters[2]. However, the significance we attach to this observation is different from that understood by Morgan. In Monroe Strickberger's 1968 book *Genetics* (Strickberger, 1968) – very favorably received at the time – the concept of pleiotropy is dealt with relatively briefly. One, illustrated example, is given: the multiple consequences of the substitution of the amino acid at position 6 of the globin chain which occurs in sickle cell anemia.

The first conclusion from this example is that, although it was known from the work of the geneticists of the 'classical' period, pleiotropy did not have the pre-eminent place it has since acquired. Furthermore, at the time, 'pleiotropy' meant that a given gene variation can have several effects on different characters, whereas today biologists use the word when a gene – and its protein product – play different, successive, roles in the development and functioning of an organism, at different places and different times.

The best examples of pleiotropy have been provided by developmental biologists. Two examples illustrate the pleiotropic action of developmental genes. *Sonic hedgehog* participates in the formation of the different cell types that form the neural tube, in limb development and in somitogenesis, a process by which mesodermic cells aggregate to form bones and muscles.

[2] Discussed in Allen (1978, p. 270).

Not only is this gene essential at different locations in the organism (Chiang *et al*., 1996), but it can have different effects: it controls the process of differentiation by which a cell adopts its final adult phenotype and it regulates (activates) cell division (Wechsler and Scott, 1999). *Notch* is a family of genes that is well known to developmental biologists, coding for receptors present in the cell membrane, whereas *Sonic hedgehog* codes for a secreted protein. *Notch* proteins are involved in the control of differentiation of adjacent cells – a process called lateral inhibition – as well as, at later stages of development, in the control of the formation of axons and dendrites in the nervous cells (Sestan *et al*., 1999).

This pleiotropic action of developmental genes is easily explained by the fact that the proteins encoded by these genes are components of pathways and networks, which have been repeatedly used during evolution for the construction of organisms.

The word 'pleiotropy' is ambiguous. At the molecular level, the action of these genes and their products is not pleiotropic: they always do the same thing. For instance, the *Notch* receptor interacts with its ligand: this interaction activates the downstream components of the signalling pathway. Pleiotropy reveals itself only at a higher level of integration, depending on the other molecular components present in the cell at a specific moment and which interact directly or indirectly with this pathway.

This functional pleiotropy should be distinguished from the possibility that a single gene – and its corresponding protein – may be formed of different functional modules or bear different functional sites – the so-called gene-sharing process that gives rise to 'moonlighting' proteins (Jeffery, 1999). This underlines the principle of economy frequently used in evolution. It can also contribute to the formation of networks if the two activities of the protein are functionally related. However, it is more a curiosity than a principle of organization of the organic molecular components.

Finally, there is another source of pleiotropy in gene action: proteins which, by their very action themselves, are pleiotropic. For instance, chaperones are proteins which interact with unfolded or partially folded proteins to protect them and assist them in folding. By the very nature of their functions, chaperones have a pleiotropic effect. Susan Lindquist recently suggested that one of these chaperones, HSP90, which interacts with many components of the signal-transduction pathways involved in development, might act as an evolutionary 'capacitor', buffering the mutations occurring in these essential molecular components and revealing them in conditions of stress (Rutherford and Lindquist, 1998). A second example was recently provided by the analysis of new mutations affecting the *hedgehog* signalling pathway in *Drosophila* (Bellaiche *et al*., 1998). Such mutations affect a

family of proteins called heparan sulfate proteoglycans that participate in the formation of the extra-cellular matrix (Perrimon and Bernfield, 2000). Cells need these proteins to trap signalling molecules, as well as to transfer them from one cell to another. Finally, proteins and enzymes involved in the control of chromatin structure, in DNA repair, in transcription or RNA splicing and in translation, also have a pleiotropic action.

As well as the organization of molecular components in pathways, networks and micromachines and their pleiotropic action, a third principle of organization which constitutes an additional limit to reductionism is the existence of redundancy. Molecular components are redundant if they participate in similar processes and if the inactivation of one such component has no effect, because its function can be substituted by another. The frequent occurrence of redundancy is correlated with repeated gene duplication during evolution. The existence of redundancy was not anticipated by classical geneticists. Redundancy is used with respect to organisms following the meaning given this word by Claude Shannon in information theory (Tautz, 1992): buffer mistakes in the use of genetic information, in particular during the formation of complex organisms, to canalize this formation as Waddington put it (Wilkins, 1997). As with pleiotropy, 'redundancy' is not a simple concept and can have different meanings. For instance, redundancy is generally only partial: the separate inactivation of two genes has a limited effect, whereas their simultaneous inactivation has dramatic consequences. However, the significance of partial redundancy is not simple: two genes can be partially redundant because they have similar, but not identical, functions or simply because they are not expressed in the same tissues and at the same time, despite having identical functions. New approaches, such as 'knock-in' and gene swapping, make it possible to substitute one gene for another without changing its environment and its regulation, to discriminate between these two forms of redundancy. These methods have already been applied to a number of 'redundant' developmental genes, such as *engrailed* (Hanks *et al*., 1995), the *otx* genes (Suda *et al*., 1999) or the paralogous genes of the homeotic complexes (Greer *et al*., 2000). Initial results show that both situations can occur. However, the regulation of redundant genes seems to have diverged more than their functions, which often remained identical.[3]

The principles of organization of elementary molecular components of living beings – the formation of networks and machines, pleiotropy and redundancy – are not independent but are closely interlinked. Pleiotropy results from the involvement of the same networks, or at least of the same functional modules (Hartwell *et al*., 1999) of these networks, in different functional processes. Redundancy makes the functioning of these networks stable.

[3] See, for instance, Li and Noll (1994).

This kind of organization precludes the simplistic reductionism described earlier which attributes a given function to a given molecule. I would like to give an example which seems to me paradigmatic of this impossibility to reduce a complex process to a single macromolecule. Higher organic forms can discriminate between thousands of different odors. The cellular mechanisms underlying olfaction remained fundamentally mysterious until the beginning of the 1990s when odour receptor molecules were described. Interestingly, in mammals at least, the recognition and perception of a given odorant molecule do not result from the activation of a unique receptor, but from the activation of a specific combination of receptors, each recognizing a different motif present in the odorant molecule (Malnic *et al*., 1999). It is impossible to reduce a given odor to a given macromolecular receptor.

This impossibility of reducing a complex process to single macromolecules explains the co-existence of different levels of explanation in biologists' molecular descriptions. This does not mean that the nature of the molecular components is of no importance, nor that the complex functions originate only from the rules of assembly of the different macromolecular components. The organization of living beings is based both on the precise nature of the molecular components and on the way that these molecular components are assembled.

The promises of post-genomic approaches

The principles of organization of molecular components described here mean that it is impossible to predict the functioning of these networks and macromolecular complexes from knowledge of the elementary components.

One way of overcoming the present limitation is to try to outline some of the second-order principles which might be involved in the construction of these networks and complexes. In a recent article, Norbert Perrimon and Andrew McMahon reviewed the mechanisms of control of signal-transduction pathways by feedback inhibition (Perrimon and McMahon, 1999). Their conclusion was rather disappointing: it appeared that these pathways can be controlled at different levels and by different mechanisms. Instead of revealing second-order principles of organization, their study emphasized once again the diversity of solutions that have been invented during evolution.

Another way of overcoming these limits is to 'stop thinking' and to observe only the global functioning of living cells, the concomitant activity of their thousands of molecular components. These global approaches have been made possible by the completion of the various genome sequencing

programs. With these new technologies, which can be described as post-genomics, it is possible, for instance, to measure the level of all mRNAs (at the moment, it is difficult to measure protein levels, but it should soon become possible), or to look at the protein–protein interactions that take place in these cells (Uetz *et al.*, 2000). For the advocates of these new technologies, the goal is not to enrich our previous knowledge but to apply a new vision to the organization and functioning of living beings. This is well illustrated by the following quotation from Patrick Brown and David Botstein:

> *The goal is to discover things we never knew or expected, and to see relationships and connections among the elements, whether previously suspected or not. It follows that this process is not driven by hypothesis and should be as model-independent as possible. We should use the unprecedented experimental opportunities that the genome sequences provide to take a fresh, comprehensive and open-minded look at every question in biology. If we succeed, we can expect that many of the new models that emerge will defy conventional wisdom'. (Brown and Botstein, 1999).*

Is it reasonable to hope that new principles of organization will emerge by themselves from the mere observation of living beings? What might be the nature of these new principles? These studies have not yet revealed any new principle of organization, but rather have complemented our existing knowledge. Perhaps such a hope is hollow: we may never be able to avoid dealing with the organizational diversity and complexity that characterize the macromolecular components that are at the basis of organic structures and functions.

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QUESTIONS AND DISCUSSION

Albert Tauber: Let us not complain here about reductionism. Rather let's do reductive studies with more sophistication, taking into account of context and complexity, which is what you have done. The philosophical issue seems to me to remain the same, if one, in fact, is going to discuss molecular biology, and stay at the level that you have. So without an alternative philosophical position, I don't see this as a criticism of reduction *per se*.

Michel Morange: In any case, I didn't want to discuss directly the value of reductionism. What I wanted to do is to note that when molecular biologists describe a phenomenon as molecular this expression can have different meanings. In one way you only look at elementary components. In another way, you look at the molecular approaches. It's not the simple reductionist molecular biology which is very often described, for instance, as looking at

genes and only genes. In fact you describe different levels of complexity in these molecular descriptions.

Albert Tauber: I would like to comment on your final slide referring to the new approach in molecular biology in relation to these high-throughput techniques, which are now being used. It may be the fact that there are new principles coming out from these techniques so far. But certainly they are helping to get rid of previous dominant hypotheses. And one simple example is the situation with the oncogene field. Now that it is possible to analyse the expression of 10 000 genes in a single-shot experiment, it became clear that in many tumours, many of these famous oncogenes have nothing to do with the tumour. They are not even expressed at all. So that's helping perhaps to open up the fields of research, to move away from hypotheses that were for some time dominant. But about the point whether or not you are criticising reductionism. The results and the observations that you presented in your talk certainly are casting serious doubts on some classical reductionist approaches to biology. For example, the problem of redundancy. It is not compatible with neo-Darwinism, and it is very striking that actually redundancy has been found in such very simple organisms as yeast. One of the great lessons of the yeast genome project is the fact that the yeast genome is highly redundant, and it's difficult to understand from a neo-Darwinian point of view how it is possible that such is the case. Nevertheless it is there.

Alex Rosenberg: Why redundancy?

Armando Aranda: The idea is that in a very simple system like yeast, if you have two genes doing the same function, and then one of the genes should be subject to continuous mutation by drift, because it can't be 'seen' by natural selection. And the amazing thing is that it is not the case that such genes, which are redundant, are subject to random mutation. That's one of the big issues now.

Alex Rosenberg: Are you talking about multiple copies, or genes that differ in sequence but have the same function?

Armando Aranda: Different sequences, which . . . .

Alex Rosenberg: No, natural selection is blind to structure, and it's inevitable that you're going to have different sequences which produce the same protein.

Armando Aranda: The striking fact is that you can actually knock out those genes. And not single genes, but whole sets of genes, which apparently are involved in independent metabolic pathways. And nevertheless, the fitness of the yeast strain suffers nothing at all.

Ken Schaffner: Could we get back to . . .

Michel Morange: Yeast is a simple system.

Armando Aranda: No, of course, I agree with you. Of course.

Michel Morange: I'm not enough of a specialist to discuss a point whether redundancy is opposed to neo-Darwinism or not. What I can say is that, in fact, redundancy was not foreseen by any neo-Darwinist. It's true that models incorporating redundancy in the neo-Darwinism models appeared very rapidly, two or three years after the real discovery of redundancy. But clearly it was not foreseen. So, I don't know whether it's incompatible, but at least its place was not evident in the classical model of neo-Darwinism. Concerning just the two other points very rapidly. What you told us about oncogenes, I totally agree with you. I might do the same as I did, for instance, for the organiser on the oncogenes. The simple models were one, two or three oncogenes explaining all forms of cancer, and the situation now where you have plenty of genes with variation involved. Exactly the same, I think, evolution of thoughts as the ones I described. And concerning the non-reductionist of these people who are in favour of the post-genomic technology. I think it's an argument also to sell post-genomic study. You see, first molecular biologist were reductionists. Now, we are not reductionists, we are looking at global things, so they were reductionists, but we are not. But I am not convinced that in fact there was a dramatic change in the way to see things.

Steven Rose: I wish you were right that molecular biologists working on behavioural functions actually no longer believed in single molecules, despite your illustration from the 1960s. The doyen of memory research in the US, Eric Kandel, for example, has patented and set up a company to exploit a single molecule, the cyclic-AMP response binding element molecule crucial for the transaction between short- and long-term memory. The argument that single molecules are crucial and can be developed and exploited by biotechnology is absolutely still there and alive and well. So I think you're very right to continue to defend networks against them.

Michel Morange: Cyclic AMP is involved in glycogen metabolism – it is not really specific of memory.

Chapter 10

Genes versus Molecules: How To, and How Not To, Be a Reductionist

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Introduction

The molecular revolution in biology, beginning in the late 1940s and early 1950s, must surely be regarded as one of the last century's most significant scientific developments. It transformed not only the practice, but the very conceptual framework of much of biology at the organismic and lower levels of organization to such an extent that it is sometimes difficult even to find continuity within the same research schools. Central to this transformation was the molecular characterization of the gene. Before the molecular era, what is now called 'classical' genetics consisted of models of transmission as well as models of expression. The models of transmission were generally highly successful: simple duplication for haploid genomes, Mendel's rules as modified by linkage requirements for diploids, generalizations for polyploids, and special constructions for haplodiploid and other odd genetic structures. The models of expression were largely vacuous: genes somehow produced traits, with luck singly, otherwise acting in concert (physiological epistasis), and sometimes not very reliably (variable degrees of expressivity and penetrance). The many failures of the classical genetic account of expression and, concomitantly, of organismic development are well known and need no repetition here; their significance will be assessed in the next section.

The critical point, here, is that, within the theories in which it was embedded, the classical gene was an abstract entity. Its transmission properties were captured by rules such as Mendel's rules, essentially probabilistic

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rules asserting the statistical independence of the transmission of alleles from different sources during reproduction. Its expression properties were supposed to be captured in the rules connecting genotype to phenotype. The chemical nature of the gene was irrelevant to both these sets of rules. Indeed, until well into the 1940s it was widely believed that genes were in the protein parts of chromosomes. Even those who were committed to finding and exploring the physical basis of heredity – most notably, the Morgan school – admitted that classical genetics required no commitment to the physical nature of the gene.[1] As late as the 1950s, Lederberg and his collaborators interpreted data from bacterial conjugation crosses to produce a branched linkage map which, as they explicitly noted, should not be interpreted as a branched chromosome (Lederberg *et al*., 1951, p. 417). Classical genetics was a formal science about an abstract entity, the classical gene. Each gene came in different versions or alleles, allelic specificity was inferred from phenotypic differences. Genes, in this sense, were 'diagnostic' entities inferred indirectly from phenotypic differences.

All that changed with the double helix. Genes were now concrete entities, identified with segments of DNA. What mattered was not the double-helical shape of the molecule but the sequence of bases, and the complementarity between them on the two DNA strands.[2] Instead of a conformational account of behavior and specificity, which had become the dominant mode of molecular explanation of biological behavior thanks to Pauling's pioneering work, gene specificity was determined by sequence identification. By 1958, this view had been incorporated into an informational account of biological behavior, at least at the molecular level.[3] Of the two central theoretical innovations of early molecular biology, one was about genes – the operon model of gene regulation; the other, however, was about proteins – the allostery model of hemoglobin function. Nevertheless, in the late 1960s and 1970s, molecular genetics became the ascendant sub-field within molecular biology and, as eukaryotic genetics began to yield puzzles and surprises, a continued source of excitement.[4]

It should come as no surprise that, once the gene was physically characterized, the 'molecular gene' came to be routinely conflated with the 'classical gene'. For molecular biologists, 'gene' usually refers to bits of DNA no matter whether the context is classical or molecular. Molecular biology is an immensely successful enterprise. Beyond genetics, it has

[1] See Morgan *et al*. (1925). This point has been extensively discussed by Sarkar (1998, Chapter 5).

[2] This point has been emphasized by Lederberg (1993).

[3] See Crick (1958). That information was a new theory of specificity was recognized by Lederberg as early as 1956 (Lederberg, 1956).

[4] Unfortunately, a systematic history of these developments still remains to be written.

revolutionized biological sub-disciplines from cytology to immunology, it has significantly permeated evolutionary studies, and it is now beginning to give a successful even, if as yet only rudimentary, mechanistic account of development that has remained elusive ever since Roux first propounded his *Entwickslungsmechanik* program in the 1890s. The trouble is that, thanks to the conflation mentioned earlier, the success of molecular genetics has been interpreted to have shown the success of classical genetics. For transmission, this is undeniably true although many details remain to be worked out; for expression, this is equally false. Perhaps the most significant conceptual confusion that has resulted from this conflation is that the gene, when conceived of as a bit of DNA, need not even be something that makes any phenotypic difference at the organismic level. In the program of deciphering what, if anything, a bit of DNA does, sometimes called 'reverse genetics', the gene is a 'constructive' rather than a diagnostic entity. It is at least arguable that it is only because of the potential for reverse genetics that talk of genes remains heuristically useful in molecular biology and cannot be entirely replaced by talk of DNA. Beyond conceptual issues, this conflation has had significant negative consequences for biology; it has been part of the rhetoric that was used to initiate the Human Genome Project (HGP).[5] More importantly it has led to the popularity of facile claims of genetic etiology for complex human behavioral traits; this obviously has significant socio-political implications which, however, remain beyond the scope of this present contribution.

The purpose of this paper is to argue against a conflation of molecular biology (even molecular genetics) with classical genetics. In philosophical jargon – which will be discarded after this paragraph – the epistemological program of classical genetics is *genetic reductionism*, the explanation of phenogenesis (the production of phenotypes) on the *basis of (inferred or diagnosed) classical genes*.[6] In contrast, the epistemological program of molecular biology (including molecular genetics) is physical reductionism, the explanation of all biological phenomena on the basis of the *physical properties of their constituent parts* at the level of molecules and macromolecules. By 'reduction' is meant an explanation of phenomena in one domain from the principles of a presumably more fundamental domain. Both genetic and physical reductionism assume the existence of a hierarchical model of the systems of interest in which lower levels of the hierarchy are presumed to be progressively more fundamental than upper ones. For genetic reductionism, this is an abstract hierarchy: at the bottom lie alleles obeying laws of transmission, then come loci, linkage groups and genotypes

[5] See Sarkar (2001) for a discussion of the role of reductionism in the HGP.

[6] For details of the positions sketched in this paragraph, see Sarkar (1998).

and, finally, the phenotypes which have to be explained. For physical reductionism, the hierarchy is given by the physical structure of the organism. The take-home messages of this paper are (i) the facile genetic reductionism inherited from the heyday of classical genetics is vacuous if the aim is to understand phenogenesis (rather than only hereditary transmission of traits), and (ii) the physical reductionism of molecular biology continues to be a fecund research program of tremendous epistemological power and interest. However, it, too, must be treated with some caution since several recalcitrant problems remain.[7]

Hegemonic geneticism

Mendel chose to study traits with modes of inheritance simple enough for algebraic characterization.[8] Only one locus was implicated in the etiology of a trait, there was complete dominance at each locus, only two alleles, and no linkage. After the recovery of Mendel's work around 1900, each of these assumptions was demonstrated to be violable within the first three years.[9] Nevertheless, departures from Mendelism were interpreted as deviations from the presumed resilient basic model, particularly in the UK. Why this strategy was adopted with very little explicit methodological discussion will require socio-historical investigation of a sort that is yet to be seriously attempted.[10] The routine complexity of the relationship between genotype and phenotype (a distinction explicitly articulated by Johannsen (1909)) remained unappreciated.

The diagnostic analysis of conventional Mendelism found its most fertile home in the United States in the work of the Morgan school. While segregation analysis (that is, the analysis of pedigrees to determine whether the pattern of inheritance of a trait could be subsumed under Mendelian expectations) have been a part of Mendelian genetics from the very beginning – in the human case, Bateson used it to infer a genetic etiology for congenital cataract and brachydactyly in 1906 (Bateson, 1906) – the first main invention of the Morgan school was linkage analysis. Starting shortly after 1910, the Morgan school used failures of Mendel's second rule (independent

[7] See the last paragraph of this chapter.

[8] This is not a historical paper; modern terminology is intentionally being used.

[9] See Carlson (1966) for a history; unless explicitly stated otherwise, all historical material in this section is from this source.

[10] It is not as if the Mendelians were unaware of this move that they made. Their opponents, the biometricians (particularly Pearson) objected vehemently but were ignored – see Provine (1971) for a history. In the German context Sapp (1987) provides some relevant historical detail, although his main focus is on non-genetic inheritance rather than alternative modes of non-Mendelian genetic inheritance.

assortment of alleles at different loci) to place loci in linear order; by 1925, 400 loci had been placed in four disjoint linear structures. Critical to the invention of linkage analysis was Morgan's 1910 interpretation of linkage as representing physical contiguity of loci on chromosomes (Morgan, 1910). The chromosome model, as the physical basis for Mendelism, was always the central heuristic of the Morgan school. Moreover, at least for Muller, the physical nature of the gene was the biological problem of central interest.[11] Nevertheless, the Morgan school was well aware that the results of linkage analysis could be interpreted purely formally. Even after associating almost 400 loci with chromosomes, they observed:

> *Were there no information as to the relation between the visible chromosomes and the linkage group it would still be possible to deal with the situation exactly in the same way by treating the linkage groups as a series of points held together in definite relations to each other. We might then speak of such groups as genetic [as opposed to physical] chromosomes (Morgan* et al *., 1925, p. 88).*

Lederberg's construction of a branched chromosome map on the basis of linkage analysis was mentioned in the last section. As late as the 1950s, Delbrück continued to hope that the physical order of loci on chromosomes would contradict their order as determined by linkage analysis: this was supposed to show the limitation of reductionist explanation in biology.[12]

While the use of linkage analysis to map loci on to chromosomes may be the most scientifically important – and uncontroversial – use of such analysis, the other traditional application of linkage analysis has been its use to posit a genetic etiology for traits. This is genetic reductionism in its purest form: if there is a statistical linkage (in the genetic sense) between the inheritance pattern of a trait and the inheritance of a known locus, the trait is supposed to have, at the very least, a partial genetic etiology. If there is a well-defined simple relationship between alleles at a single locus and the trait, such an inference is unproblematic.

The customary use of linkage analysis is far less straightforward: it is the preferred strategy of the genetic reductionist to posit a genetic etiology for 'complex' traits, sometimes called 'polygenic' traits, such as human behavioral traits. The adjectives used to describe these traits – 'complex' suggesting that 'simple' means 'genetic', and 'polygenic' suggesting that the only

[11] See Carlson (1971) on this point.

[12] See Fischer and Lipscomb (1988); Sarkar (1989) reconstructs the history of Delbrück's idiosyncratic anti-reductionism and the influence on him of Bohr's hope for the discovery of 'complementarity' in biology.

etiological alternatives available are single genes or several – already indicate a prior commitment to genes as the source of traits. That phenogenesis will not so easily succumb to genetic reduction is clearly indicated by the history of such attempts. Restricting attention to human behavioral traits, linkage analysis has been used to claim a genetic etiology for, among other traits, alcoholism, autism, bipolar affective disorder, and schizophrenia (see Sarkar, 1998, p. 2). Initial positive reports have been greeted with much fanfare and publicity. In *every* single case, later reports indicated a decrease and, usually, a loss of linkage. Negative reports have so far never received the same publicity as the positive ones. To the extent that incorrect public perceptions harmfully influence the medical choices made by individuals, genetic reductionism has become a public health menace.

One example will suffice to indicate the general nature of the problem with linkage analysis. In some families of the Amish community in Pennsylvania (USA), bipolar affective disorder (manic depression) appears to be inherited. In 1987, a linkage was reported between this trait and the H-*ras* locus on the short arm of chromosome 11 (Egeland *et al*., 1987). Bipolar affective disorder was thus supposed to be explained on the basis of genes (alleles) at this locus. However, studies of other pedigrees failed to confirm this result (Baron *et al*., 1990, 1993). Finally, additional information on the original pedigree, when two previously unaffected individuals succumbed to the disease, undermined the statistical basis for the original assertion of linkage (Kelsoe *et al*., 1989). The negative result generated little publicity compared to the fanfare surrounding the original positive report.[13]

Unless one is a committed genetic reductionist, these negative results are not unexpected. An organism with its complement of traits is a product of its complex history-dependent developmental processes in which it uses internal resources (genes and other inherited units), along with external resources, to produce its phenotypes. Trivially, no organism would exist or have the form it has, without its genes. Equally trivially, no organism would exist or have the form it has, without its particular environmental history. What genetic reductionism assumes is that genes *alone* bear the epistemological weight in explanations of phenogenesis. That this is unlikely except in a tiny minority of cases has been obvious since almost the earliest days of genetics.

As early as 1909, Woltereck, while studying pure lines of morphologically distinct strains of *Daphnia* and *Hyalodaphnia*, showed that continuous traits (such as helmet size) varied between pure lines and were affected by

[13] See Sarkar (1998) for more detail and other examples.

a spectrum of environmental parameters (Woltereck, 1909).[14] Woltereck introduced the term '*Reaktionsnorm*' to capture these relationships; later the 'norm of reaction' came to be used to describe the curve showing a single genotype's phenotypic response to an environmental parameter. A constant norm of reaction showed uniform genetic etiology across varying environments. The separation of distinct genetic and environmental components of the etiology of a trait required parallel norms of reaction for all of the genotypes in a population. The sensitivity of the norm of reaction to gene–environment interactions was noted as early as 1933 by Hogben who also observed that, even in experimental populations of *Drosophila*, selected and maintained for generic uniformity (becoming what are now called 'model organisms'), norms of reaction were not parallel (see Hogben, 1933). In the West, the norm of reaction was generally ignored as classical genetics focused on phenotypes with constant norms; these were phenotypes which were easiest to fit into genetic expectations. However, the norm of reaction came to be viewed as the unit of inheritance in the Soviet Union as geneticists there – no doubt, at least partially because of the Soviet states' ideological bias towards environmental rather than genetic determinism – struggled for an interpretation of genetics less rigid than the conventional Mendelism of the West. (The concept of the norm of reaction was eventually repatriated to the West by Dobzhansky in the 1930s (see, e.g. Dobzhansky, 1937).)

Meanwhile, instead of addressing the variability embedded in non-constant norms of reaction, genetics in the West came to endorse a reticulation of its basic conceptual structure to maintain the primacy of the gene (see Sarkar, 1999, and Laubichler and Sarkar, 2002). The experimental work initially came from the Soviet Union but its interpretation within the constraints of conventional classical genetics was due to the German neuroanatomist, Vogt (see Vogt, 1926). In the Soviet Union, Romashoff and the Timoféeff-Ressovskys studied different mutations of *Drosophila funebris* (Romashoff, 1925; Timoféeff-Ressovsky and Timoféeff-Ressovsky, 1926). Romashoff found that homozygous mutants sometimes exhibited the mutant phenotype to different degrees. The Timoféeff-Ressovskys even found that a pure-line homozygous for a mutation sometimes bred untrue, and that the fraction of deviants appeared to be fixed *for each pure line*. Vogt ignored the relevance of the background pure line and interpreted these results by positing two new properties of genes (alleles) beyond the traditional (and sometimes problematic) properties such as dominance – (variable) degrees

[14] The history of the norm or reaction has been reconstructed by Sarkar (1999) – historical details in the rest of this paragraph are from this source.

of *expressivity* and *penetrance*. The former is supposed to be the degree of manifestation of a gene (note how the gene is the sole repository of agency), while the latter is the probability of any manifestation at all of a gene.

By now, expressivity and penetrance have become part of the standard repertoire of genetics, particularly medical genetics. Those who would maintain the primacy of genetic etiology in the face of phenotypic complexity have recourse to variable expressivity and incomplete penetrance to maintain the primacy of the gene. Yet few scientific concepts are less well-founded. The degree of expressivity is often impossible to distinguish from the degree of dominance. Without a background pure line – ethically, if not technologically, difficult to create for *Homo sapiens* – there is no empirical reason to expect that two different instances of the same gene have the same probability of being manifested as a trait (because of having the same penetrance). Experimentally measured penetrances are no more than empirical frequencies masquerading as theoretical propensities. It is hard to escape the conclusion that the role played by 'penetrance' and 'expressivity' in contemporary genetics, particularly human behavioral genetics, is ideological: to maintain a genetic etiology in the face of recalcitrant detail. Penetrance and expressivity rescue genetic agency in the face of equivocal, even absent, data. If there is a putative gene for a trait, but the presence of the trait is nevertheless capricious in the presence of the gene, there is still a gene *for* that trait, but the gene has *variable expressivity*. If the trait does not deign to manifest itself at all, there is still a gene *for* the trait: it is just that the gene is *incompletely penetrant*.

In recent years, the repertoire of diagnostic genetic techniques has been extended from traditional segregation and linkage analyses to include new techniques such as quantitative trait locus (QTL) mapping, allelic association studies and the allele-sharing method (see, e.g. Lander and Schork, 1994). These have undoubtedly increased the degree of diagnostic resolution possible but the interpretative problems noted in this section remain unresolved.[15]

The molecular vision of life

When the molecular revolution in biology began, segregation and linkage analysis were perhaps the most quantitative parts of biology other than population genetics and ecology. Consequently, it should hardly come as a surprise that the genes (alleles at specific loci) that became targets for molecular elucidation were the ones with the simple phenotypic effects that

[15] See Sarkar (1998, Chapter 5) for a detailed appraisal of these methods from the point of view of establishing genetic etiologies.

were routinely studied by linkage and segregation analysis. Nevertheless, molecularization initially paid as much, if not more, attention to proteins as to nucleic acids. This is not in the least surprising; even if genes were the focus of interest, until the mid-1940s it was generally believed that genes consisted of proteins.[16] Nucleic acids, consisting of only four base types, were presumed not to have sufficient variability to be able to specify the huge variety of genes that were known. Pauling's α-helix model for secondary protein structure set the stage for successful physical reductionism in molecular biology (see Pauling and Covey, 1950, 1951). Most importantly, from Pauling's work, there emerged a new model of biological specificity determined by molecular structure, more precisely, by the shape of active sites. This is how enzymes catalyzed their substrates, how antibodies recognized their antigens, or how the chains of hemoglobin interacted with each other in the allostery model for co-operative protein behavior. There was no chemically necessary relation; in 1970, Monod introduced the concept of *gratuity* to capture the type of stereospecificity that lay at the theoretical core of molecular biology.[17]

While the DNA double helix, showing how gene replication must occur during cell reproduction, and the operon model of bacterial gene regulation were undoubtedly intellectually interesting developments, it is far from clear that they should have sufficed to force a myopic focus of molecular biology on genetics especially in the 1970s. Once again, no proper sociological history of these developments has been reconstructed and any claim of historical explanation must remain speculative. However, a reasonable conjecture is that the apparent simplicity of the gene–protein relationship – captured by the genetic code – and an expectation that the protein folding problem would soon be solved, led to a heady confidence that molecular genetics, having largely successfully provided a mechanistic account of heredity, would now similarly provide one for phenogenesis. The aim was a predictively robust model of both heredity and development in which epistemic primacy resided in the genome.

That expectation was not borne out; within genetics, it fell foul of what has aptly been called the 'unexpected complexity of eukaryotic genetics (Watson *et al*., 1992). Starting in the 1970s, five sets of developments destroyed the simple informational model of the genome in molecular biology:[18]

[16] The shift towards viewing nucleic acids as the genetic material begins with the critical paper by Avery *et al*. (1944).

[17] See Monod (1971); this work also provides accessible and interesting accounts of the allostery and operon models.

[18] For details, see Sarkar (1996a, 1996b).

(i) Although the genetic code is nearly universal, it is not entirely so. Consequently, before any prediction using the code can be made in a truly novel context, it must be determined which variant is in use.

(ii) There is no natural synchronization of transcription, and frameshift mutations are known to exist, thus allowing the same DNA to be used in a variety of ways. Once again, for prediction, the exact point of initiation of DNA transcription must be known.

(iii) Even within coding regions of DNA there are regions that are transcribed but not translated (introns). Consequently, all intron–exon boundaries must be known for prediction.

(iv) Similarly, much of eukaryotic DNA (between genes) has neither a structural nor a regulatory role. In fact it has no known functional role (hence, it is sometimes, perhaps unfairly, referred to as 'junk DNA'). The boundaries of genes must also be determined for each case for prediction (although there are patterns here and the initiation regions are not random).

(v) Finally, mRNA is sometimes copiously edited before translation, sometimes to such an extreme extent that it becomes misleading even to say that the corresponding DNA 'codes for' the eventual protein product.

The upshot of these developments is that, the molecular 'gene' or segment of DNA is at best a constructive gene (in the terminology of the opening section above), to be studied by using reverse genetics. Whether it should even be called a 'gene', thus contributing to the conflation of classical and molecular genetics that is being criticized in this paper, is largely a matter of taste. What is important is that the molecular gene *qua* piece of DNA lacks agency; it is a molecular tool used by organisms for a variety of purposes.[19] Perhaps the most radical version of this position is to view the genome as a sequestered molecular template used by cells to transfer specificities to subsequent (cellular) generations.[20] There are subtle questions here, for instance, should the cell or the individual organism be regarded as the primary repository of agency? Intuitions from 'higher' animals suggest the latter, but 'higher' animals form a tiny sub-class of the biological world. Questions such as these now form part of the research program of the emerging field of developmental evolution.[21]

[19] An interesting possible consequence of this position is that the classical gene lacks agency (as noted in the last section), at least partly because its molecular substrate does no better. The development of this argument will be left for another occasion.

[20] This position is developed by Sarkar (2002).

[21] See Wagner (2000) for 'developmental evolution' and Sarkar (2002) for a treatment of this question.

The new focus – and some success – of molecular accounts of development has also led away from the gene. Although molecular developmental biology has its historical origins, at the level of experimental technique, in molecular developmental genetics, recent progress has revealed surprising elucidatory patterns at the protein level. Now, if developmental interactions required protein specificity in the way it seemed central to molecular biology in the 1950s and 1960s, then, because of the coding relation between DNA and protein, however enfeebled that relation has become (recall the discussion of eukaryotic genetics above), one could still maintain some epistemic primacy for DNA over proteins in accounting for development. However, confronting development, in particular, the study of development comparatively across phyla has led to the replacement of specificity by the ubiquitous *tolerance, redundancy* and *genericity* of molecular interactions.[22]

These developments began with the realization of the rather remarkable conservation of many cellular structures and processes at the protein level across almost all phyla. For instance, Cdc2 is a protein that is central to the regulation of the cell cycle of yeast (*Saccharomyces cerevisiae*). However, the human homolog of Cdc2 can take over all of the latter's functions in the yeast cell cycle, including yeast-specific functions such as sensitivity to nutritional signals and response to hormonal signals for mating, meiosis, and mitosis (Gerhart and Kirschner, 1997, p. 30). The globins from all five kingdoms show functional conservatism in spite of sequence divergence. Among eukaryotes, of the 226 globin sequences that are known, there are only two invariant amino acid residues and between any two members of a pair, agreement of residues at corresponding positions can be as low as 16% (Gerhart and Kirschner, 1997, p. 26). Yet, functionally, these are all globins. Because of the degeneracy of the genetic code, divergence at the genetic level is even greater.[23] Tolerance of some structural differences lies at the core of such functional conservatism at the protein level.

Redundancy is seen when cells have available more than one protein for the same function. In such a situation, during evolution, one of the proteins – and the corresponding DNA – can be co-opted for another function. For instance, the prokaryotic protein FtsA and the eukaryotic protein actin are believed to be derived from a common ancestor. Both bind ATP but, in spite of structural similarity, are only 20% identical in sequence.[24] They

[22] On tolerance and redundancy, see, especially, Gerhart and Kirschner (1997); on genericity, see Newman and Comper (1990) and Sarkar (2002, Chapter 4).

[23] This is known to be true of globin genes; however, because of the possibility of RNA editing, divergence at the amino acid sequence level need not necessarily imply diversity at the DNA sequence level.

[24] Details are from Gerhart and Kirschner (1997, p. 25).

are not known to have similar functions at present: actin forms filaments and is a major cytoskeletal protein of eukaryotic cells; FtsA is present in all prokaryotic cells where it is involved in septum formation. In eukaryotes, actin is not required for this function for which it has become redundant. Genericity is seen when a small subset of mechanisms are used for a variety of purposes, especially when relatively simple and robust physical interactions are used instead of highly specific – and, presumably, highly evolved – mechanisms. A standard way of linking intra-cellular biochemical reactions to extra-cellular signals is through the use of ion channels that depend on the membrane potential, that is, a difference in the electrostatic potential across a membrane because of the presence of different polyelectrolytes on the two sides. There are only six kinds of channels which can even be structurally distinguished (Gerhart and Kirschner, 1997, p. 100). Only four types of ions are routinely used for signaling, i.e. Na^+, K^+, Ca^{2+} and Cl^-.

These are exciting times for molecular biology, now that the beginnings of a molecular account of development seem within reach. From this point of view, the role of research on DNA was similar to the role of the collection of facts of natural history in the formulation of the theory of evolution, an important stage but, ultimately, of little theoretical significance. The interesting structures and the interactions that make them possible all occur at the protein level. The cell co-opts for its use whatever resources it has available in its inherited DNA (and other units of inheritance).

Discussion

It is a truism that there is more to biology than molecular biology. The levels of biological organization that were of concern in the last section are far from the communities and ecosystems studied by ecologists and conservation biologists. If 'molecularization' of these disciplines is supposed to mean their representation by molecular models, not only is this impossible in practice, it is hard to see why the results would even be interesting. The interesting questions that are asked, and the answers that are expected, are at levels far from the molecular. Moving to the molecular level will hardly help resolve the stability–complexity or other such debates in community ecology. There is an interesting reductionist question here, that of methodological individualism, whether the individual-based models, typical of population ecology, can explain all the phenomena of community ecology (see Husto *et al*., 1988, and Sarkar, 1996a). However, that is a far cry from molecular/physical reductionism. Even if it is accepted that reductions successively go to lower levels or organization, it is still hard to see how the molecular level would add to ecological insight.

Nevertheless, even ecology and conservation biology cannot altogether avoid questions of development at the molecular level. For instance, only research at the molecular level can reveal the mechanisms and the extent to which UV radiation can be implicated in the apparently global decline of amphibian populations.[25] The response of the mammalian endocrine system to molecular cues affecting reproduction underscores the importance of *some* analysis at the molecular level in population studies that are relevant to ecology and conservation biology. Molecular knowledge may thus well be critical to determining the environmental parameters that are critical for the continued survival of populations. At least to this limited extent, the molecular level is relevant even for the study of ecological systems.

However, leaving ecology aside, it is hard to see how the future of biology can be anything but molecular.[26] This is a reductionist vision but this type of reduction has nothing to do with the primacy of genes, the obsessive deification of DNA that increasingly marked the biology of the late twentieth century. Rather, in a sense, it is a return to the mechanistic vision of the seventeenth century, attempting to understand complex phenomena from simple structural and interactive principles. Reductionism, in this version, is a piecemeal vision: choosing problems that seem tractable in a given context and explaining wholes in terms of parts and parts of parts, recursively, but often simultaneously employing a multiplicity of levels, i.e. molecular moieties, molecules, macromolecules and macromolecular assemblages. There is a rich tapestry of molecules with epistemic efficacy always percolating upwards, although often starting at different levels depending on the experimental context. It is surprising how successful this vision has so far been for biology up to the organismic level.

However, one should nevertheless resist the temptation to dub this as a triumph of physical reductionism for at least two reasons:

(i) Even in the context of development, at present, systemic properties – for instance, properties of a developing organ as a whole – are often just as necessary for the explanation of morphogenesis as local molecular interactions. It is possible that these systemic properties will themselves eventually succumb to molecular reduction. However, it is also possible that irreducibly systemic properties – for instance, the number or frequency of a particular molecular assemblage in a

[25] See Sarkar (1996a) for more discussions of this point.

[26] Note that even evolutionary studies have moved to the molecular level over the last generation (mainly because this is the level at which genetics is now practiced). Using these studies to understand phenotypic evolution will require a molecular or, at least, a physical account of development.

developing tissue – may continue to be required for explanation. The important methodological point that should be made is that complexity should be embraced, not avoided merely to save the reductionist cause.[27] This may well be the most important lesson to be learnt from the failure of genetic reductionism.

(ii) Some robust organismic phenomena have stubbornly resisted all attempts at physical reduction. Dominance is a common property of traits. There is, as yet, no satisfactory account of dominance. To the extent there is at all a molecular account, it relies on the topological properties of biochemical reaction networks.[28] Topological properties are not physical properties; consequently, the epistemological weight in such explanations is not borne by the physical interactions involved. Topological accounts provide systemic explanations. The future will show the extent to which they are necessary, even at the molecular level.

There is thus no reason for a reductionist triumphalism. Reductionism is an empirical issue and the evidence for or against it is not all in: only the future will show whether all biological phenomena at any higher level of organization will succumb to the lure of physical reduction. Genetic reductionism is demonstrably vacuous as a research program at present, no matter what its past history of success has been. The jury is still out on physical reductionism. One way to investigate its limitations is to push it to its limits; this is the tenor of much of biological research today. However, the exploration of non-reductionist research strategies is another way to test the limits of physical reductionism. It deserves more support than what the biological community affords it at present.

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[27] For an elaboration of this argument, see Gilbert and Sarkar (2000).

[28] See Kacser and Burns (1981); this example is discussed in detail by Sarkar (1998, pp. 168–173).

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QUESTIONS AND DISCUSSION

Armando Aranda: We are actually trying to address this problem technically in order to be able to do comparative studies. But the problem behind that, is the idea that penetrance is still justifying that kind of . . . .

Sohotra Sarkar: Yes, but what I wonder is whether or not ultimately they'll be molecular or penetrance, or as I more strongly suspect, we'll stop talking about it all together, because the phenomena, even at the phenotypic level, were not even as well defined as dominance was, for example.

Armando Aranda: Yes, true, true.

David Hull: I think that reaction norms are absolutely essential to our understanding of genetics, evolution and what have you. I have an historical question to ask – Why has so little been written about reaction norms? I realise that a book was published recently devoted entirely to reaction norms (Shlichting and Piglicci, 1998). With great enthusiasm, I bought the book, read it, and discovered I already knew everything in that book. Why is such an important notion left so unanalysed.

Sohotra Sarkar: Which of those, penetrance, or the reaction norm?

David Hull: Reaction norms. Penetrance too, but primarily reaction norms.

Sohotra Sarker: I have two papers on the history of the reaction norm and plasticity. One of them came out in the volume dedicated to Lewontin, *Biology and Philosophy*, in 1999. The second, is in a book on phenotypic plasticity, edited by Dewitt and Sheiner, which is currently in press with Oxford University Press. The first paper covers the history of the norm of reaction and plasticity, all the way up to about 1945, after it was invented in Germany, becomes parts of Soviet genetics, and then gets picked up and repatriated to the West, by Dobzhansky, because Dobzhansky moves from the Soviet Union to the US. The second one just summarises this history and takes up the story as to why Bradshaw, in the case of plant genetics, reintroduced the idea of plasticity and then the dispute that broke out as to whether or not plasticity is adaptive, and if it is adaptive, then whether it is directly selected for, or if it arises while selection is operating on other traits. There are models of all of these, and also optimisation models. The optimisation of models, as often is the case, do not work. But the two sets of models remain with us to this day. And the final part of what I therefore try to show is why molecularisation might help us to understand how exactly plasticity evolved. And the question that comes up here, is very, very interesting – why is it that we have managed to avoid going to the molecular biology of plasticity for so long? And here the answer is very, very contingent. I think it's dependent on a variety of experimental choices that were made. And all of them are related to the fact that genetics has dominated biological research in the twentieth century. If the nineteenth century was Darwin's, the twentieth century belonged to Mendel. One of them was that, for a variety of reasons, most of the work was done on animals and micro-organisms, not all, most, which do not show plasticity as much as plants. The second one was that, as model organisms were being selected, the criteria that were applied were applied in such a way so as to make plasticity as minimal as possible, so that you could reproduce your results. And finally very often, because everything was being motivated with

genetics partly in mind, a lot of the strains of the model organisms that were used were often selected for in extreme environments, which ignores what happens in normal environments where you see the variability and plasticity. So yes, there is a story there, and I've told part of it. I'm actually writing a book on it, but that's a different issue.

Ken Schaffner: Just a very brief comment before we go on. About three years ago, I was doing some work on *C. elegans*, and I asked Corey Bargman about norms of reaction. She's a distinguished UCSF experimentalist. She said she had never heard about it. At least in that term. After I described what it was, she said 'oh wait, we use that'. But she'd never heard of the terminology, and I suspect that it's just not widespread in the molecular community.

Sohotra Sarkar: By the way, one of the reasons why the paragraphs describing the importance of the norm of the reaction disappeared from the book is because one of the referees who read the book, reacted to those two paragraphs by claiming that the norm of reaction was the most useless thing ever introduced in genetics.

Alex Rosenberg: This partly reflects the ideological split between Lewontin and some others with respect to the acceptance and the interpretation of molecular biology. The norm of reaction, as a concept, is closely associated with Lewontin, and as you point out both in your book and today, has an interesting Soviet pedigree.

Sohotra Sarkar: Yes, and in fact the only reason the molecular work is being done right now – partly I agree with Alex – is those of us who do some of that work do not talk about the norm of the reaction at all, we replace it by talking about plasticity, but it's a cluster of concepts very connected to each other.

Stan Shostak: Your historical analysis of Morgan leaves a great deal out and I wanted to mention that his real target here was Karl Pearson, and the whole problem of smoothing rather than chromosome versus the particulate, which he supported in any case.

Sohotra Sarkar: No, at the time I'm talking about, the dispute had become one between Castle and Morgan. The chromosome theory over there was primarily being used by Morgan and the detailed linkage analysis was used to try to show that genes were laid linearly on a chromosome, rather than the trap model where there was a three-dimensional structure to it. But the point over there was that at the time when Morgan was writing, several people, including some at Columbia itself still held very strongly, all the way up to 1926 or 1927, the possibility that what were being called Mendelian factors were actually reactions and reaction networks that were

occurring inside them all. And they did not correspond to physical parts on chromosomes. And in this context what he was doing was just pointing out – 'well even if that is true, what the formal calculus is telling us will remain true'. After Weldon dies, in 1907, I think, or 1908, something like that, Pearson just retreats from genetics and gradually becomes a pure statistician.

Chapter 11

Limits of Reproduction: A Reductionistic Research Strategy in Evolutionary Biology

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The problem of evolutionary transition

The great problems of adaptation and diversity have occupied the bulk of evolutionists' time since Darwin presented his theory of evolution by natural selection. Since the 1960s, the problem of extending this theory to multiple levels of spatial organization from molecules to complex social groups, species and ecological communities has been widely discussed and debated. Two approaches to the problem of units of evolution emerged to address the theoretical and empirical questions, centering on the *spatial* organization of life into a hierarchy of parts and wholes and on *functional* organization into units of genetic replication and selective interaction (reviewed in Hull, 1988, Lloyd, 1988, and Brandon, 1990). However, these have by and large considered the conditions for the operation of evolution and selection *at* given levels of organization.

In the last 20 years, a new problem, the evolutionary origin of levels of organization, or evolutionary transition, has been added to those celebrated since Darwin (Buss, 1987). In their recent book, *The Major Transitions in Evolution*, Maynard Smith and Szathmáry (1995, p. 6) identified what they considered to be eight major originations of new levels of organization (Table 11.1). For most of these, they claimed a common feature: '... entities that were capable of independent replication before the transition

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TABLE 11.1 The major transitions and levels in evolution (after Maynard Smith and Szathmáry, 1995)

Evolutionary transition			*Level*
Replicating molecules	⇒	Populations of molecules in compartments	Compartment
Independent replicators	⇒	Chromosomes	Chromosome
RNA as gene and enzyme	⇒	DNA + protein (genetic code)	?
Prokaryotes	⇒	Eukaryotes	Cell symbiosis
Asexual clones	⇒	Sexual populations	Sexual pair
Protists	⇒	Animals, plants, fungi (cell differentiation)	Multi-cell
Solitary individuals	⇒	Colonies (non-reproductive castes)	Colony
Primate societies	⇒	Human societies (language)	?

can replicate only as part of a larger whole after it' (Maynard Smith and Szathmáry, 1995, p. 6).

The problem of evolutionary transition is to formulate a coherent theory that can explain these transitions and guide evaluation of empirical evidence for each. Part of this work involves describing units of evolution adequate to explain the evolutionary origin *of* new levels and not merely evolution *at* levels (Griesemer, 2000c). The key insight into the units problem afforded by consideration of evolutionary transition is that units of evolution themselves have an evolutionary history. Differently put, there is a temporal or 'processual' dimension to the units problem as well as spatial and functional dimensions. Because the spatial and functional perspectives on units mentioned above were not articulated with the evolutionary transition problem in mind, they are not clearly suited to its theoretical solution. In particular, if a perspective assumes the existence of levels of organization or embeds assumptions about these products of evolution in their analysis of units, then it has assumed what is to be shown by a theory of evolutionary transition.

In this essay, I argue for a new perspective on units of evolutionary transition. I analyze the process of reproduction, which leads to a conception of units of evolution as *reproducers*. These units resolve to more familiar ideas of replicators or interactors at levels of spatial organization when explicit spatial and functional models are imposed on abstract reproducers. I also sketch a heuristically promising program of reductionistic research that flows from the new perspective.

Perspectives on biological organization

There are two dominant perspectives on units of biological organization: (1) 'additivity' models of spatial units of selection (Lewontin, 1970; see also Wimsatt, 1980, and Lloyd, 1988), and (2) functional models of units of replication and interaction (Dawkins, 1976, 1982; Hull, 1980, 1981, 1988). The additivity approach assumes the existence of a compositional hierarchy of parts and wholes and generalizes Darwin's principles to all levels from molecules to species. The functional approach distinguishes two functions of entities satisfying Darwin's principles: replicators with sufficient longevity, fidelity, and fecundity to form lineages of copies, and interactors whose interactions with the external environment cause replication to be differential. Dawkins analyzes replicators in terms of the concept of copying, while Hull writes of entities that pass on structure directly or largely intact. Both functionalist approaches treat as empirical questions the spatial level(s) at which selection acts, as well as which functions (replication or interaction) are satisfied at a level.

Notice that the common feature of many evolutionary transitions identified by Maynard Smith and Szathmáry involves a change in the status of *replicators*. Once the replication of a class of entities becomes dependent on a larger whole, they do not become independent replicators again. So new replicators at the emergent level must exist and replicate independently in order for there to be a still higher level transition. Given the nature of replicators as analyzed by both Dawkins and Hull, there is a problem with this characterization of the common feature: only one or possibly two evolutionary transitions are at all likely to have occurred in the history of life.

Dawkins' and Hull's analyses suggest that only in very unlikely circumstances, such as pure asexual cloning in which the whole parent cell's structure is passed on to offspring directly or largely intact, will entities above the spatial level of molecules function as replicators. Spatial entities above the molecular level tend not to persist in the form of copies or transmit their structure directly, or largely intact, to subsequent generations. Thus, once the transition to compartmented populations of molecules, i.e. cells, occurred (see Table 11.1), evolutionary transition would be over. Dawkins considers the possibility of a second transition to memetic, conceptual evolution. My focus, however, is on the inadequacy of the replication concept to interpret the *biological* transitions listed by Maynard Smith and Szathmáry. If there has been a series of transitions, their common feature cannot be fully interpreted in terms of a change in the status of Dawkins- or Hull-replicators.

I diagnose the difficulty as follows. The distinction between independent and dependent replication is too crude to explain the evolution by natural selection of replicator dependency at successive levels of organization. This dependency is a property of *developmental* processes at each level. If replicators are entities of which copies are made (Dawkins) or which pass on their structure largely intact in replication (Hull), then making copies or acquiring the capacity to pass on structure is the developmental process through which replication takes place. However, the gross or aggregate property of mere dependency on the larger whole gives no clues to the general character of the evolution of such developmental processes, in either structural or functional terms. Thus, although the replicator concept was designed to 'black-box' the process of development, recapitulating the historical separation of embryology from the more tractable problem of hereditary transmission, the problem of evolutionary transition highlights the considerable extent to which the problem of units of evolution *is* a problem of development.

I offer a different and complementary perspective on units which accommodates developmental processes explicitly and which articulates the intimate relationship between units of hereditary transmission and developmental expression. I argue that a process perspective on the temporal dimension of the transition problem, focusing on the propagation of developmental capacities, is a helpful addition to the spatial and functional perspectives. Reproduction is the process that, in general, forms the basis for evolution at a level and also for evolutionary transition to new levels. Processes of inheritance and replication can be understood as special cases of reproduction. In order to formulate a view of how processes of development and hereditary propagation are intertwined in reproduction, let us consider development further.

What is development?

Traditionally, development is described as the growth and differentiation of the cells of a multi-cellular body, from initiation in a spore or zygote to adulthood or senescence. This characterization covers the whole temporal span of the process of interest to developmental biologists. However, it is not suitable for dealing with the problem of evolutionary transition because it is defined with respect to a single level of spatial organization, i.e. multicellularity, which is a *product* of evolutionary transition. A more general approach to development is implicit in Maynard Smith's analysis of units of evolution. This approach suggests that the multiplication of entities required by evolution must result in offspring entities 'of the same kind' (Maynard Smith, 1987; discussed in Griesemer, 2000c).

Sameness of kind, or acquisition of sameness of kind, is a more general notion of development than the traditional idea and thus better suited to characterizing development at any level of spatial or functional organization. However, it is so vague that it provides little guidance in units analysis. What is the same *relevant* kind at any given level? Is there a single relevant kind applicable at all levels of transition? A common view of development is that offspring are of the same species as their parents, i.e. that the relevant kind, assuming we are not typologists, is some set of species-typical traits. However, surely species-typicality is also tied to the traditional notion of development, if not obviously to the single level of multi-cellular organisms.

The dilemma in characterizing development generally is that we need a theory of development in the conceptual tool kit to frame a robust theory of evolutionary transition, but it appears that we need to understand the transition process in order to go beyond traditional thinking about development. Instead of offering a theory of development, then, I propose instead to place bounds on the process of development that are tailored to the evolutionary transition problem. I will offer below a heuristic strategy for producing models of development that may facilitate a more nuanced account, or at least may make more precise the problem of 'bootstrapping' a general theory of development.

I suggest that we take the acquisition of the total set of species-typical traits (however that is to be measured empirically) to be a maximum specification of the process of development. Anything more exhaustive than species-*typical* might entail that new species could not evolve. As a minimum bound, I suggest the following evolutionary specification – development is the acquisition of the capacity to reproduce. It will become clear in a moment why I bracket the process of development in this way. First, though, let us consider the sorts of questions about development at multiple levels of evolutionary transition that must be addressed if we are to understand units of evolutionary transition in terms of the propagation of developmental capacities.

Questions of development at multiple levels of evolutionary transition

The problem of evolutionary transition was first clearly stated as a general problem applying at all levels of organization by Leo Buss (1987), although he focused on the evolution of multicellular development – the evolution of individuality. A units analysis suitable for the transition problem in general must also be able to address questions such as whether the molecules of autocatalytic chemical cycles are developmental stages or are instead distinct, non-evolving natural kinds. One level up, does the passage of a single cell through the cell cycle count as cell development or merely cell

growth? Should the transmission of cell differentiation states through cell division, e.g. differentiation into an epithelial or mesodermal state during the development of the multi-cellular whole, count as development or rather as heritable transmission in a cell line? Finally, skipping above the familiar level of multicellular organisms to the level of groups, does organism reproduction within a group that multiplies by subdivision count as part of group development? In other words, do evolutionary processes at the group level, such as Sewall Wright's 'shifting balance process' or experimental interdemic selection in the laboratory entail group development as well as group reproduction? To begin to address such questions as these, I next offer an account of the process of reproduction.

A process perspective on reproduction

In order to analyze the process of reproduction, two more basic concepts are needed: 'progeneration' and development. Development was described briefly above. Here, I will adopt the evolutionary minimum concept of development as the acquisition of the capacity to reproduce. The evolutionary minimum concept is very general, although limited to the context of evolutionary processes. More precise notions of development could be substituted that specify mechanisms by which the capacity to reproduce can be realized, although it remains to be seen whether more precise, non-evolutionary concepts can be general enough to apply to all levels of evolutionary transition.

Progeneration plays, in some respects, the genealogical role of a concept of hereditary transmission or 'replication.' However, unlike the Weismannist view of heredity and development as logically or empirically separable processes, I view progeneration as fundamentally intertwined with development. The aim of my analysis of reproduction is to articulate this intertwining.

Progeneration is defined as the propagation or multiplication of entities with material overlap of parts.[2] Material overlap means that at least some

[2] Readers might prefer the term 'propagation' here rather than Maynard Smith's term 'multiplication' to avoid the following potential confusion: many people think that a *multiplication* of entities means that there must be more entities existing at a time after the multiplication 'event' than at some time before. Simple cell division by binary fission fits: before there was one ancestral individual and after there are two offspring individuals. Sexual reproduction fits as well: before there were two parent individuals and after there are three (two parents and one offspring). However, if we count gametes rather than organisms, two gametes fuse to form a zygote yielding two ancestors before and one offspring after – a violation of common sense multiplication. I intend the terms 'multiplication' and 'propagation' both to mean 'numerical increase of distinct individuals independent of time.' In this sense, which I think Maynard Smith intended in his analysis of units of evolution, the sexual case implies that two gametes fuse to form a third individual distinct from the ancestors, so that two multiply to make three. The fact that the gametes *no longer* exist is just as irrelevant to this technical sense of multiplication as would be the fact that some parents *die* in the process of bringing forth an offspring generation.

spatial parts of the parents become parts of the offspring. Cutting a loaf of bread in half progenerates bread. Tearing a painting in half is also progeneration. Each process of division results in new objects which are made from, i.e. have parts that once belonged to, the parent. The offspring in these cases are numerically distinct from the parent in virtue of their non-overlapping spatial boundaries. Less stringent, or even non-spatial criteria, such as functional autonomy (Christensen *et al*., 2000), might be used to distinguish offspring and parents. The requirement of material overlap distinguishes progeneration from copying: they are two different kinds of multiplication processes (Griesemer, 2000b).

Copying processes result in 'offspring' that are similar to the parent, but not by means of material overlap. Dawkins gives the example of photocopying to illustrate important aspects of his copy-based concept of the replicator (Dawkins, 1982). A paper photocopy of a painting resembles the painting in certain respects, but it is not made of paint on canvas, let alone the very paint and canvas of the original. Because the *pattern* in the original is transferred through an electrostatic drum intermediary (or analogous mechanism), photocopies do not *materially* overlap their parents.[3] Because of its non-material, purely informational nature, I have argued that copying is not the right basis for a fundamental understanding of biological processes (Griesemer, 2000a, 2000b, 2000c). However, material overlap is so general a requirement of the *process* of reproduction that the notion that *entities* multiply is only made precise by adding explicit models of spatial and functional organization to the abstract analysis of progeneration. Thus, the process perspective complements rather than replaces spatial and functional perspectives on biological organization.

With the processes of progeneration and development defined, I now analyze the process of reproduction. Reproduction is the progeneration of mechanisms of development. Mechanisms are things (physical, spatial entities) whose behavior causes the states that realize capacities (see Glennan (1996) on mechanism; see Cummins (1974), Cartwright and Mendell (1984), and Cartwright (1989) on capacities). The works inside an analog watch is a mechanism whose gear-turning behavior realizes the capacity of the watch to mark time. Mechanisms can be said to 'carry' and 'confer' capacities. They confer capacities in virtue of their integration into entities in appropriate ways.[4] They carry capacities into whatever contexts

[3] One could, of course, cut an original document in half and feed one half into a copy machine at each end. However, this would be merely making a copy on a progenerated substratum, not a demonstration that copying amounts to the same kind of process as progeneration.

[4] Indeed, in just those ways that make possible articulation of parts explanations of the behavior of the whole (Kauffman, 1971).

the mechanism can be moved without violating their integration into the carrying entity, constituting what Nancy Cartwright has called 'nomological machines' (Cartwright, 1999, Chapter 3). A watch carries its time-telling capacity to a variety of environments, although not to all possible or even actual environments. My water-resistant watch stopped having this capacity after it was submerged in a swimming pool for several hours. Corrosion disrupted the integration of the gears and water destroyed the paper face with the numerals marking the hours.

Mechanisms of development are those things transferred from parents to offspring in progeneration that confer developmental capacities. Genes are mechanisms of development par excellence. The idea that reproduction is the progeneration of mechanisms of development thus captures a fundamental insight of genetics since its historical beginnings: genetic units must be units of transmission that somehow play a role in development (Griesemer, 2000a). However, reproduction is a more general process than what is captured by modern genetic theories to the extent that there are entities and mechanisms of development besides genes that can be progenerated. Students of epigenetic and cytoplasmic inheritance have been arguing that there are such units of development for as long as the science of genetics has existed (Jablonka and Lamb, 1995). Moreover, if it is true that evolution at the group level entails group reproduction (Brandon, 1990), then it follows from my analysis of reproduction that group evolution entails group development.

Since I have defined development as the acquisition of the capacity to reproduce, reproduction is the progeneration of mechanisms for the acquisition of the capacity to reproduce. The definition threatens circularity because reproduction is defined in terms of progeneration, progeneration is defined in terms of development and development is defined in terms of reproduction. The circle can be broken if reproducers are organized in spatial or functional hierarchies that make the process of reproduction recursive (Griesemer, 2000b). The mechanisms of development may, for example, be *spatial parts* of the progenerated entities. Their development may entail the reproduction of still lower level entities.[5] For example, multi-cellular organisms reproduce in virtue of having developed (acquired the capacity to reproduce), which in turn depends on their developmental mechanisms (which are made of cells) having reproduced. Further, the cells reproduced in virtue of their molecular collectives having reproduced, which in turn depends on these molecular collectives having developed.

[5] I agree with Brandon (1996, Chapter 11), however, that mechanisms need not be *lower*-level spatial parts of entities. They may be higher-level functional parts, or 'contexts,' which are parts of the 'systems' which contain the entities in question. Thus, mechanisms may be at higher spatial levels rather than at, or in addition to, lower levels.

At the bottom of the recursion, there must be entities that are capable of reproducing without needing to acquire that capacity in development. These are the 'null-developers' out of which a level of reproduction must be built. The bottom of the recursion might not be the lowest level of a spatial hierarchy: perhaps sexual organisms cannot reproduce unless their social context develops. This recursive structure makes reproducers much more congenial units to the problem of evolutionary transition than are replicators. Changes in the developmental status of reproducers at one level of spatial organization need not preclude the emergence of new levels of independent reproduction.

Examples of 'reproducers' that are not organisms include the so-called 'genetic membranes' that propagate their kind without genes through growth, accumulation and incorporation of constituent molecules, and eventual division (progeneration) into offspring resembling the parent membrane. Perhaps Oparin's primordial coacervate droplets, Gánti's chemotons, and Morowitz's proto-cells were reproducers (see Gánti, 1979, and Morowitz, 1992). Another example is the demes in interdemic group selection which give rise to more groups by sending out 'propagules' of organisms to find new groups and which, therefore, materially overlap their parent groups (Wade, 1977, 1996; Wade and Griesemer, 1998; Griesemer and Wade 2000). If organism propagules can be said to develop, then their progeneration at the group level counts as reproduction. Both examples assume a process of the development of units at a level that leads to the acquisition of a membrane's or group's capacity to reproduce.

Inheritance is a special case of reproduction in which the progenerated mechanisms of development are *evolved* mechanisms. Mechanisms must arise before they can evolve, even if they are built out of evolved components. One expects that, for each evolved mechanism, there was a time when it was a newly emergent collection of simpler parts that had not yet evolved at the level of collective reproduction. While it may seem unlikely that organism reproduction in groups is an *evolved* mechanism of group development or that avatar selection yields community-level units (Damuth, 1985), it is clear that lower-level phenomena, such as cytosine methylation of DNA, are an evolved mechanism of cellular development (Bestor, 1990). Methyl groups are attached to cytosine nucleotides of DNA. When the latter are transmitted to offspring cells semi-conservatively, patterns of methylation are also transmitted semi-conservatively, so that parent cell methylation patterns are progenerated with material overlap of patterns. The role methylation patterns play in cell heredity in transmitting

states of gene regulation from parent to offspring cell is an evolved mechanism by which differentiated cells acquire the capacity to reproduce. DNA methylation systems thus constitute inheritance systems (Jablonka and Lamb, 1995) and the units of methyl regulation of development are 'inheritors'.

Replication is a special case of inheritance and therefore a special case of reproduction. Replication can be defined as the progeneration of evolved, *coding* mechanisms of development. For present purposes, let us assume that 'coding' encompasses those properties of DNA that underwrite Dawkins' concept of copying and Hull's concept of direct or intact transmission of structure, setting aside the interesting problem of articulating what coding means (see Szathmáry, 1999, on 'unlimited heredity,' and Godfrey-Smith, 2000). Here I intend only to emphasize the relationship between my analysis and theirs, not to argue for any advantages of my view of replicators. A key difference in my approach is that since reproduction depends on material overlap, processes which do not transmit copies with material overlap are not replicators in my sense (see Griesemer, 2000b, for further discussion). Perhaps many cases of so-called memetic replication fall in this category.

If replicators are a special class of 'reproducers,' the feature common to evolutionary transitions can be redescribed: entities capable of independent *reproduction* before the transition reproduce only as dependent parts of an independent *reproducer* at the new level afterward. Thus, evolutionary transition might involve reproducers, inheritors, or replicators. Even if Dawkins and Hull are right that biological replicators above the molecular level are unlikely, the conclusion that only one or two evolutionary transitions occurred no longer follows. It could well be that higher levels of transition involve change in the status of reproducers that are not replicators. Evolutionary processes that stabilize new levels against disorganization from below – contingent irreversibility and central control (Maynard Smith and Szathmáry, 1995, p. 9) – may drive the evolution of reproduction or inheritance at the new level without the advent of new, independent replicators (see also Griesemer, 2000c). Although these processes are often characterized in terms of genetic mechanisms – the transfer of mitochondrial genes to the nucleus is a paradigm example of contingent irreversibility – they need not depend only on genes.

Two general empirical questions about replicator transitions arise, i.e. (1) whether any (biological) replicators besides genes have evolved, and (2) whether the emergence of DNA-based genes and of human linguistic communities (the question marks in the last column of Table 11.1) are genuine transitions? These questions turn on the following issues. First,

what are the properties of coding mechanisms of development that must have evolved for a transition to have generated a new level of replicators? Secondly, did the questioned transitions in Table 11.1 result from a transition of progenerators with material overlap of mechanisms of development? It is not obviously or trivially the case that the changes in mode of transmission of 'genetic information' from RNA to DNA + protein, or from primate communication to human language involved the evolution of material overlapping mechanisms of development. Thirdly, under what conditions does evolution favors information transmission by energetic induction of patterns (copying) rather than by propagation of material propagules (progeneration)?

Most centrally to present purposes, we can use the analysis of reproduction, together with our knowledge of transmission genetic theories, i.e. theories of replication, in a heuristic search for a better theory of mechanisms of development than the evolutionary minimum concept stated above. This is because the relation of replication to reproduction is in the nature of a special case to the general case. That is, we may use theories of the special case to explore *possible* theories of the general case.[6] Transmission genetic theories tell us very little about development *directly*. Nevertheless, they do place constraints on theories of development by virtue of the fact that units of transmission, e.g. genes, must also serve as units of development, even if not as the 'master molecules' implied by the genetic determinism assumed in simple models of gene transmission (Sapp, 1987; Keller, 1995). We know that genetic determinism is false. Nevertheless, it has been forcefully argued by Wimsatt (1987) that false models can be used *heuristically* as the means to the construction of truer theories. In this spirit, I outline a proposal for a heuristic search for theories of development.

Heuristic reductionism

Theory reduction is classically interpreted as an explanatory principle along the lines of a deductive nomological model of explanation (Nagel, 1961). From a powerful general theory, the 'reductans,' together with bridge principles that translate terms and boundary conditions, a less general theory, the 'reductandum,' can be deduced (Schaffner, 1993). This kind of derivational relation is called theory reduction (see Figure 11.1, upper left). The reductandum is reduced to the reductans. The classic example of this kind of explanatory process is the derivation of phenomenological

[6] Because the heuristic strategy explores possible general theories, it may appear explanatorily weak. However, 'how possibly' explanations are characteristic of evolutionary biology (Brandon, 1990).

thermodynamics from statistical mechanics (Figure 11.1, lower left). The key to successful reduction is the discovery of bridge principles (highlighted in Figure 11.1, upper left) that translate terms of the reductandum into terms of the reductans so that the laws of the two theories can be deductively linked. In the reduction of thermodynamics, a key bridge principle is the equation relating gas temperature with mean molecular kinetic energy.

In the heuristic use of theory reduction, the 'reduction' runs 'in reverse.' From the reductandum, together with specified boundary conditions and certain invariance principles that do the work of bridge principles, various possible reducing theories – 'reductans' – can be formulated (Figure 11.1, upper right). The heuristic goal is theory construction rather than explanation. In addition, instead of term translations, we have principles stating that entities of the reductandum are invariant to changes described by the reductans. Invariants make useful theoretical units because they have convenient properties for representation in models and in experimental interventions, e.g. they don't change during the course of experiments so that their properties can be represented by constants in mathematical

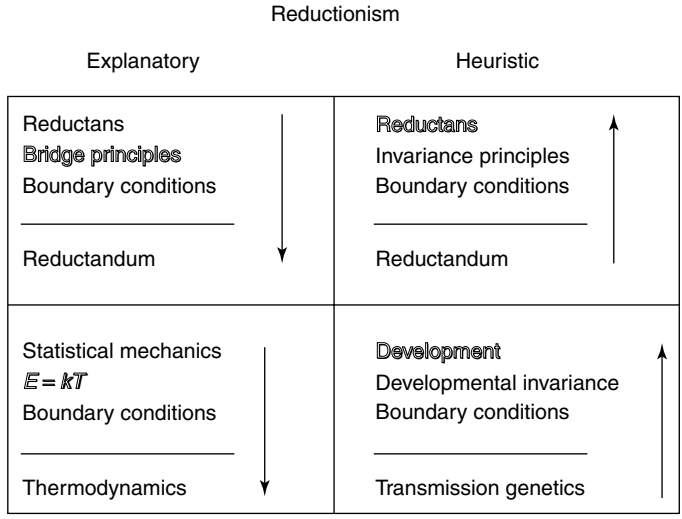

FIG. 11.1. Reductionism, explanatory and heuristic. The left side illustrates the classical view of theory reduction as an explanatory relation, while the right side illustrates the heuristic use of theory reduction in the text. Highlighted items are those whose discovery drives reduction. In explanatory reduction, the reducing and reduced theories (reductans and reductandum) are in hand and the discovery of bridge principles completes the reduction. In heuristic reduction, the reductandum and invariance principles are in hand and the goal is construction of a reducing theory

models (see Woodward, 1997). Moreover, the behavior of entities described by the reductandum and possible reductans need not be expressed in the same terms, so problems of term translation can be avoided, at least during theory construction. Invariance principles guide us in the use of reductandum descriptions of the behavior of its objects in the context of reductans theories.

The analysis of reproduction presented above, together with the notion that transmission genetics is about replicators, suggests a possible heuristic strategy for constructing a general theory of development, provided that we can express a suitable invariance principle. I am thus led to propose the unorthodox heuristic strategy of using transmission genetics as a guide to constructing theories of development.

An odd consequence of the analysis of reproduction

Reproduction is about the propagation of mechanisms of development. Because replication is a special case of inheritance and inheritance is a special case of reproduction, and because reproduction is the progeneration of mechanisms of *development*, it follows that if transmission genetics is a theory of replication, then transmission genetics is about development as well as about 'transmission.'

This seems an odd consequence because standard historical interpretation suggests that transmission genetics was constructed by scientists who consciously cut the ties of genetics to problems of embryology in the name of progress and practical achievement (e.g. Gilbert, 1978, and Allen, 1978). The Weismannian separation of germ and soma meant that the transmission process could be studied without regard for the process and problems of gene expression in development. Although the *fields* of genetics and embryology went their separate ways – geneticists locating the primary explanatory power in the nucleus, embryologists locating it in the cytoplasm (Sapp, 1987) – this does not mean that geneticists stopped thinking about the relation between heredity and development, transmission and expression, for even a moment. Historically, geneticists have always talked about genetic factors in developmental terms – as units of developmental *stability* (Griesemer, 2000a).

The gene is a developmental invariant

Indeed, the founders of transmission genetics spoke of factors or genes as developmentally stable. Mendel wrote that his theory (distinct from his laws) was a theory of the development of hybrids (Mendel, 1866, p. 20). The

law of segregation is a principle of developmental invariance: factors that are isolated in pure lines are brought together by hybridization which then segregate in subsequent generations bred from the hybrids. Segregation implies that factors are stable to the change of developmental context from that of a pure line organism to a hybrid and back again (see Griesemer, 2000a). To take just one other prominent founder of transmission genetics, in his 1926 book, *The Theory of the Gene*, Morgan wrote that 'Mendel's theory of heredity postulates that the gene is stable. It assumes that the gene that each parent contributes to the hybrid remains intact in its new environment in the hybrid' (Morgan, 1926, p. 292).

A similar interpretation of the gene as a developmental invariant could be seen at work in the development of the operon theory of Jacob and Monod (Griesemer, 2000a). Their investigations of relations among genes, their regulatory states, and the states of their cells' internal and external environments raised questions about the stability of classical genes. These questions posed a dilemma for those who would limit the gene concept to structural features of nucleic acids. Shrinking the gene concept to a subset of structural features that are stable to the newly discovered regulatory instabilities would cede the new phenomena to other disciplines. Expanding the gene concept to include regulatory features would deny the gene concept its fundamental property of developmental invariance. The dilemma is to decide whether it is the classical gene or classical genetics which has to go.

Extending this historical notion of the gene as developmentally stable, I suggest that genes be thought of as developmentally invariant mechanisms of development. That is, genes are mechanisms of development that are stable to (some class of) changes in development. The capacity to reproduce specifies a maximal *class of developmental changes* – everything that can change in development and still realize a developmental process in evolution, i.e. the acquisition of the capacity to reproduce. Therefore, theories of units applicable to transmission genetics (replicators, inheritors, etc.) can be used heuristically to explore theories of development that specify less maximal classes of developmental changes to which a given unit is invariant as well (see Figure 11.1, lower right).

The theory sketched above describes reproduction as the product of two intertwined processes, i.e. progeneration and development. Progeneration is the process of transmission of material from parents to offspring that is capable of causing development. Transmission genetics traces inferred (classical) or observed (molecular) material (genes) transmitted from parents to offspring. However, it is in virtue of our understanding of the *second* component process of reproduction – development – that we follow some

materials rather than others through progeneration. Classically, and according to Weismannism, *genes* are the materials that are most relevant to explaining development, and therefore following these substances is of greatest explanatory value. The view suggested here is that there may be other transmitted materials that are now, and in the early history of life *must have been*, important in development. Therefore, transmission 'genetics' is a wider phenomenon than was classically recognized. Its formal models can be taken to cover this wider domain if the notion of genetic units is expanded to encompass units of reproduction – reproducers – more generally. It is a separate, empirical questions as to how *adequately* transmission genetic models represent phenomena outside of the classical domain.

The heuristic aim is not necessarily to support the claim that an adequate general theory of development *will* take the form of a model of transmission genetics, fixed by some specified principle of developmental invariance. Indeed, it is more likely that pursuit of the strategy will reveal ways in which such a theory is *inadequate*. It is clear, for example, that genes are not invariant to all classes of developmental change. In particular, they are unstable to the operation of repair enzymes, whose evolved function is to change DNA when it has been inaccurately progenerated. Many other developmental stabilities, e.g. canalized developmental pathways, are invariant only by virtue of active maintenance. Their invariance does not result from some structural stability to all classes of developmental change induced by the original generating process (see Wagner and Misof, 1993, for examples).

Instead of blazing a deductive path to a 'theory-to-be-reduced,' successful application of the reductionist heuristic described above may fail to yield a reducing theory (see Figure 11.1, right-hand side). It is in the nature of heuristics that their correct application can nevertheless lead to systematic failure (Wimsatt, 1980, p. 220). In the case at issue, transmission genetics can be expected to provide only one model-type for possible theories of (parts of) mechanisms of development beyond the genes. Much of the interesting work to be done with such a class of models is to explore systematically what developmental phenomena are left out of account, that is, to explore how the heuristic and its basis in classical genetics has failed. In a way, heuristics of this sort are explanatory promises we don't intend to keep. Their utility is not grounded in explanatory power in the sense manifest in theory reduction. Rather, heuristic strategies of theory construction aim to overcome limitations of classical modes of thought which suppose that new theories must not only be consistent with explanatorily successful theories, but that they must be expressible and interpretable in their terms. The new perspective on units of reproduction sketched here aims to show that the

problem of theorizing development is illuminated by taking seriously the intertwinement of heredity and development. Weismannism, the doctrine underlying the classical separation of germ and soma, and the fields of genetics and embryology, has historically diminished the problem to the point that it seems almost irrational to take it up (again). The approach developed here shows that we can have our reductionist cake (see the essay by David Hull) and eat it too.

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QUESTIONS AND DISCUSSION

David Hull: Jim, finally after all these years, I think I have a pretty good idea of your views. I hate to ask you a real hard question right off the bat, but does your analysis fit the reaction of the immune system to antigens?

Jim Griesemer: Well all questions of that kind are hard because we have to give an explicit spatial characterisation of the process. I would hope so, but ... I would think so, insofar as there's a material overlap ... well ... it's a good question. I don't want to try to answer questions I don't know enough about. Because I take that to be an interesting scientific question.

Alex Rosenberg: You have some suspicion that it won't David?

David Hull: The only part of your analysis that bothers me is the requirement of material overlap, but then I'm not an immunologist. Is there an immunologist in the house? Does the immune system fulfil the material overlap requirement?

Albert Tauber: I think I can answer that. If one is talking about the generation of diversity, certainly the gene shuffling that goes into making an antibody of a T-cell receptor would be the same kind of process that one looks at in terms of replication of germ cells.

Alex Rosenberg: Memetics? Does memetics causation satisfy the material overlap?

Jim Griesemer: No, it doesn't.

Alex Rosenberg: And yet photocopying is a causal process in which there is a sequence of material compositional changes across district existences with what, may be representational but certainly at least, topographic homologies.

Jim Grisemer: Some cases may and some may not. So one place where I part company with, for example, the development systems view of cultural evolution as not distinguishable from biological is over the issue of material overlap. It seems to me that some kinds of cultural transmission are dependent of transfer of matter, material artefacts. And when they do, there might be something at that level that would count as an instance of my biological process. And other cases, probably not. I'm not saying that there aren't copying procedures in the world that satisfy, for example, dynamical equations that would apply to a system, but which are not, for example, replicator dynamics, but which are not material overlap.

Alex Rosenberg: Does photocopying not satisfy your requirement of material overlap?

Jim Griesemer: No, it doesn't.

Alex Rosenberg: Why isn't there a transfer of material in photocopying? If we think about the process of photocopying, it doesn't look as though the, say, semi-conservative character of DNA copying, is a physically different process in kind for the electrostatic planting involved in say, Xerox machines.

Jim Griesemer: Yes, that's right. And the question is an empirical one why it is that in the biological world, transmission of information, if you

want to use that language, depends on transfer of material. Oh absolutely it's different, because offspring DNA molecules are made out of the parts of parents. The are not identical with the parents. There's no material transfer in photocopying but half of the DNA parent molecule ends up in the offspring. And so there are two kinds of questions. One is – is that somehow an essential property of the DNA process? And the other is a dynamical question – if it's true that all-biological reproduction is as I've characterised it, how come? It could well be, and my speculation is that when you can't count on the environment, when the environment is untrustworthy, the transmission of information is much more reliable if you send a propagule of matter that can develop. In cultural transmission of the memetic sort which does not involve any material overlap, e-mail, photocopying, history, well, I think there's a lot of material overlap going on in the human historical world that counts for something. You move people and books, not just ideas. 'But in those cases, what makes it possible for e-mail to be a reliable means of communication is that there is a huge number of engineers making sure that the environment, the channel conditions are extremely stable. And so I think that there's an interesting dynamical problem for the biological world because the conditions of transmission from parent to offspring can't – they count on their environment.

Michel Morange: There were some models in the 1950s at the beginning of molecular biology, trying to explain the reproduction of the functional steady state without genes. Do you think these models are related with what you intend to do, and you can find in them something interesting?

Jim Griesemer: You're thinking of Delbruck's model? Yes, those are interesting. To interpret those in my way I have to add an explicit spatial account of parts and wholes. And once one does that then those strategies of representation I think are very interesting. Jablonka and Lamb (1995) have tried to represent the evolutionary process for epigenetic inheritance on a par with those kinds of models for exactly that reason, that even though you can't have a cytosine methylation system without DNA, you can talk about the evolution of methylation patterns against a homogeneous sequence background, so you can use effectively a non-gene way of thinking about these kinds of problems. To me, those are the empirical realisation of the program I'm only gesturing at here.

Sohotra Sarkar: Jim, I'm wondering can we press you to say a bit more about what you envision this theory of reproduction to be. Once you have a spatial model, one possibility is the following: that we have our standard model inheritance of replicators, we add to them epigenetic inheritance, cytoplasmic inheritance, and things like that, so that at the level of what it is that is being transferred from generation to generation through the germ

cells or something like that, we have what would be a modest extension of classical population genetics. Separate from that, let's say we have finally, 'and this is where I'm sceptical we'll ever quite get there easily', a theory of phenogenesis, where we have some sort of theory that tells us through the process of growth and all of that how you start out with what it is that got transmitted from the last generation, add in environmental history and you have at the end a reproducing adult organism. So now when you couple these two theories together, what you end up with would satisfy your requirements of a theory of reproduction. Is that what you're trying to say, in which case it just ultimately becomes the traditional quest for a theory of phenogenesis, or do you think that, so to say, they'll be a different theory directly going from adult organism to adult organism, from which it will take some modifications, special case applications and things like that to get the individual transmission genetics out and a theory of phenogenetsis possibly out? Which is your vision of this?

Jim Griesemer: I'm not sure I'm clear on the difference. But I don't see it as a minor extension, because the kinds of problems of transmission for other levels are undoubtedly quite different than . . .

Sohotra Sarkar: The only part I was thinking of was a minor extension, to get a theory of transmission that was beyond just DNA transfer.

Jim Griesemer: So as long as phenogenics, in your sense, extends to all levels of organisation, then I think it's that harder project.

Marc Van Regenmortel: I'm trying to apply your idea to viruses and their replication. If you have a single-strand virus, lets call it 'plus', it gives rise to a 'minus' and 'plus' double strand; in your case it's a half picture which gives the full picture of the other half without material overlap or actually only half of the overlap. Then the negative strand is used to make more positive strands, and there is no material overlap anymore. Now how does that fit into your scheme?

Jim Griesemer: Well the issues about viruses are interesting because the minus strand doesn't overlap the plus strand obviously; the other interesting questions are about the developmental context, that is, the conditions under which viruses acquire the capacity to do that again. Now if there's no material overlap, and this is more a philosopher's point than an interesting scientific one, we just don't have to say that viruses reproduce, even though that's common parlance. But the significant germ of an idea there is that we already know that viral reproduction, so called, depends heavily on the host. Much of the action is host action, not virus action. So I think my view is quite compatible with the idea that viruses are, a lot of them, secondarily derived. That fits quite well. I'm also quite happy to talk about things that are parts of reproducers rather than reproducers

themselves. It doesn't seem to me at that level that I'm doing anything more than imposing some semantic rigor in the discussion. The interesting questions have to do with the developmental process of the host by which a virus acquires a capacity to do whatever it does once again.

John Dupre: I suppose the question is exactly whether you are imposing semantic rigor or whether you're getting pushed into some somewhat uncomfortable statements from the rigors of your theory. It seems to me a question that arises in connection with the last question, but I'm still a little concerned about the cultural evolution matter. Perhaps you have a little bit more to say. Suppose you have some culture in which some important mythology or something is passed on by oral tradition and one day somebody writes it down and makes a few books. I take it on your view at that point you've moved to a totally different process, something radically different that relates quite differently to other processes of evolution has started to happen, and I find that a little plausible. It seems like something you've talked yourself into, and I wonder whether you really want to insist on being there or whether you have another way out.

Jim Griesemer: It's radical in the sense that I showed in that picture, that copying is radically unlike progeneration. So in that sense it's radical. But there's no reason that different kinds of causal process can't produce quite similar patterns, so I'm not scared off by the possibility that an oral tradition could mimic some material overlap process. What's interesting to me is not *whether* but *what* the dynamics are of those systems and whether they have different characteristics as evolving systems, if indeed they are.

Chapter 12

Evolutionary Psychology: A Case Study in the Poverty of Genetic Determinism

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Imagine you are an alien watching a cocktail party with a social scientist. You ask – Why are these people all in this room? The reply comes back – the human species evolved a gene for the metabolism of ethanol. They have all come here to consume ethanol, which they will then go home and, more or less successfully, metabolise. This is, of course, a parody of evolutionary psychological explanation, but it will serve to introduce a crucial point. It is, first of all, a necessary condition for the social practice of cocktail parties that humans have evolved the ability to metabolise ethanol. So, the evolutionary fact is, in some sense, a part of the full explanation of this phenomenon. However, it is pretty clearly not a very illuminating explanation. One of the most general problems with reductive explanations is not that they focus on a wholly irrelevant factor, but that they fail to get at what is interesting and illuminating about the causal, functional, or whatever, background to the event. There would be no cocktail parties if people could not metabolise alcohol, and perhaps the minority of people who lack this ability avoid such occasions. However, all of this is irrelevant compared to the information that these are all members of the Tunbridge Wells (Kent, UK) Contract Bridge Club, and this is their Annual General Meeting!

Let us move a bit further into fantasy. I suppose that the evolutionary function of alcohol metabolism is probably that it prevents one from being poisoned by very overripe fruit. However, suppose, for the sake of

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argument, that it was actually to enable people to go to cocktail parties.[1] Cocktail parties are, no doubt, good occasions for cementing social alliances, and two mildly drunk people may, for all I know, form stronger social bonds than their sober fellows. So now evolutionary history explains not only the possibility of cocktail parties, but also shows that this possibility evolved precisely because going to cocktail parties (or some prehistoric equivalent) furthered our ancestors reproductive interests. This additional hypothesis, nonetheless, does little to make the evolutionary explanation more relevant. It is still the calendar of the bridge club that provides the salient explanation. The hypothesised fact that cocktail parties at annual general meetings are an instance of a general strategy for increasing biological fitness would be interesting in its own right (I suppose) but reflect a curious misunderstanding if offered as an answer to the question posed by the alien with whom I began this illustration.

My aim in this paper is to investigate what constitutes the inadequacy of reductive explanations. I should first say what I mean here by 'reductive'. The paradigm of reductiveness that has been most widely criticised by myself and others is physicalist reductionism, the attempt to explain the behaviour of everything in terms of the properties of constituent parts and thus, ultimately and in principle, in terms of particle physics.[2] Here I mean more broadly the attempt to explain complex phenomena in terms of any one kind of factor. It might include, for instance, so-called 'vulgar Marxism', the project of explaining all cultural phenomena in terms of economic factors. Very often, though surely not in the example just cited, this broader kind of reductionism derives philosophical support from the more specific kind – this is surely the case with most genetic reductionisms. Here, however, I don't want to worry about physicalist reduction. One reason for this is that an almost invariable response to critics of genetic reductionism is to accuse the critic of some kind of sociological or cultural reductionism, a reductionism, if such it be, that is surely not supported by any kind of physicalism. This conception of the debate, at any rate, leads to one of the more notoriously sterile exchanges in contemporary intellectual life. Both sides accuse the other of one or other version of reductionism, and both generally claim that they, unlike their benighted opponents, really acknowledge a rich interactive conception of human life. Apart from the natural insistence that I myself advocate a subtle and richly interactive conception of human life, I do not propose to go too deeply into the intricacies of this debate. Rather, I shall explore what goes

[1] I here assume an account of biological function in the tradition deriving from Wright (1973), according to which (very roughly) to say that the function of trait T in species S is to f, which entails that the reason members of S have T is that f-ing increased their fitness.

[2] For details see Dupré (1993).

wrong with reductive explanations, with special attention to contemporary evolutionary psychology. However, I hope that my conclusions will have some relevance to the project of saying what, if anything, is wrong with comparably unifactorial culturalist accounts.

Returning to my original fanciful example, the first thing to note is that reductive explanations may fail to be relevant or appropriate even when they do introduce factors that are at least preconditions for the phenomenon in question. (Perhaps there is always some kind of reductive explanation that does this much.) This possibility is obvious for evolutionary psychology. To take an extreme (in the absurdity of the evolutionary explanation) and notorious example, there is no doubt that men have evolved both the capacity to commit rape, and a disposition, under some circumstances, to do so. This much is true for any behaviour that actually occurs, although the disposition to play the sousaphone or to extract cube roots is something that requires extremely special circumstances.

This points towards a general problem with inappropriately reductive explanations. It is not that evolution has nothing to do with the behaviour; indeed it is a necessary condition for any behaviour. It is rather that reference to evolution does not capture the gap in our understanding that requests for explanations of behaviour typically indicate. Most obviously, they do not tell us why one person performs the behaviour in question and another doesn't. It is a logical possibility, I suppose, that some gene, possessed by all and only rapists, causes them to rape people. Then the genetic story would hold the answer to the question why Smith, but not Jones, is a rapist. Even then the interesting question may be rather why Smith rapes today but not tomorrow, i.e. what triggers the biologically inclined to express their inclinations. However, certainly recent advocates of the evolutionary basis of rape have not provided any evidence for such a simple (and indeed wholly implausible) genetic story.

It may be helpful to consider what would make evolutionary explanations uncontroversially correct and illuminating. Imagine that for many years ancestral human populations were the subject of experimentation by aliens with the scientific skills typical of fictional aliens. In one experiment, the aliens scatter a few grand pianos around the Pleistocene environment, and also engineer a gene, which they transplant into a few ancestral humans, that facilitates rapid acquisition of a facility for piano-playing. More specifically, it directs the production of a brain module which, when activated by a few minutes contact with a piano, subsequently directs the expert playing of the piano. The gene is, by the way, engineered on the Y chromosome, and transplanted only into males. When one of these genetically modified humans encounters a piano he rapidly discovers how to make beautiful

music on it. This proves to be very attractive to ancestral females, and these males have great reproductive success. Unfortunately, a few millennia later the research team has its funding removed and the pianos are sold off to a promoter of dance bands on Alpha Centauri.

Back to the present. An evolutionist wonders why some people have so much more facility for playing the piano than others and also, being a traditional sexist, wonders why all of those are men. He hypothesises a gene on the Y chromosome, and suggests that this is a gene for musical ability that attracted mates in the Pleistocene. In addition, as we have seen, he is absolutely right! I want to suggest that the uncontroversially correct nature of this explanation derives from the coincidence of three factors (and these do not include the intervention of aliens). First, the behaviour is directly caused by a specific structure in the brain, secondly, the structure in the brain is caused by a specific gene (this could, of course, be a set of genes), and thirdly, the genes are there because they were selected for their ability to produce this brain structure. The natural piano players have a piano-playing module in their heads, it is caused by a specific gene, and this gene was the beneficiary of sexual selection.

Moving now from science fiction by philosophers to science fiction by scientists, we can describe circumstances under which evolutionary psychological explanations would be indisputably correct. Suppose, for instance, that rape was indeed caused by a particular module in the brain. This can be a module possessed by all males but activated only under certain circumstances (in which case, the explanation of rape will of course be incomplete), or a module peculiar to rapists. It must be a module produced by some set of genes, and those genes must have been selected in part, at least, because of their tendency to produce rape-generating brain modules. Generalising, we can identify the following three principles:

(i) evolution selects genes because;
(ii) genes build brains and;
(iii) brains cause behaviour that is selectively advantageous.

When evolution selects the genes that build the parts of brains (modules) that produce a particular kind of behaviour, and evolution selects them because of the fitness benefits of that kind of behaviour, we have the conditions for a perfect evolutionary psychological explanation.

It would be unfair, no doubt, to expect perfection in an explanation, and we should not, in the present case, expect these principles to be absolutely and unqualifiedly correct. The trouble is, however, that each of them is in general implausible or, more bluntly, false. In addition, given this lack of any fit whatsoever with the ideal explanatory conditions, it is doubtful whether

the explanation pattern has any use at all.[3] In a moment, I shall briefly explain why I take each of these principles to be false, but first I should mention one further difficulty with most actual evolutionary psychological explanations. The actual theories generally derive from speculations about the conditions of human life in the Pleistocene. Since it is usually admitted that evidence for the behavioural tendencies alleged to have evolved is equivocal at best, these speculations carry a great deal of weight. In fact, however, they are capable of carrying no weight at all. First, there is room for considerable doubt about what those conditions were.[4] Most interestingly, the general argument for the advantage of 'hard-wired' behavioural programming is that conditions were extremely stable for several million years, and hence that the same behaviours would remain appropriate. However, this assumption is open to serious doubt and if it is untrue selection may well have favoured far more flexible behaviour-controlling mechanisms. Secondly, even if we knew everything about Pleistocene conditions, this would not enable us to infer what would have evolved. For the only way of grounding such an inference is to assume that the behaviour that would maximise fitness will necessarily evolve. Once we abandon the optimum, there will always be a range of suboptima, and only empirical investigation can choose between them. However, no one, or almost no one, now supposes that the best possible will necessarily evolve. Optimality can, at most, be a good heuristic for generating hypotheses. Given the dubious empirical evidence for the modules postulated by evolutionary psychologists, this simple point is enough to dispose of most of their claims. However, I shall leave that for now, and return to the main thread of the present argument.

The question whether evolution selects genes is one about which many millions of words have been written and I won't add many more here. The present consensus, I believe, is that while it may be useful to record evolutionary change in terms of genes, items at many levels of structural complexity may be the targets of selection. The relevance of this issue is not, however, entirely clear. Evolutionary psychology is an atavistic theory, and the vehicle for the atavistic tendencies it promotes must be genes. However, these genes perhaps need only, in Elliott Sober's well-known terms, be

[3] I should perhaps reiterate, as it is a point that seems very easily to be missed, that I am *not* saying that only if each of these propositions were strictly true could evolutionary psychology be justified. The point is rather that evolutionary psychology offers a model and invites us to see the model as providing a useful account of some aspect of behaviour. If the assumptions of the model have little connection with how things really are, however, the model will be unlikely to provide a useful account of anything.

[4] Such speculations often come very close to what Steven Rose has nicely referred to as the 'Flintstone model'. That is, it assumes that life in the Pleistocene was roughly the same as life in an American suburb in the 1950s.

selected, not selected for.[5] The reason that evolutionary psychologists have tended to favour gene selectionist models of evolution is, of course, that if the genes were the actual targets of selection it would be easier to see how the optimal genes became established in our ancestors. It is not clear, however, that these could not become established, even given a more sophisticated conception of the processes of evolution.

What is clear, at any rate, is that the atavistic tendencies of evolutionary psychology must be recorded in the genes, and that these genes must be capable of building brains, or bits of brains, with the dispositions they allege. So, in what sense do genes build brains? Certainly genes are among the necessary conditions for the proper assembly of a brain, and differences in the genes may well make significant differences in the final structure of the brain. However, this isn't anywhere near what is required for the sorts of behaviour guiding modules that evolutionary psychologists postulate.

Purported evidence for the genetic control of behaviour comes not so much from evolutionary psychology as from behavioural genetics.[6] In a way, these disciplines are naturally antagonistic to one another, as evolutionary psychology is officially concerned with the search for human universals, whereas behavioural genetics is typically addressed to differences between humans – what makes some people homosexual, exceptionally smart or stupid, criminal, aggressive, etc. Actually, I think the hostility between these two approaches is illusory, partly for a reason I shall mention in a moment, and partly because behavioural genetics is responsible for the public perception that great strides are being made in the genetic explanation of behaviour, progress that is simply assumed without independent evidence by evolutionary psychology.[7]

It is worth digressing here to mention what is surely one of the shabbiest argumentative gambits in this whole area, the argument for genetic control of behaviour based on genetic defects. It is no doubt true that children with the gene, or one of the genes, for phenylketonuria will, if contrary steps are not taken, often suffer adverse effects on their behaviour.[8] They may, for example, develop lower intelligence than they would otherwise have. The same is true if during early childhood they are frequently hit over the

[5] See Sober (1984). This is the locus classicus for the multi-level view of selection to which I have just referred.

[6] I am indebted to Steven Rose for pointing out that the distinction between these approaches was dangerously blurred in the version of this paper originally presented to the Philippe Laudat Conference.

[7] It has become one of the commonplaces in this area, however, that such behavioural genetic stories are regularly trumpeted in the popular press and almost always withdrawn without ceremony in the professional scientific literature a few weeks or months later.

[8] The case is, however, considerably more complex than is generally acknowledged. See Kaplan (2000) for a detailed discussion.

head with a hammer. The inference that genes, in some interesting sense 'control' behaviour is as cogent as the argument from this latter observation that behaviour is controlled by little hammers inside the head.[9] Our concern is with the properly functioning production of behaviour, not the countless ways in which proper functioning can be derailed, and the evidence for specific genetic effects of this kind is virtually non-existent. The temptation to use examples of malfunction to argue for the genetic control of behaviour arises only because of the deficiencies of positive examples.

The general answer to the question about genes and brains is that genes are, of course, necessary for the production of a brain, but are, by no means, the only, or even in many respects the decisive, determinant of the specific characteristics of a brain. Enthusiasts for genetic determinism spend a lot of energy investigating correlations in behaviour between monozygotic twins. What they tend not to emphasise is the considerable *differences* between monozygotic twins. It is true that having a homosexual twin makes it more likely that you will be homosexual, but it makes it by no means certain. So, if there were a brain module that determined sexual orientation, it would certainly be a module the construction of which was not wholly under the control of the genes. All of which is of course obvious, because, since we are all good interactionists we all know that environment plays some role in development, as do genes.

Let me return to the point referred to above, that largely reconciles behavioural genetics and evolutionary psychology. One might suppose that genes build modules which, under some circumstances, will produce the behaviour of interest, or we might suppose that some genes produce, necessarily, a module for producing the behaviour, so that variability in the behaviour reflects variability in the genes. Crudely, it is cases of the first sort that provide grist for the evolutionary psychologist's mill, while behavioural genetics addresses cases of the second kind. It is true that behavioural genetics is currently committed to methodologies that preclude the study of supposedly universal traits, but there is no reason why evolutionary psychologists should be thus committed to universality. Paradigms of the two kinds are rape (a universal but not generally invoked disposition) and homosexuality (a genetic disposition found only in a minority of the population). Evolutionary psychologists make up stories about the adaptive function of homosexuality, for instance, through facilitating the acquisition of a position from which to do favours to kin. Presumably, if this were an

[9] I don't mean to deny that fascinating information can often be derived from damaged brains. Very specific behavioural deficits associated with damaged brains can give interesting insights into the way that tasks are organised in the brain. None of the arguments I have seen in behavioural genetics, however, come close to the standards of evidence that are needed for this kind of project.

adaptive strategy it would be one that would decline in value as it becomes more common, and kin become rarer. Hence, one might even predict a stable polymorphism. In addition, as I noted above, even this case cannot be of a deterministic gene, so the picture must be of a gene with partial penetrance that is a necessary but insufficient condition for the production of a homosexual orientation module.

There is no reason to think that the other kind of hypothetical module, the kind exemplified by the rape module that directs different responses to different situations, will be any less susceptible to developmental variation than quasi-deterministic modules such as the homosexuality module. Plus, for that matter, there is no particular reason to suppose that there will be less initial genetic variability in cases such as the rape module. So perhaps the perspectives of evolutionary psychology and behavioural genetics should not be seen as fundamentally disparate.

In light of this discussion, we can summarise the position for the allegedly evolved disposition to rape as follows. Men will have some unknown but variable disposition to develop, to an extent depending on the environment under which they develop, modules which, under some circumstances, will lead them to commit acts of rape. A combination, that is to say, of a particular genetic endowment, a particular developmental context, and particular life conditions, will lead to men committing rape. All I want to say about this is that it is something we already knew. Some men do commit rape, and those men have particular genes, particular upbringings, and particular life circumstances. We have, to put it mildly, no reason whatever to think that the really illuminating part of this story is the genetic part. Real empirical work, that is to say, might discover factors common to rapists, but there is little or no reason to go back down this complex causal chain as far as genes in the search for such factors. Fantasies about life in the Stone Age or the criminal activities of ducks[10] provide no such reasons.

I shall not say much today about the third premise listed above, that brains cause behaviour. My own opinion is that this is in some ways the most philosophically confused of the three. Very briefly, I think it is confused because it treats our understanding of human behaviour with an internalist, mechanistic model that is ultimately continuous with our understanding of the behaviour of planets, trees and beetles. However, or so I believe, in understanding humans we are interested in the reasons for actions rather than, as this parallel assumes, the causes of bodily motion. In addition, the proper individuation of actions requires the resources of language and meaning which, finally, depend not on the properties of the individual

[10] Mallards have been favourite examples of raping animals (see, e.g. Thornhill and Thornhill, 1992). For a trenchant criticism of this kind of argument, see Fausto-Sterling (1985).

brain but on networks of irreducibly social roles. This is not, I should insist, an appeal to mysticism, simply an insistence that different kinds of things may need to be investigated differently. Since this is a controversial line of argument, it is just as well, for present purposes, that evolutionary psychology falls apart before its dependence on this set of philosophical assumptions really comes into play. I do think, on the other hand, that considerations of this kind must be properly addressed if we are to move beyond the futility of such projects as evolutionary psychology. With this in mind, I shall say a bit more about what I take to be distinctive about human evolution.

My argument so far, if correct, shows that systematic connections between natural selection, particular genes or sets of genes, and categories of human behaviour, are improbable objects of investigation. However, even if this were accepted, might we not insist that the dispositions or capacities to interesting kinds of behaviour evolved, even if the circumstances of the exercise of those capacities is too complex to derive any definite consequences from the consideration of their evolution. This is, of course, undeniable. We evolved, and we, or some of us at least, have evolved the capacities to behave in the ways about which evolutionary psychologists theorise. The main thing that must be stressed here is that human evolution is not just the differential survival of genes (whether or not anything else is). Even if evolutionary psychology were right, and our basic psychological dispositions are constant across the human species and essentially unchanged since the stone age, actual human behaviour has changed dramatically much more recently, and the sense of 'evolution' relevant to my concession a moment ago must include the processes by which such changes have taken place. They must include, that is to say, cultural evolution or even simply the human history of the last few thousand years. I take it that these are substantially different processes from those of the purely biological evolution that preceded them.

It is often insinuated that to suggest that different resources are required for the explanation of human behaviour from those required for explaining the behaviour of other creatures or things is to embrace the mysterious or even 'spooky'. I do not propose to embrace any 'spooks'. I have mentioned the essentially social dimension of human action, a feature that differentiates it from the behaviour of non-language-using animals. I have mentioned also the extent to which the biological evolution of our species has been inextricably intertwined with processes of cultural evolution for the last several millennia at least. These are distinctive features of human evolution and call for distinctive modes of understanding. I might also mention that I take this not as a case for ('spook-free') dualism, but rather (equally

'spookless') pluralism.[11] The principles for understanding trees and beetles are at least as different from those appropriate to electrons or quarks as they are from those appropriate for human behaviour. If anything is 'spooky', it is the idea that the understanding of everything is somehow encapsulated, as if in the mind of God, in the ineffable profundities of the laws of physics. It is no surprise that only the mind of God is able to penetrate these supposed profundities.

This leads me to the first of my two concluding remarks. Reductionism, as I am very broadly construing it in this talk, is the search for simplicity. It is the attempt to understand complex phenomena in terms of a very few simple principles. This cannot, in general, be done. The failure of evolutionary psychology can be traced to its assumption of a sequence of such indefensible oversimplifications. The really crucial question which arises from such failures, I think, is this. The paradigms for scientific achievement are in the illumination of very simple systems, and in the construction of machines. The scientific understanding of naturally occurring systems has been found possible to the extent that those systems have relatively simple, even machine-like, behaviour.[12] The attempt to abstract investigative methods from these past achievements and apply them to objects of study as complex and unmachine-like as humans has not, I think, been a success. My own view is that while we can certainly hang on to such excellences of scientific method as sensitivity to empirical fact (something sadly neglected by such quasi-scientific projects as evolutionary psychology), only the incorporation of insights from a variety of very different approaches is likely to make really useful progress in this area. I am perhaps less concerned by this conclusion than I would be if I were not convinced that no general method can be abstracted from the successes of science anyhow.

Finally I would like to make a point that I generally find to be more unpopular than any criticisms of the scientific credentials of evolutionary psychology. This is to insist that deterministic views of human nature are not only epistemically bad, but they are politically bad too. I don't, of course, mean to deny that evolutionary psychologists are perfectly decent, well-meaning folk, and perhaps may sincerely believe that their understanding of human nature will help to alleviate human ills. I think they are wrong, as is their understanding of human nature. Elsewhere, I have emphasised the determinism tendencies of evolutionary psychology, and their inevitable tendency to cast doubt on the advisability of radical social

[11] As elaborated in detail in Dupré (1993).

[12] This will not, I hope, be interpreted as meaning that these achievements are easy. The solar system is surely a simple and machine-like system. Understanding its operations was hardly a trivial accomplishment.

change and to provide a prima facie case for the status quo.[13] Here, I shall very briefly mention two rather different issues, namely anti-empiricism and atavism.

It seems to me fairly obvious that if we are interested in improving the conditions of human life (perhaps quite generally an unfashionable idea these days) we need to know what are the current conditions and what are the processes by which the conditions of human life move from one state to another. These are enormously complex questions: those conditions vary greatly from place to place, and history and the social sciences have vast quantities of often confusing and conflicting suggestions to make about the processes. Still, there is no reason yet to suppose that the task is hopeless. The sort of thing that will impede this attempt is the insistence on naive and excessively universalistic theories of the human condition. Quite generally such insistence can, and plainly does, divert attention from the complexities of real empirical work on these questions. More specifically, the idea that we should focus on conditions in the Stone Age rather than the conditions of the present, the atavism to which I just referred, seems to me to have nothing valuable to offer this investigation, and serves merely as an obstacle in the way of scientific progress. Plus, of course, the idea that we are basically prehistoric creatures under the veneer of civilisation hardly encourages optimism about progress. Evolutionary psychologists do claim that their theories have bearing on social policies. They are mistaken and the attempt to apply their theories to social issues can only do harm. It is, I believe, the responsibility of their critics to insist upon this point as much as on the scientific inadequacies of these theories.

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[13] See, for instance, Dupré (1998).

QUESTIONS AND DISCUSSION

Robert Richards: So when you have those traits, which do not seem to have any purchase on success and reproduction, then I think you're perfectly right to be very sceptical about that, but take some other kinds of traits, something that is almost as ambiguous as rape. Because rape occurs under a lot of different conditions and in some cases you're not quite sure how to evaluate the behaviour and so on. But, as we were talking at coffee, what about maternal attachment? Now that's a fairly vague concept as well. It is the kind of response a mother will have for an infant. That attachment, and again, very often vaguely described, but one can focus on particular aspects of it. Let me just ask you – do you think this is ripe for evolutionary analysis? So that's the basic question.

John Dupré: Perhaps I just go back to one thing you said earlier. I don't see this as particularly obvious – that rape is a bad evolutionary strategy. I mean if you were good at it, and you did a lot, I suppose, particularly before people had invented morning-after pills or anything, I suppose it might be a very good evolutionary strategy.

Robert Richards: Well, but probably not evolutionary derived. You may have to look at the whole population to see whether it's a trait that it is. Talk about maternal attachment. That's a ubiquitous phenomenon. It has certain essential features, and the evolutionary advantage seems pretty straightforward.

John Dupré: I guess what I want to point to is not to deny that there is any evolutionary basis for maternal attachment. The question that I put to you after your talk – what do we learn more than the fairly banal empirical observation that people have certainly made before anybody had ever heard of natural selection, that 'mothers are generally attached to their children'? This is an empirical fact. It's one certainly that is entirely consistent with and indeed even implied by the theory of evolution by natural selection. So what do we learn, what have we learned, other than that evolutionary . . .?

Robert Richards: Well we've learned what the explanation is. The maternal attachment would seem to be the fact. Now we want an explanation or an account of it. Now a lot of explanations in science have that character that you said: to know that heavy bodies fall faster than lighter bodies, which is of course true of air resistance and so forth, but to understand the principles of fall does seem to have . . .

John Dupré: But look. The principles of fall have enabled us to put spaceships on the moon. The suggestion that mothers often take care of their children and that maybe that this has some connection with Darwinism adds absolutely nothing to what we knew already, it seems to me. And what have we discovered, what we maybe can say we now know, is that most

combinations of human genes and human developmental environments lead human females to have some attachment to their children. Well I think we knew that already.

Robert Richards: Well, we can continue this conversation. Just one thing to be pointed out. We know, for example, that when mothers are deprived of immediate behavioural interaction with their children, the attachment is less. That is something we didn't know before.

John Dupré: I'm sorry. We know that . . . what . . .

Robert Richards: . . . that the immediate contract that the mother had with her child if that is delayed a great deal, the attachment, the kind of what I would think of as an instinctive response of the mother to the child, is proportionately less. So that's something we didn't know before. We do know it now. But all of this . . . even though these are facts one would think of as a very simple sort, they do cry out, or they need an explanation. And it seems to me the evolutionary explanation is straightforward, and I doubt that many people in this room would deny it.

Dorothy Nelkin: Following up on your last point on social policy, from the material that I read in sociology and social policy, what I worry about most is the naturalistic fallacy: the move from 'is' to 'ought'. Yet after the last session, I was told that this is no longer a problem, that nobody worries about this anymore. So is this just simply a problem of my philosophical naivety, or does evolutionary psychology encourage the naturalistic fallacy?

John Dupré: Well actually, I'm on the other side of this argument from what perhaps you assume. When I say things like this, what evolutionary psychologists almost invariably say is 'but you're committing the naturalistic fallacy'. Sometimes they say you're committing the 'naturalist fallacy', which, I take it, is taking real animals seriously or something. But I take it that this has become a very quick way of denying any responsibility for the things you say. It seems to me clearly false. Just looking at the kinds of examples, and I'm sorry if I carry on with rape, but that seems to be such a striking example, I mean to say that 'men are naturally disposed to rape' certainly may not have the consequences that one would expect. One consequence that is suggested is that we should have more severe penalties, because whatever we do, men will commit rape, and the only way we're going to discourage them is by threatening castration or execution or something to those men who do. But it seems to me still that when we're looking at this as a social policy issue, and it's a very serious one, I don't think it's helped by having unfounded stories about where it comes from. So I do think the naturalistic fallacy *is* a fallacy.

Steven Rose: I should say that most rape is not conducted against the category of fertile females.

Eugene Dowdle: You dismiss the interpretation of behavioural abnormalities with genetic defects. For example, the XYY genotype that is consistently criminal. Is that not evidence for genetic inferences on behaviour?

Steven Rose: Well I think there are a lot of problems with that claim. There was a huge statistical error made in the original presentation of that, which I think has since been widely recognised. I take it that the likely story is that this chromosomal abnormality tends to produce a lower intelligence. And people with lower intelligence tend to do less well and be more likely to end up in criminal activities.

Steven Rose: . . . or to be caught.

John Dupré: . . . or to be caught. Indeed. But look – the argument was not dismissing genetic abnormalities as affecting behaviour. But generally when people say 'we've got lots of evidence for the genetic abnormalities that cause characteristic deficiencies in behaviour'. My point is only that this is not even the vestige of an argument for the genetic control of behaviour in properly functioning people without those kinds of serious genetic abnormalities.

Panayiotis Tsakalis: You said that what we need is to discover the reasons for human action, and not the causes of bodily movements. So, is there no common ground between reasons and causes, either ontologically or conceptually? And second, you suggested that, in order to make that discovery we need to study the meaning, which depends on networks of social relations and not on brain states. Do I understand correctly what you have said? Do you mean to say that mental states or brain states are totally irrelevant to the specification of meaning?

John Dupré: I think I said this is a somewhat controversial set of issues, but to get an idea of what I'm saying. I take it that when – this is a horrible standard philosophic example – I raise my arm there are characteristic muscular, neuronal processes that go on when my arm goes up. At the simplest level, all I'm pointing to is the fact that in society, which has many rich conventions and interactive forms of behaviour, there are many different things I may be doing by raising my arm: I may be hailing a taxi, I may be waving to somebody, I may be saying 'please, I'd like to ask a question'. There are all these different things and the explanation of why I raised my arm is not adequately given by saying certain contractions happened in my muscles. What it requires is saying what I'm doing. To say what I was doing in most of these cases requires that you understand a whole system of meanings which I believe are held in place by a system of social rules and so I think that there one is moving to a quite different level of causation and explanation.

Alex Rosenberg: John, do you think that some forms of mental retardation are caused by the single-gene defect that leads to fatal PKU?

John Dupré: I imagine that that's probably so.

Alex Rosenberg: Do you think that the sickle-cell anemia is the result of double-recessive single-gene deletion in the . . .

John Dupré: I understand that there's good evidence for that, yes.

Alex Rosenberg: I actually don't see how you can endorse those claims on the basis of the arguments that you gave in your paper, because the arguments you gave in your paper would undercut those claims as effectively as they undercut the claims made by evolutionary psychologists.

John Dupré: Well, can you elaborate? I have . . .

Alex Rosenberg: Yes, because you're requiring of evolutionary psychologists that they establish that the genes which they identify as the underlying causes be more than insufficient, but necessary, components of a set of conditions which might be sufficient in the circumstances but not necessary. And the most I think that one could ask of evolutionary psychology is that (it) identifies interesting and fairly robust conditions, as in the case of human physiology and single-gene deletion defects. And you're demanding a whole lot more, and of course the evolutionary psychologist can't produce it, and it's on that basis you stigmatise it as pseudo-science.

John Dupré: I don't quite know where the 'interesting but fairly robust' came from. I've conceded throughout this talk a couple of points, that there are causal determinants of people's brains that included genetic determinants. What I'm denying is the evidence for any interesting robust genetic determinants that are relevant to the kinds of behaviours that they're (frequently) talking about.

Alex Rosenberg: You're just saying that the evidence isn't in, not that there's a fundamental methodological error involved.

John Dupré: Well I'm saying that there are fundamental methodological errors in the arguments that they present for supposing that there are the kind of genetically caused modules that they produce. Now my science fiction concedes that there are conditions under which there would be genetically casual modules, causing particular kinds of behaviour. I don't say that's a conceptual impossibility. So yes, if you like, I'm saying there's no evidence of the . . .

Alex Rosenberg: So you are saying that the evidence is insufficient or that they're guilty of methodological sins.

John Dupré: I'm saying both.

Alex Rosenberg: Then why are you not open to stigmatise the physiological research with the same methodological error.

John Dupré: Because I don't think that there are methodological sins in those cases. You take sickle-cell anemia. The whole causal story is largely known. If somebody came up and gave me a set of genes, and a set of developmental pathways that led to a module that could be shown to fire and produce a kind of chasing behaviour when confronted with this rape-victim, then . . .

Alex Rosenberg: Aren't you asking evolutionary psychology to run before it can walk?

Steven Rose: Can I just make a distinction here, because I think there's a confusion between the claims of behavioural genetics and the claims of evolutionary psychology which is running partly through this. It's the behavioural geneticists who are primarily concerned with differences (of the sort Alex is talking about), and they're guilty, in particular, John's sense, of one sense of sins, whereas evolutionary psychologists are talking about the reversals and are therefore not interested in those particular genetic defects that you're talking about. The issues are comparable. There aren't distinct camps within the genetic community.

Stan Shostak: I regret, and this is a reproach, that you chose to use rape as a model for your talk. I think it's a brutal thing to talk about and although I believe I am sympathetic to your points, I would rather that you had chosen to make then in another way. To use sex as a vehicle for talking and brutal sex as the vehicle for talking about abnormal human behaviour or genetically controlled human behaviour, I think is something we ought to be more sensitive to. But beyond that, knowing very little about evolutionary psychology, I have a question. Is it your view that there is such a thing as normal human behaviour? And in which case you may set up these alternative paradigms? But if it is your view that there is no such thing as normal human behaviour, what are you talking about? When Mendel began the study of genetics, he had pure lines and genetics was a study of deviation from a pure line without any assumption about normality. Now, in *Drosophila*, of course, we talk about 'wild types' when we mean normal, but indeed in the case of human beings you neither have pure lines, nor wild types, so what is your best comparison?

John Dupré: Start with the first question. I'm certainly sorry if this is offensive to people. I guess my only defence is that being as it is currently a very widespread discussed claim by evolutionary psychologists. But perhaps one should let that be and not sink to the level that one's opponents may have fallen. And as I said, I'm certainly sorry if I've offended people. I don't really understand the second part of your question. I am reluctant to say there is no normal behaviour because I think there is a kind of bedrock of, for example, the example earlier of the mothers taking care of their

children, which I think one could perhaps call normal. But generally I am extremely critical of the assumption of normal human behaviour, and one of the fundamental differences I have with evolutionary psychology is that evolutionary psychology is all about trying to characterise normal human behaviour, human behavioural universals. I think the evidence for these behavioural universals is extremely slight, and empirical evidence seems to go the other way and suggest that human behaviour is enormously variable under different circumstances. On the whole, without making the extreme statement you perhaps invited me to make, that I don't believe that there is any normal human behaviour at all, I think there's a great deal less than, say, evolutionary psychologists claim.

Sohotra Sarkar: I just want to emphasise something that Steve said and then add one thing to it, which is that I don't think it's fair to look at evolutionary psychology as being the latest thing of genetic determinism, which is more connected with the behavioural genetics part, and evolutionary psychology adds the whole idea that the behaviour is selected for which you don't have inside the behavioural genetics camp and more of the evolutionary psychologists sociologically resist the behavioural geneticists, because they think they're talking about differences, and not about universals. With respect to the differences, like Alex, I don't understand why you're objecting to behavioural genetics following exactly the same thing we follow – looking at differences in traits, to trace back things to genes, that is you use abnormalities, as you routinely did with *Drosophila* to find where some particular gene was controlling hairiness in legs or something like that, and that seems to be exactly the strategy you always follow.

Steven Rose: I'm prepared to confess to being a little sloppy in moving between evolutionary psychology and behavioural genetics. Evolutionary psychologists do believe that genes cause behaviour, and conveniently can appeal to work carried out by people who belong in the behavioural genetics camp. But I agree, they should be kept separate.

Armando Aranda: My points, perhaps, are in defence of John Dupré in the same sense that by going to a similar level, but talking about complex things being controlled by genes, and about the technology used for establishing this situation, for example, sickle-cell anemia, or whether hair colour is controlled by genes or not. In molecular biology, many of us are ready to accept that yes, it is true that a gene controls sickle-cell anemia or whatever, and there is a perfect explanation for that. But then you also can do a knock-out experiment, and knock out the Hox 11 gene from a mouse, and then the mouse develops without a spleen. And it will be very silly to believe that Hox 11 is the gene for spleens. And actually, there are papers published claiming that Hox 11 is the critical gene that in some way

codes for the pathway for the development of the spleen. And it happens – it is a fact. But I think it's very difficult to infer from such a fact that there really is a gene which in itself has in some way the coding potential for a very complex structure such as the spleen.

John Dupré: I take that as just a remark in support of what I'm saying . . ..

Terrence Brown: Well, I continue to have a lot of trouble with the application of explanatory strategies to the wrong level. I don't think that the sickle-cell example has much to do with behavioural examples, because sickle-cells 'behaviour' is not meaning-mediated.

John Dupré: I agree.

Michel Morange: Another example of knock-out which is interesting concerns what you were talking about. There is a mutation in the mouse, fos-B gene. When you have mutated female mice, they have completely lost their maternal instincts, and they don't mind the pups. So apparently there is a link between a single gene and maternal care. But mind when you look at this gene – it is expressed in a part of the brain, the hypothalamus, which is very important for all kinds of behaviour. What happens is that when this gene is not functional, you have a development or an activity of this structure which is not correct. So probably the behaviour is unable to develop normally.

Steven Rose: So this would be another example of the error of arguing from genetic defects to genetic control of behaviour.

Alex Rosenberg: The research on the knock-out of this particular gene and its effects on the failure of mice to engage in maternal behaviour is very beautiful research, and very sensitive to a variety of different alternative competing explanations. And the research has been at pains to show that the competing alternative explanations can be excluded so we have what looks in the mouse to be very narrowly a gene that shockingly controls maternal behaviour, feeding behaviour, and not, for example, olfaction, or cognitive processing, or recognition of kin, or anything else like that. It's quite remarkable for the sensitivity of the researchers to alternative competing explanations.

Michel Morange: Yes, but you have another mutation in another gene which is involved in dopamine metabolism which affects the same brain structure, and which gives rise to exactly the same problems with maternal behaviour. So it's an argument to show that you have nothing specific with maternal behaviour but something specific with one brain substructure.

Alex Rosenberg: I think I'm going to have to give you my reference, and you're going to have to give me your reference.

Michel Morange: Exactly.

Albert Tauber: I'd like to give a reference that everyone knows. Sickle-cell is commonly evoked as a great reductionist victory. I treat many patients with sickle-cell anemia, and I can tell you that the genetic defect is not the disease, because the disease manifestation is highly variable. Some patients have an enormous number of pain-crises. Some patients have a lot of haemolysis: that's red-cell destruction. Other patients have pulmonary hypertension. And it's obvious that the disease that we call sickle-cell anemia is an extraordinarily complex phenomenon interacting with many many different systems and many other genes. And the bottom line, from a clinical perspective, which is the phenomenon that we call sickle-cell anemia, is that the sickle-cell gene is necessary but not sufficient for the disease.

Claude Debru: Yes, a very small remark, which has been already done in a way. I didn't understand from Michel Morange's argument on this gene that this particular gene controls maternal behaviour. I understood only that it controls hypothalamus development, which is something perhaps different. What about this gene in males? Has it been made knocked-out in males?

Alex Rosenberg: The knocked-out in males has no effect on behaviour, in male mice.

David Hull: I think you're off the hook.

Round Table Discussion 2: Chair – Marc Van Regenmortel

Marc Van Regenmortel: I want to ask Alex whether he believes that explanations must necessarily possess causal efficacy or efficiency. In other words, if you take a reductionist approach, must you necessarily go on believing in linear causality . . . ?

Alex Rosenberg: I think that all parties to the dispute had better agree on what counts as reasonably satisfactory explanations. It's unlikely that they will be able to agree on a full account of the nature of explanation, but they ought to at least agree on the paradigm cases of good explanation, and then go on to suggest that the explanations that they demand, or that they reject the possibility of, meet some agreed-upon criteria drawn from these paradigm cases. Certainly it seems to me reasonable to demand of scientific explanation that it identifies contingent nomologically connected distinct events, processes and states. Whether you want to call these causal or not is a terminological matter. I'm friendly to such a terminology. Others are not. And I'm not prepared to allow that the debate between reductionists and anti-reductionists turns on that matter. I think it might well turn on alternative accounts of explanation. Because, while the anti-reductionist holds that certain explanations are perfectly adequate, complete, and cannot be improved upon, and the reductionist denies this, the dispute between them may turn on the nature of adequacy conditions for explanation. And if that's the case, then our dispute isn't particularly one about methodology or metaphysics, as Sahotra pointed out – it's about what counts as good explanation. I for one don't think that's a very interesting dispute in the present context.

Marc van Regenmortel: I am asking that question because as you know the complexity jockeys are saying that linear causality is no longer applicable.

Alex Rosenberg: I didn't address your point about linear versus non-linear causality. I guess for the last three generations, opponents of quantitative and other kinds of empirical natural and social sciences have been making heavy

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weather by a series of fashionable 'nouvelle vague'. Whether it's catastrophe theory or chaos theory or systems theory, and in each case, I think, there have been vast exaggerations about the degree to which either of these theories can handle complexity or the degree to which the complexity phenomena are not linear and therefore not available to reduction or not otherwise understandable. Causality seems to me to be a species of that kind of mystification and obfuscation. I don't see any incompatibility between complex feedback and feed-forward systems and plain old Humaen causation. Naturally, these will be more complex by degree than push–pull billiard ball models of, say, gases. But there's no reason in principle why we shouldn't be able to apply the kinds of approaches which enable us to explain the kinetic theory of gases in terms of billiard ball models to very complex feedback and feed-forward systems. Even chaotic systems with attractors, seem to me not to be recalcitrant to the kind of understanding that has been hitherto successful in physics.

Sohotra Sarkar: I want to add something to what Alex was saying. It's that there is a certain kind of anti-reductionist consensus or hysteria, however you want to describe it. And there are two things that have been said here a couple of times that needs to be unpacked. One of which is that the existence of feedback by itself is not an argument against reduction. In fact, to get proper macromolecular reduction going in molecular biology and for philosophers to begin appreciating it, a crucial event was the formulation of the operon model, which showed that feedback phenomena can be explained reductionistically. The second one is that several times both yesterday and today there has been this idea that co-operative phenomena by themselves provide challenges to reduction. And that too is clearly incorrect. Co-operative phenomena, somebody said at one point, involves metaphorical talk. It doesn't. It's simply a case where there's non-linearity in the interaction between parts. Sometimes, co-operative phenomena cannot be given reductionistic accounts, as for example, in superfluidity or superconductivity. But the real villain there is not co-operativity – the real villain there is entanglement: that you can't individuate the parts of a quantum system properly.

Another example, and here Claude Debru will probably disagree with me, where co-operative phenomena have been given reductionistic explanation very, very successfully is the allosteric model, where, even though the model is complicated, which is a separate issue, it's purely mechanistic interactions that ultimately do give explanation.

Claude Debru: What I wanted to say is that such explanations make things understandable, but surely not amenable to calculation. That's the difference.

Sohotra Sarkar: Yes, but what you call the WC model is a quantitative model.

Claude Debru: Not quantitative: a statistical model based on correlations, not causation, I would say.

Alex Rosenberg: I think the example of allosterism that you gave is particularly pressing. Once we understood the interaction of the subunits of the haemoglobin with DPG and the sigmasoidal character of oxygen-uptake in the lungs and output in the cells, we have what was in fact a beautiful reductionistic explanation of a kind of phenomenon, hitherto claimed to be not understandable from the point of linear causation. There's nothing particularly complicated about this once we unpacked all of the parts into their constituent chemical interactions. Whether its lock-and-key or allosteric interaction, we now understand this phenomenon from a reductionist point of view.

Robert Richards: Not again to jump on John too much, so I'll jump on Steve Rose simultaneously. Are there any traits, either simple behavioural traits, responses that human beings exhibit on a behavioural level, that you would think are adequately accounted for in evolutionary terms?

Steven Rose: Can I just talk about haemoglobin first. It addresses precisely the same point. The fact that one has got a good chemical explanation of how haemoglobin functions in particular contexts as an oxygen carrier and so on is actually a classical example of a good reductionist explanation of particular properties of a molecule. What is does not and cannot address, and this is, I think, where the reductionist explanations cannot be complete, is the function of the haemoglobin as an oxygen-carrier in a living organism. Because that is embedded in the properties of the organism and indeed its evolutionary history and current physiology and not embedded in the properties of the haemoglobin in isolation. And it is that crucial issue where it seems to me that your insistence on causal explanation is inadequate because it is not complete. It cannot answer the functional question that is being asked by psychologists, or is being asked by evolutionary biologists. Now let me turn, if I may, to the question. I think the question is wrongly posed in all of these contexts, because the assumption is that there is a trait. It's very hard to define what a trait means in behavioural terms. It's pretty hard to define what a trait means at the level of a living organism, anyhow. And to reduce the trait to either evolution or to genes is to miss what Susan Oyama calls the 'ontogeny of information'. We just need a different way of thinking about these processes that understands the unfolding of an organism, I would say autopoietically. And also the raw materials which are given by genes and environment and its own experience. And it's that which creates, as it were, the phenomenon, which you then try

to partition out. So, of course, evolution is fundamental to all of these processes. So is development, in the sense that I'm using it. I'm not sure it's quite the same sense as Jim was using earlier on today. And so is the context: social, cultural, for humans, technological within which those developments are embedded. So it's the partitioning out in that sort of way which I'm . . .

Robert Richards: But isn't that what scientists actually want to do is try to partition out what are sort of global effects to try to find particular causes that account for various aspects of those effects.

Otherwise, you wind up saying: 'everything is caused by everything else', and that doesn't seem too terribly helpful.

Steven Rose: To some extent, everything is caused by everything else, and of course . . .

Robert Richards: But it's not . . .

Steven Rose: The task of good science, it seems to me, is undoubtedly to try and find a determining explanation of the phenomenon, at a level which actually makes sense in terms of the questions that we're asking. And Lisa Lloyd put forth a much more elegant version of that earlier on today. It depends on what you want the explanation for. If we want the explanation to understand the relationship of genes to Huntington's disease, for example, to take a good bit of determinist genetic causation, then we have to understand the genetics. If we want to know why there's an incidence of drive-by shooting in Los Angeles, we don't need to know why there's an incidence of drive-by shooting in Los Angeles, we don't need to know the genetics of aggression, insofar as there is a genetics of aggression.

Robert Richards: This is just a simple question about – are there behaviours, not drive-by shootings in Los Angeles, but simple behaviours that human beings exhibit, that seem to be most perspicuously analysed by giving an evolutionary adaptable account? And this won't be the account. And not only that – any evolutionary account, I think we all agree about this, is going to take into perspective the environment, because evolution, we presume, does count on certain constant environments in order to exhibit the kinds of effects that it can select.

Steven Rose: So we've got everything again.

Alex Rosenberg: No, we don't have everything. We make distinctions about things that are more important and things that are less important . . .

Steven Rose: I agree with that. But then let me . . . .

Robert Richards: The phases of the moon probably have an effect on various traits that we exhibit, but we think them unimportant to consider.

Steven Rose: The problem is partly defining what is an adaptation, what is an exaptation, and what is a spandrel, in the sense that people have

used it before. The second problem is to assume that everything that is evolved by a mechanism of either natural of sexual selection, as opposed to contingency, drift, molecular drive, many of the other factors which generate evolutionary change. It's the reduction of the ways in which we are offered a monocasual explanation of evolution (which means change over time) which I think some of us object to in this particular context. As a Darwin scholar, you yourself will remember that Darwin said in this particular context 'great is the power of steady misrepresentation'. He never argued that natural selection was the only mechanism of evolutionary change, and I don't think we should either.

Robert Richards: He certainly did not. But on the other hand, those were the particular kinds of explanations that he specialised in and thought the most important. And he did on individual traits, I have to say, and tried to give and account for them which was a reasonable account.

This may be a bit orthogonal to the discussion going on, but I keep being bothered by three things. One is the idea that explanations are casual – that causes are explanations. Explanation is of higher logical order than cause. It's true that you may give a causal explanation, but that has to do with a logical co-ordination of causal effects. Second, explanatory strategy should be specific to level, and how you explain subatomic particles has very little to do with how you explain human behaviour, as far as I'm able to tell. And I just would like to say one other thing, that might make the discussion even more confusing. Nobody's talking about what I learned was reduction from the lower to the higher, but I see it all the time particularly in my analytic colleagues, where they give intentional psychological explanations to things that are not intentional. We saw the same thing in teleology, so 'reductionism', if you want to call it that, can go the other way. Such explanatory mistakes, however, really represent misattributions of an explanatory strategy to a given level. So levels remain really important when we're trying to talk about all of these phenomena.

Robert Williams: Just on the haemoglobin thing, very quickly, I totally agree with Steven. I don't think, I'm afraid, that the explanation that can be given is satisfying as far as the living organism is concerned, and the reason is the methodology that is used is the study of isolated molecules in crystals, and you can't therefore find out the physiological explanation. Neither can you do anything about the rate constants, which are necessary. Neither can you solve the values of the equilibrium constants, in this sort of procedure. And you just have to go to statistical procedures in order to do that, and then you remove yourself from necessary molecular explanation which you have just analysed. So, let me just say – that is one sort of thing which I have said before, and I would say again, that once you come into this sort

of area, you're in really grave difficulties with a simple reduction. Another slightly more complicated level, and then you're all right. Nobody worries much about haemoglobin. So I'd like just to say – forget it. Can I introduce a completely different thing, which is where it may join the course of the day? What I'm worried about is the way we're discussing evolution. I think Maynard Smith divided up the major steps: and what he did was to say the last major step that he put down was the development of human beings. There's a suggestion then, which the humanities definitely love, that in some way the human being is different. The question I want to know is – is that what this community really believes? Is it somewhat different? And there is something special about it in that the way in which the brain has developed, which is uncommon, different from all other species, makes it such that in the human population, the individual becomes so important relative to the group, that in fact the matters that are applied to groups are not necessarily sufficient or useful when applied to human behaviour. That would seem to me to come out of that last lecture we had, that somehow or other the human being is something special, and maybe different. And it could be that that is the case. That would mean that something is special, and maybe different. And it could be that is the case. That would mean that something is special once the brain becomes very large indeed and can dominate the organism.

Sohotra Sarkar: Let me go back to the haemoglobin example, both with respect to you and what Steve Rose said earlier. I think there's some equivocation going on here about the word 'function'. If what is actually being said is that we are worried about what interactions of haemoglobin are with the rest of the circulatory system, with oxygen, carbon dioxide and things like that, I do not see any problem in giving purely individuated, physicalistic explanation, that kind of reductionist explanation. If by 'functional' what you're talking about is, why does haemoglobin have the form it has, you ask the evolutionary question, the question of origin, then clearly we need something else, we have to fall back on natural selection, and that explanation is clearly not a reductionist explanation. The interesting question here is whether that can ultimately be embedded, as Alex Rosenberg would want to, in a chain of things that you can explain mechanistically?

Alex Rosenberg: Why can't you even give a reductionist explanation of the functional character of haemoglobin by appeal to considerations about lay-haemoglobin (?) and cross-species transfer, and the role of the globin centre of nitrous oxygen fixation in . . .

Sohotra Sarkar: I can give a lot of explanations about why, say, a mutation in the haemoglobin gene right now would not be selected for

using that. I'm still not giving you a complete story of how haemoglobin happened to have arisen in evolutionary history, and that's a lot more complicated. It depends on the question being asked.

Alex Rosenberg: But that's entirely reductionistic.

Sohotra Sarkar: The second one is, the first one you might be able to give depending on the question.

John Dupré: This is just a response to Professor Williams' last remark. I did certainly say in that talk that I consider human evolution to have taken us to a different state from pre-human evolution, but I think the opposite of what you said. What I think our brains have enabled us to do is actually become more complexly dependent on the social rather than the more individual and that's what I was trying to get at with very brief remarks about the importance of language and meaning. Can I just say one other thing which is a totally different point but which we might want to discuss at some point as a kind of 'meta-comment' on this meeting. Sohatra said a few minutes ago – he referred as several people have, to the anti-reductionist consensus. My perception has been that there is a very strong anti-reductionist consensus among the biologists in this room, but I think Sohatra was talking about philosophers. I take it we have a fairly good representation of contemporary philosophers of biology and my impression is that we have about a bell-curve distribution with a couple of clearly reductionistically inclined, a couple of rather strongly anti-reductionistically inclined, and a number of people who want to maintain sort of modulated positions in between. So I would say that there is no anti-reductionist consensus among philosophers, but apparently there is among biologists if this sample is obviously maybe less representative of biologists than the sample of philosophers of biology.

Steven Rose: I'm not aware that there is an anti-reductionist consensus amongst biologists – I seem to regard us anti-reductionists as something of a minority. But can I come back – and I'm sorry Bob, just to come back to the haemoglobin example because I think it is a very instructive one – I think that what I'm uneasy about is the assumption that there is one, and only one type of explanation which is appropriate for understanding and this relates to what Sohatra was just saying. Let me just suggest that if one is interested in any particular biological question, for example, the haemoglobin molecule, there are at least five types of explanation which you can offer of it. One is, as it were, what I think was called earlier on the physicalist one – how can we understand the properties of this particular molecule in terms of the amino acid chains, etc., etc.? The second is an evolutionary one – how do we understand the evolution of this particular molecule in this system? The third is a developmental one, which is a non-genetic one. A fourth is a

physiological one which is the functional one, that is what function does it fulfil in the context of this living organism? A fifth is always the ecological one in terms of the organism in its environment. Now those explanations, it seems to me, are not mutually competitive, but they are not reducible or collapsible into any one sort of explanation. So this is an argument that biology has always existed through epistemological pluralism and we should be allowed to continue to do so because we have different purposes for which we are asking the questions.

Marc Van Regenmortel: I would just like to add one – if I remember correctly, there are only two amino acid residues conserved in all the haemoglobins. That's also an interesting question.

Alex Rosenberg: It's not so different since mutations will be allowed to persist over time and in fact they will multiply over time if they do not harm the functional activity.

Chapter 13

The Ethical Imperative of Holism in Medicine

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A morality play

The setting – municipal hospital emergency ward. Dr Alfred Tauber is taking morning report from the resident on-call, Jim Watson.

Tauber: 'Good morning, Dr Watson. Tell me about the cases last night'.

Watson: 'Well, we were quite busy. There were seven people admitted to the hospital'.

Tauber: 'Fine. Tell me about them – but be brief!'.

Watson: 'Here, let me give you the list'. The resident hands Tauber the following roster:

(1) *16 year old Black man with a gunshot wound to the buttocks; no past medical history; taken to the operating room.*

(2) *24 year old Arab woman with threatened pregnancy; admitted to High-Risk Obstetrics.*

(3) *30 year Black man with priapism following sexual intercourse; admitted to the Urology Service.*

(4) *12 year old Black girl with chest pain, shortness of breath; fortieth hospital admission; placed in the Intensive Care Unit.*

(5) *5 year old child with jaundice; otherwise asymptomatic; admitted to Pediatrics.*

(6) *40 year old Black woman with acute left-sided paralysis and slurred speech; admitted to the Neurology Service.*

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(7) *27 year old Black man with severe left hip pain; no trauma; no fever; admitted to Orthopedics.*
Tauber: 'Hmm. Interesting. They each have the same disease'.
Watson: 'What! How do you know?'.
Tauber: 'Elementary, my dear Watson. Elementary'.[1]

Introduction

Medicine poses a particularly important case for the holism–reductionism debate. In many ways, the organismal basis of medicine, that is, the commitment to viewing and treating the patient in his biological entirety is a fundamental demand of clinical practice. We can hardly be satisfied with 'fixing' one problem and leaving any number of other dysfunctions to fend for themselves. In short, the physician is trained to address the biological entity as a whole – going from molecule to organ and finally to integrated systems. Integral to the physician's science is this commitment to 'holism', so while focusing on a particular derangement, the framing of any disease must account for all other systems which by necessity interact with it. This is one way of looking at the limits of reductionism, one that may fairly be regarded as the epistemological question, or expanded to methodological or theoretical reductionisms if taken by such classifications. However, here I wish to remind us that the holistic construct is ultimately, at least in medicine, a moral demand. The mandate to integrate does not stop at the physiological, but extends 'up' to the highest faculties of being human – the social, the psychological, the moral and the spiritual. So, in short, the epistemological challenges or limits of reductionism in the biological sciences and medicine are not my topic. Instead, I will present another basis for considering the legitimate claims of a holistic approach in medicine.

My basic claim is that medicine, by its very nature, demands a holistic understanding of the organism and a holistic approach to the care of the patient. This orientation is not only epistemological, indeed, it is also a moral imperative. This exposition first draws the historical outline of the Nineteenth century roots of reductionism and its parent philosophy, positivism. From that discussion, I will offer a sketch of how these philosophies altered the basic ethos of medicine and thereby posed what I take to be the essential crisis in contemporary medicine – the direction of its moral orientation. Within this context, I emphasize what I believe are the major implications of the debate about reductionism, and allude to an agenda to solve our impasse. Perhaps fittingly, given the place of this meeting, I acknowledge that Emmanuel Levinas has guided me in this venture (which is explored in greater detail in Tauber, 1999).

Before I proceed, however, note an important caveat about the opposition of holism and reductionism – there is an unsteady balance between holism and its constituent opposite, reductionism. Holism is ultimately defined in contrast, and in context, with the prevailing reductionism of the era: holism and reductionism are inexorably coupled and cannot be defined independently of each other, and thus as Charles Rosenberg wryly observes-, 'the more one looks at Twentieth-century holism, the more elusive it becomes, the more it dissolves and reconfigures itself into its opposite' (Rosenberg, 1998, p. 348). So before becoming entangled in attempts at definition, let me state clearly that I will not be preoccupied with defining holism beyond the general rubric of 'considering the patient as a person'. How and why that definition suffices will hopefully become clear as I develop the moral argument. The second key precept, one that undergirds my discussion, is that I do not argue *against* reductionism, but rather I embrace a pluralistic approach. In general, the case for holism is not an either/or proposition – accept holism rather than reductionism. I understand holism to warn against premature and unsophisticated reductionism, where the limits of a reductionist approach are either unknown or unacknowledged. In my discussion, the moral consequences of not balancing reductionism with its necessary alternative is emphasized.

Historical roots

Positivism

The historical development of Western medicine as it became a product of the scientific ethos of the mid-Nineteenth century is well known. At that time, two philosophies of science – positivism and reductionism – emerged which decisively shifted the character of medicine towards a new scientific ideal. Neither were totally novel philosophical strategies, indeed each have venerable histories dating back to at least the early modern period, but by the 1850s they were articulated within a new context and were joined to set a new agenda for clinical medicine. By the end of the century, medical training had been transformed and application of a laboratory-based approach to therapeutics established revolutionary aspirations for medical practice. While there are strong social and political reasons for this shift (Foucault, 1963), I wish to emphasize the reification of the patient as a consequence of positivism, and highlight the moral consequences of that approach.

For the past century and a half, mainstream science has assumed a positivist stance, one which increasingly seeks to describe the world in non-personal terms (Simon, 1963; Kolakowski, 1968). Positivism carries several meanings and has been notoriously difficult to define, yet certain precepts

may be identified, especially as espoused in its Nineteenth century format. Foremost, it championed a new form of objectivity, one that radically removed the personal report to one that was universally accessible. Thus knowledge, to be 'true' and 'real', must be attested to by a community of observers who shared a common observation. This move from the private sphere of experience to a communal one had begun at the dawn of modern science, but in the mid-Nineteenth century this ideal of truth became clearly enunciated as a scientific principle. Thus positivism sought a collection of rules and evaluative criteria by which to distinguish true knowledge from what Wittgenstein famously called 'nonsense', a normative attitude which would regulate how we use such terms as 'knowledge', 'science', 'cognition' and 'information'.

As developed in the 1850s, positivism came to be understood as a philosophical belief which held that the methods of natural science offer the only viable way of thinking correctly about human affairs. Accordingly, empirical experience – processed with a self-conscious fear of subjective contamination – served as the basis of all knowledge. Facts, the products of sensory experience, and, by extrapolation, the data derived from machines and instruments built as extensions of that faculty, were first ascertained, and then classified.

Positivism contrasted with, indeed, was constructed in opposition to, the romantic view of the world by denying any cognitive value-to-value judgments. Experience, positivists maintained, contains no such qualities of men or events as 'noble', 'good', evil' or 'beautiful'. In radical reaction against the romantics, positivists sought instead to objectify nature, banishing human prejudice from scientific judgment. The total separation of observer from the object of observation – an epistemological ideal – reinforced the positivist disavowal of 'value' as part of the process of observation. One might interpret, but such evaluative judgments had no scientific (i.e. objective) standing. Simply put, where the romantics privileged human interpretation (exemplified by artistic imagination), the positivists championed mechanical objectivity (e.g. thermometer, voltmeter, chemical analysis, etc.) (Daston, 2000).

The radical separation of the observing/knowing subject and his object of scrutiny is the single most important characteristic of positivist epistemology. Because of this understanding, positivists claimed that science should rest on a foundation of neutral and dispassionate observation. The more careful the design of the experimental conditions, then the more precise the characterization of phenomena, and the more likely the diminution of subjective contaminants. Thus, the strict positivist confined himself/herself to phenomena and their ascertainable relationships through a vigorous

mechanical objectivity. In the life sciences, positivism exercised new standards in the study of physiology that applied the objective methodologies of chemistry and physics to organic processes. This approach allowed newly adopted laboratory techniques to establish physiology as a new discipline and gave birth to biochemistry, whose central tenets held that the fundamental principles of organic and inorganic chemistries were identical, differing only inasmuch as the molecular constituents of living organisms were governed by complex constraints of metabolism. This led to a new declaration for the application of a reductionist strategy to biology and medicine.

Reductionism

Positivism's methodology was intimately linked to the assumption that all of nature was of one piece, and the study of life was potentially no different in kind than the study of chemical reactions, the movement of heavenly bodies, or the evolution of mountains. Thus, if all of nature was unified – constituted of the same elements and governed by the same fundamental laws – then the organic world was simply on a continuum with the inorganic. So, according to this set of beliefs, there was no essential difference between animate and inanimate physics and chemistry, and the organic world was therefore subject to the same kinds of study so successfully applied in physics.[2] The new problem was both to reduce the organic to the inorganic, that is, to exhibit the continuity of substance and operation, and concomitantly understand the distinct character of life processes. To accomplish this twofold agenda, positivism was soon coupled to another philosophy, namely reductionism. It is important for my argument to distinguish these two philosophies, and appreciate that while reductionism might be regarded as a product of the positivist program, it is, in my formulation about medicine, subordinate to the dominating question of objectification.

The reductionists were initially a group of German physiologists, led by Hermann Helmholtz, who in the 1840s openly declared their manifesto of scientific inquiry (Galaty, 1974). They did not argue that certain organic phenomena were not unique, only that all causes must have certain elements in common. They connected biology and physics by equating the ultimate basis of the respective explanations. Reductionism, specifically physical reductionism as opposed to the later development of genetic reductionism, was also a reaction to romanticism's lingering attachment to vitalism, that notion that life possessed a special 'life force'. Vitalism was seized upon because it belied the unity of nature offered by various mechanistic philosophies. The debate was largely resolved by three key discoveries, i.e.

Helmholtz's demonstration that heat generated by contracting muscle could be accounted for by chemical metabolism (1847) (sic – no special vitalistic force was necessary), Louis Pasteur showing, about a decade later, that bacteria could not arise through spontaneous (sic – vitalistic) generation, and finally Darwin, who in the *Origin of Species* (1859), presented the case for a blind materialism to explain the evolution of species. The appeal of vitalism was not totally extinguished by mid-century, but certainly a new scientific ethos had taken over the life sciences by 1890. In addition, medicine was radically changed as a result of these developments – in the United States the establishment of the research-based medical school, Johns Hopkins, the subordination of contenders to biomedicine through the Flexner Report (1910), and the enthusiastic application and still unrealized expectations for the elimination of infectious diseases each date to this period (Tauber, 1992).

The impact of reductionism, in my view, was to apply methodologically the underlying philosophical program of the positivists. This new objective attitude had a profound influence on the doctor–patient relationship, and even more importantly gave new meaning to illness and the body (Foucault, 1963, 1973). The holistic construct of Man and the medicine which served him were replaced by a fragmenting clinical science that, in its powerful ability to dissect the body into its molecular components, failed to address the person *qua* person. In other words, the laboratory context replaced the integrity of the individual with a different standard of fragmenting analysis.

However, the epistemological shift also carried a moral corollary. The repercussions of this movement away from a holistic approach to one that celebrated the reductive scrutiny left medicine with a deep contradiction. Initially designed to address the patient's illness as experienced in an array of meanings directly accessible to the sufferer, disease of a system or organ became the focus of concern, and medicine thereby made a Faustian pact with valueless science. Amending, and often at times foregoing integrated care – one that addressed the psychological and spiritual dimensions of illness as well as the pathophysiological – medicine too often was accused of losing its deepest commitment to the patient.

The holist response

Medicine, of course, was never monolithic, and well into our own century renewed challenges to reductive orthodoxy have appeared, even within mainstream conventional medicine: constitutionalism, psychosomatic medicine, neo-Hippocratic medicine, neo-humoralism, social medicine, Catholic humanism, and, in Europe, homeopathy and naturopathy (Lawrence

and Weisz, 1998). These 'holistic' systems have been espoused not only by various kinds of practitioners, but in noteworthy instances, championed by 'legitimate' basic scientists, e.g. Henry Head, Walter B. Canon and Alexandre Besredka (Lawrence and Weisz, 1998). Through historical reflection, we can see that the discussions of today are directly linked to similar debates held between 1920 and 1950, which in turn were reframed arguments dating back to the Nineteenth century.

The term, 'holism' was coined by Jan Smuts in a bio-philosophical text entitled, *Evolution and Holism* (1926). He saw the initial challenge of wholes in terms of 'causation', recognizing that simple mechanical cause was inadequate to explain the behavior of complex systems. While few subsequent studies explicitly embraced this issue, the general tenor of his approach was explored well beyond evolutionary theory (e.g. embryology, physiology, ecology, etc.), and was applied to medicine. There, holism referred not only to the relational character of medical description and therapy, but to the scope of the medical gaze. In this format, holism's banner was employed primarily in epistemological discussion (Lawrence and Weisz, 1998), specifically the requirement for seeking a synthesis of increasingly fragmented knowledge to understand the character of integrated wholes. This was both an epistemological project and a moral one – the ethical imperative to maintain human relations always marked holism, in all of its various applications, in opposition to the underlying positivist orientation that sought to minimize the human element (Hughes, 1974). The conflict has been rightly seen as an extension of deeper cultural conflicts, and in some contexts, like France and Germany, the polemics extended quite clearly into the broadest of political and philosophical ideologies. This is hardly the place to pursue this aspect of the holism/reduction debate, other than to note its broad application beyond medicine proper, suggesting that the cultural forces at play in the specific medical setting are composed, at least in part, from contributing elements arising from other social and intellectual agendas. So while the holist rejoinder of the inter-war years has been well studied, it is perhaps less evident how our own era may reflect similar protestations and unease with the conditions of contemporary life that are reflected in the current espousal of alternative therapies.

The ethical challenge

I believe the holistic rejoinder to reductionist medicine is both epistemological and moral. Here, I will focus my remarks on the latter aspect of the issue. From the moral perspective, we begin by acknowledging that the doctor–patient encounter is, by its very nature, a negotiated attempt to

co-ordinate, if not combine, different frames of reference – treating disease (medical science) and experiencing illness (the patient). From this point, it seems to me that the recurrent question plaguing a reductionist, positivistic clinical medicine is to what extent the mechanistic, dehumanizing experience of becoming a medical object of scrutiny and therapy can be mitigated by counterbalancing factors. I have argued that a response to this question must begin with re-evaluating the doctor–patient relationship and seeing it as fundamentally ethical in character (Tauber, 1999). My thesis, very simply, is that science and technology are in the employ of medicine's primary moral responsibility, and that the ethical dimension of care supervenes and orders all other aspects of medicine. By this I mean that the requirement of recovering the full personhood of the patient to again become an autonomous free-living individual is the fundamental telos of medicine. This is an ethical mandate, and from this perspective, science is fundamentally in the employ of a moral goal. From this perspective, a humane doctor–patient relationship remains a basic requirement of contemporary medicine (Tauber, 1999).

Here I want to draw the implications of this position for understanding the relationship of biomedical reductionism as the dominant positivist orientation to holism – in this case, the restitution of the intact person to his or her full personhood. I maintain the following:

(1) In any clinical encounter, the experience of the suffering patient and his or her reification as a medical object requires a negotiation between the two points of view.

(2) While the successful application of rational, scientific knowledge is expected, this application can only be framed by the particular context of care.

(3) This so-called 'context of care' is fundamentally moral in character inasmuch as it is framed by the particular values and needs of the patient.

(4) Based on those values, science has been developed to address disease, but the care of illness, the care of the suffering patient, requires more.

Ergo, effective medicine is compassionate medicine, and the reductive practice must be regarded, always, as only part of the therapeutic encounter. Note, there is no argument *against* reductionism per se, but there is a complaint lodged against radical positivism, where the patient is regarded as the disease, e.g. 'the cancer in bed 3', or 'the pneumonia in room 506'.

There are many implications and directions we might pursue, but I wish to focus on how ethics supervenes over epistemology in this discussion.

In a trivial sense, values direct knowing. For instance, we constantly choose to pay attention to certain elements of our experienced world and ignore the vast majority.[3] Values determine what we study and indeed, as Hilary Putnam has cogently argued (Putnam, 1990), even the positivist standards or aspirations of science are values, historically arrived at and chosen in everyday practice. In medicine, this adage is overwhelmingly self-evident and hardly needs recitation. However, the implications of this understanding apparently require restatement. From the socially based policy decisions of healthcare administrators to the attention paid to the individual patient, the healthcare delivered is allocated by a distillation of value choices. When the American government essentially ignored AIDS during most of the 1980s, that reflected a policy decision, one based on a value-laden ideological orientation. The implications were horrific, and its reversal, gratifying. Moving to the individual case, if a doctor in an intensive care unit chooses to replace an elderly man suffering from pneumonia with a 30 year old woman in coma, that is also a value-based decision.

From the community to the individual, medicine is embedded in a value system, and patients understand that they are subject to such underlying choices. They demand, and expect, that their physician will negotiate the maze of choices for them, be their advocate, and protect their interests. For instance, whether I administer an aggressive chemotherapy to an elderly patient depends on many factors beyond his/her physiology, and must include such factors as expected quality of life, support structures, other confounding medical problems, etc. These are choices that must be negotiated with the patient and family. Simply put, medicine is hardly objective in its applications, nor in its practices, and must engage the social world of the sufferer, as much as the biophysical and genetic domains of the body. The boundaries are not firmly demarcated. The positivist attitude simply will not suffice in the care of the patient. Furthermore, it is an encumbrance. Patients are social creatures as well as organic ones, and the caring physician must recognize that care is multidimensional.

The existential state of being a patient is perhaps an even more immediate domain of the moral. The loss of autonomy, the fear of the unknown, the dissolution of identity accompanying pain in its multifarious forms, the dehumanization of being subjected to the administrative processes of healthcare, and the psychological dependence each of these challenges fosters combine to make the physician the patient's advocate in a different way to the social one described above. Here, individual concerns are paramount, and the most immediate response must be a humane one.

However, physicians are trained to be medical scientists and testaments to the conflict inherent in that orientation are legion.[4]

This positivist attitude is well-established in the biomedical world, and, to be sure, it was hard-won and hardly to be disparaged. However, at the same time, the price for objectifying disease has diluted, if not too often replaced medicine's ancient calling of care. I mean by 'care,' attention to each facet of the individual, namely, treating the patient as a person, as a whole. A medicine that fails to address those elements of personhood that have no scientific basis – the social, the emotional, the moral – is ultimately fractional and therefore incomplete. Only by the physician committing to comprehensive care can the multifarious elements of being ill be addressed effectively. There is no one else to assume that responsibility, and we must invoke the ethics of responsibility to re-define the entire enterprise.[5]

Conclusion

I believe, at least in medicine, the argument between reductionism and holism is a hollow one. From the epistemological perspective, the organism as an integrated, functioning entity frames all approaches to the patient. Medicine is, by its very character, holistic in orientation, endeavoring to address all systems at once and to effect full function of each. This requires a global view of function, from molecule to intact organism. However, medicine is more than a science of an organic entity, and ultimately must be judged as how effectively it addresses the person, the individual with illness. Disease is an objectified account, but disease is only one component of illness, and all those other elements of dysfunction that might arise from disease also require care. In this sense, the patient has moved from being an entity – an organic construct – to one of personhood. This latter characterization is a moral one, one laden with values and choices. If one regards medicine as dealing finally with this larger conception of the patient, then reductionism must be viewed as a tool, albeit a powerful one when applied to certain questions, but only an instrument in the employ of another agenda. The ethical demand of medicine simply disallows satisfaction with the positivist stance, either in practice or as an aspiration. To accede to the resulting fragmentation of reductionism is to surrender medicine's ultimate concern, the care of the patient.

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Notes

[1]Each of these patients has sickle cell disease (SCD), noteworthy as the first 'molecular disease'. First identified as arising from an abnormal hemoglobin in 1949 (Feldman and Tauber, 1997), the molecular anatomy and biochemical consequences of the amino acid substitution in the beta chain have been detailed in extraordinary detail. Indeed, it is fair to assign SCD as the reductionist model illness if, sometimes in the future, gene replacement effaces the faulty gene with a normal one. However, at present, SCD exemplifies the reductionist failure inasmuch as despite the singularity of the molecular lesion, the disease has protean manifestations, because the molecular defect is only the initiating cause of a complex clinical phenotype. Basically two syndromes arising from the sickling of hemoglobin dominate the clinical picture: hemolytic anemia (giving rise to jaundice, as in case 5) and various manifestations resulting from the obstruction of small blood vessels. Because the red cells are both non-pliable and 'sticky' (as a result of secondary changes to their exterior membranes), they are prone to forming 'plugs'. These obstructions then give rise to pain (due to impaired oxygen

delivery) and ultimately end-organ damage (again resulting from repeated or prolonged oxygen deprivation). Thus, cases (2), (3), (4), (6) (stroke) and (7) are each due to obstruction resulting from sickled red cells. Most interesting, perhaps, is the first case, where the patient is totally asymptomatic despite having the same molecular lesion as the others. Compensatory mechanisms apparently allow this individual to lead a 'normal' life, that is, if he can stay out of harm's way!

[2]Considering the penchant for defining organic processes at their elemental level, it is perhaps ironic to note that the battle over vitalism, and the character of the organic world more generally, may be regarded as an aspect of the quest for a single unity of the world. This was a fundamental romantic tenet, so in at least one sense, the romantic notion of vitalism was overturned, but on the other hand, the more important precept of nature's unity was reconfirmed by the reductionists, and adamantly so. However, in the process, an insidious shift had occurred. Man had been displaced from his metaphysical perch and had assumed a more democratized, or perhaps better, universalized standing. Medicine was to treat the body essentially composed as a machine, governed by uniform chemistry, and thus susceptible to mechanical repair.

[3]The limits and consequences of epistemological selection is hardly a new problem, and I think the issue was best described by William James almost a century ago:

> *We work over the contents of the world selectively. It is overflowing with disorderly arrangements from our point of view, but order is the only thing we care for and look at, and by choosing, one can always find some sort of orderly arrangement in the midst of any chaos .... [Nature] is a vast* plenum *in which our attention draws capricious lines in innumerable directions. We count and name whatever lies upon the special lines we trace, whilst the other things and the untraced lines are neither named nor counted. There are in reality infinitely more things 'unadapted' to each other in this world than there are things 'adapted', infinitely more things with irregular relations than with regular relations between them. But we look for the regular kind of thing exclusively, and ingeniously discover and preserve it in our memory. It accumulates with other regular kinds, until the collection of them fills our encyclopedias. Yet all the while between and around them lies an infinite anonymous chaos of objects that no one ever thought of together, of relations that never yet attracted our attention (James, 1902, 1987, p. 394).*

[4]The issue is succinctly stated in a recent book review about schizophrenia:

> *Despite their reputation for vanity, many mental health professionals, and medical students in particular, fail to recognize their own importance. They 'come and go among patients as if their knowledge and skills were all that counted, their persons not at all'. The remark is pertinent, for it points to the underlying vision that drives the profession. The medical students are not looking for personal engagement with the patient. They don't really want their 'person' to make a difference. That is not the 'importance' they are after. Rather they want to learn (why not?) to heal the patient with a precise and controlled intervention, the exact dosage of the exact drug chosen after an exact diagnosis based on meticulous and exact analysis of spinal fluids and brain scans. They are in thrall, that is, to the great and credible dream of Western medicine (Parks, 2000, p. 15).*

[5]Here we turn to Levinas. I can hardly do justice to summarizing the philosophy of Levinas, but suffice it to note that he based his philosophy on the demand of the other that requires a response, an ethical answering, and in that response a moral attitude is established. The encounter alone defines both parties – in this case, physician and patient. I have argued elsewhere (Tauber, 1999) how this act of response in the medical setting need not be negotiated or otherwise sought after, but is intrinsic to the medical setting. The physician assumes, as given, a posture of response as part of his or her professional identity, and so beyond the richness of the doctor–patient relationship for exploring the implications of Levinas' moral philosophy, it serves as a ready structure by which to frame my own views about holism, for if one accepts this general formulation, it seems self-evident, at least to me, that the epistemological discourse in medicine must assume a position relative to the overriding ethical concern. In this sense, ethics supervenes all other voices of medicine. And in terms of our topic, we might well appreciate that the issue of holism has now moved from an argument between different approaches to knowledge, to one whereby knowledge might be judged.

QUESTIONS AND DISCUSSION

Ken Schaffner: Fred, I liked the presentation. I noticed when you covered a variety of people who had addressed holistic perspectives that you did not mention George Engel's biocycle social model. I found that model, which is contrasted in the literature with the so-called biomedical model which is

reductionistic, a kind of a useful framework, although limited. I think what your presentation adds to that is both the ethical dimension which is really not part, as I understand it, of the biocycle social model. There is a social element, and an economic element, but not an ethical or a normative ethical element, nor does he have the doctor–patient negotiation which you were describing which is an important element of humaneness. The question I have is whether you've found a lot of people used to pay lip service to the biocycle social model, whether you found it at all useful or limiting as I just mentioned, or completely useless?

Fred Tauber: I'm glad you added that. It is clear that American medicine at least, and that is the only context I know, is becoming increasingly sensitive to the issues I have raised. Medical students are being increasingly trained to incorporate these social factors and the moral ones, not to the extent that I think is appropriate because the professionalisation of the physician is primarily in the reductive biomedical mode, and these other things are considered auxiliary. They're considered necessary but they are always subordinated to the technical mastery of disease and therapeutics. And so I take, what I assume to be a radical approach, of putting ethics first, because I think that, unless that is done, the entire moral structure of the enterprise is distorted. But young physicians who are training need to master an extraordinary body of knowledge, and they are preoccupied by that. Established physicians complain when I give such a lecture that they don't have time to address the social, emotional and spiritual issues of their patients driven by the administrative concerns of healthcare delivery. So there's a conspiracy, not only with the scientific attitude, but there's the administrative restriction which makes humane care increasingly difficult.

David Hull: You have just raised the point that I was going to raise with respect to both research scientists and physicians, and that is time. The reductionist scientist knows he should replicate his own experiments, not to mention those of other scientists, but no one has the time to do what they know that they ought to do. This is true of physicians as well. We hear about all this good stuff that physicians should do when they can spend only 2.3 minutes per patient. I have never met a doctor who did not say that he wished he could do better, but given the contingencies of how medicine is practiced, he has no time.

Fred Tauber: I think the physician is becoming increasingly a patient advocate. One has to be radical and oppose those forces. There are beginning to be movements in the United States of physician collective bargaining, not only for increased personal wealth, but in terms of how care is administered, and one of the primary issues is to devote more time to each patient. It's

going to take a major political move to change the medical orientation as it exists today.

Eugene Dowdle: You have not mentioned the effects of Medical Aid schemes on physician–physician and physician–patient relationships. One of the keystones of the Oslerian ethic was the sense of collegiality that bound the medical profession and provided, indirectly, a form of peer review that was of benefit to both patients and to medical practitioners. Medical Aid schemes, by their monetarising effects, have done much to damage those professional bonds.

Furthermore, now that we have a situation where a Medical Aid scheme pays, over-servicing, kick-backs, and excessive demands on resources have now become prevalent. There was, for example, a time when a careful history and physical examination with, perhaps, one or two inexpensive investigations, together with aspirin and the passage of time, were sufficient to identify the small percentage of patients with headache as a presenting symptom, who required more intensive or detailed investigation. Now the patient is subjected to a CAT scan, an MRI scan and, often, a lumbar puncture on the first visit in an expensive approach that reduced clinical assessment to a technological exercise.

On the other hand, you rightly emphasised the problems that arise when dealing with patients whose value systems or cultural backgrounds are different. In Africa, one is frequently confronted by patients whose faith in sangomas, or witch doctors, is profound and whose language presents a barrier that requires the intervention of an interpreter and hence the loss of the interpersonal relationship that the holistic approach requires. Under these circumstances, reductionism is often the easiest answer to providing a good deal by Western standards.

Fred Tauber: Well, you've raised many points. I'd like to address the first issue about the headache. The reason that the patient has a CAT scan, etc. is because the element of trust has been dissolved, and we practise what is called defensive medicine. In other words, in the very few instances where one might be missing, let's say a tumour, if you will, or a subdural haematoma, you're concerned about being charged with malpractice. Your best medical judgement is that the patient does not need a CAT scan, but the possible consequences from a legal point of view are so horrific that physicians very often over-prescribe tests in order to defend themselves against liability. So the trust issue is really at the bottom of that as far as I'm concerned, and the medical aids of course also are an interference, if you will, between the doctor and the patient. In regards to the different cultures, there is a wonderful book written by Anne Fadiman called *The Spirit Catches You and You Fall Down*. It's a story of a young girl with epilepsy – she's

Hmong, which is the Laotian Chinese nomadic group that has come to the United States in great numbers. The book is about the negotiation between the physicians and the family in treating the epilepsy, and it failed. There was no negotiation because the family couldn't understand the medical approach, and the doctors didn't understand what they were doing. It's a wonderful case study, if you will, for what happens when the negotiation fails. Now, as it turns out, it's problematic as to whether medicine would have been effective in her case or not, which is what makes the book particularly ironic and interesting. But the general point to be made is that it can be very difficult to make the negotiation, but ultimately it's the values of the patient that are going to determine what kind of care is going to be given, and that's what a physician always has to respect.

Terrance Brown: The point that I wanted to raise has to do with the issue of opposing value-laden systems with scientific methods. Science is terribly value-laden. If we look at the evolution of intelligence itself, both phylogenetically and autogenetically, what you see is that you have a powerful system of decision-making which is based upon values, which we experience as feelings or affects, and that this remains throughout human life by far the most important decision-making system. Rationality is actually possible in only very very small areas of human experience. Every one of us gets through the day making decisions about the adaptability of what we eat. Nobody really knows if that thing on the plate is going to kill us or if it's going to help us – we are hungry, it smells good and we eat it. There's no science of choosing a wife, there's no real science of deciding whether to prolong a life that may not be of any quality. The power of the value system or the affective system to make decisions is so much greater than the power of reason, and one of the very interesting things that you see in the developmental psychology of intelligence is how objective values are constructed, they are never complete, how they are differentiated from what's called generally subjective value by the construction of logical necessity, which is very long and slow.

Robert Richards: Not only, I presume, do doctors refer to patients by their disease, but doctors refer to one another by their technical abilities, with the 'knife', for example, as a surgeon. If you were a hospital administrator (and I know what the answer to this question is going to be, but I'd like to hear it anyway) and you have to make a decision not unlike individuals in a university department have to make a decision about hiring, and you have the 'knife' who has that kind of technical expertise, but not noticeably is this person an ethical paragon. You have to weigh different values, and I guess

the question is how do you weigh those values? That's one question. The other is, I presume, both in Europe with various social medicine regimes and in the United States now with HMO regimes, that the kind of model you have of the physician is not the one that's held dear by corporations that run HMOs.

Fred Tauber: HMOs have the bottom-line 'dollar' as their telos and physicians have a different ethical structure governing what they do, so there's obviously a conflict. I would say that if you have to hire a 'knife' you would look for the 'knife' who is going to be the most humane. If you don't have the choice, obviously you are going to hire the 'knife' as he or she is.

Robert Richards: Presume you have just chosen one path almost immediately, namely you hire the 'knife'.

Fred Tauber: Well, you obviously you need a 'knife'.

Robert Richards: But I mean a good 'knife', as opposed to just an OK 'knife', but he might be a very nice person.

Fred Tauber: Well, I don't accept those choices!

David Hull: In our society and many societies, the individual is paramount. He or she gets to decide what happens. But former students of mine have come from cultures where the family is the most important, not the individual. They are just part of the family, and the family could decide against the individual and expect the doctor to go with the family's decision not the individual's decision. What do you do?

Fred Tauber: If the individual buys into that family ethical structure then you obviously have the problem solved. If he in fact is going to choose a more autonomous model, then presumably you would follow the individual. I will give you an example. I just had a patient about a week ago, a Jehovah's Witness. Jehovah's Witnesses do not take blood products and this patient needed blood products. Because the Church was negotiating for him, we were going to follow the Church's dictates. Then he became increasingly alarmed as he recognised he would probably die, and he chose in fact to become autonomous and we gave him the blood. So the dynamic, at least in America, shifts dramatically because the structure really can fall apart very quickly.

Ken Schaffner: Could I just add a quick comment to that. I have seen lots of cases of this sort that David referred to because they seem to be endemic in Washington DC.

Fred Tauber: Ken serves on the Ethics Committee.

Ken Schaffner: Though I don't practise, and I don't do very much ethics consultation, I have done it in the past. It's a useful vehicle to have a group

of people who are trained in bioethics and know the dimensions of the hospital rules, as well as the cultures that are involved, to get involved in some of these discussions and sometimes to be able to mediate, but sometimes it just falls apart.

With Islamic husbands and Islamic wives, I've seen things just fissure, but in other cases they have been able to come to some kind of an appropriate compromise.

Chapter 14

Levels of Explanation in Human Behaviour: the Poverty of Evolutionary Psychology[1]

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A biological fable

Let me begin with a fable. Once upon a time, five biologists were having a picnic by a pool, when they noticed a frog, sitting on the edge, suddenly jumping into the water. A discussion began between them – why did the frog jump?

Said the first biologist, a physiologist – 'It's really quite straightforward. The frog jumps *because* the muscles in its legs contract; in turn, these contract because of impulses in the motor nerves arriving at the muscles from the frog's brain; these impulses originate in the brain because previous impulses, arriving at the brain from the frog's retina, have signalled the presence of a predatory snake. This is a simple ''within level'' causal chain: *first*, the retinal image of the snake; *then* the signals to the brain; *then* the impulses down the nerves from the brain; *then* the muscle contraction, with one event following the other over a period of thousandths of a second'.

However, this is a very limited explanation, argued the second, an ethologist. The physiologist has missed the point, and has told us *how* the frog jumped but not *why* it jumped. The reason *why* is *because* it sees the snake and jumps *in order to* avoid it. The contraction of the frog's muscles is but one aspect of a complex process, and must be understood in

[1] This contribution is derived from material in my book, *Lifelines: Biology, Freedom, Determinism* (Rose, 1997) and my chapter in the edited collection, *Alas Poor Darwin* (Rose, 2000).

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terms of the goals of that process – in this case, to escape being eaten. The ultimate goal of avoiding the snake is essential to understanding the action. Unlike the physiologist's explanation, the ethologist's is not causal in the sense of describing a temporal chain of events in which first one thing, the nerve firing, and then another, the muscle contraction, happens one after the other in time. The jump inevitably precedes achieving the goal towards which it is directed.

The third was a developmental biologist, and for her neither the physiologist's nor the ethologist's explanations are adequate. For the developmentalist, the only reason that the frog can jump at all is *because* during its development from a single fertilised egg through tadpole to mature animal, its nerves, brain and muscles have become 'wired up' in such a way that such sequences of activity are inevitable, or at least, the most probable given any set of starting conditions. Thus, in this account the past individual history of the frog becomes the key to understanding its present behaviour.

The fourth biologist, an evolutionist, found none of these earlier explanations very satisfactory. The frog jumps, the evolutionist argued, *because* during evolutionary history it was adaptive for its ancestors to do so at the sight of a snake; those frog ancestors that failed so to do were eaten, and hence their progeny failed to be selected. Such evolutionary explanations combine the historical with the goal-directed and are, the evolutionist insisted, therefore *the* fundamentally causal question, the others are 'merely functional'.

The fifth was a molecular biologist, who smiled sweetly and pointed out that all the others had missed the point. The frog jumps *because* of the biochemical properties of its muscles. The muscles are largely composed of two interdigitated filamentous proteins, actin and myosin, and they contract because the protein filaments slide past each other. This property of the actin and myosin is dependent on the amino acid composition of the two proteins, and hence on chemical, and thus on physical properties. In the last analysis, the molecular biologist insisted, following James Watson, we are all nothing but subatomic particles.

However, this reductionist chain is not causal in the sense that the physiologist means. It is not a question of *first* one thing happening (the actin and myosin sliding across each other), *then* another (the contraction). If the word 'cause' is used at all here, it must mean something quite different from how it is used in physiology. Such confusions have of course bedevilled scientific thinking since the days of Aristotle. Perhaps we might be able to see things more clearly if we restricted our use of the word to clear temporal sequences in which first one and then another event occurs. Each of these events, the image on the frog's retina, the processing in the brain, the transmission down a motor nerve and the muscle contraction itself

can be *translated* into the language of biochemistry, and it is, of course, possible to describe this biochemical sequence in temporal terms too, in which one set of biochemical processes (the molecular events in the nerve), produces another (the sliding actin and myosin filaments). At issue then I would argue, is the relationship between the two temporal sequences, that of the physiologist and that of the biochemist.

The orthodox reductionist position will have none of this. It claims, first, that while 'higher-level' accounts such as those of the physiologist merely *describe* a phenomenon, 'lower-level' ones such as the molecular *explain* it. (Witness the discussion between myself and Thomas Nagel Novartis Foundation, 1998).) Secondly, it argues that physiology, development and ethology provide mere 'proximal' accounts while evolutionary biology offers 'ultimate' explanations, to use Ernst Mayr's term. The theological overtones of this formulation are apparent, which is why I prefer the more modest 'distal'. I challenge both of these reductionist assumptions, and argue a pluralist position: each of these five types of explanation are legitimate and none of them can properly be submitted to the philosophically eliminative programme of full-blooded reductionism. Explanation does not occur in a purpose-free context. If we want to understand and treat a wasting muscular disease, the genetic, molecular and biochemical accounts serve well as explanations of a clinical condition that physiology can describe (but see Tauber's paper in this collection). If we are interested in athletic prowess, biochemistry merely describes, while physiology helps explain. Similarly an evolutionary account might provide general distal explanations for population differences in human muscle distribution, but developmental and contextual proximal explanations will explain better why particular individuals, perhaps from particular social groups, become champion athletes. There are, as Gould has put it (Gould, 2000), pleasures in such pluralism that a puritanical reductionism attempts to limit at its peril.

Nonetheless, there can be no doubt that we are living in an era in which more and more extravagant claims concerning the roots of human behaviour are being made in the name of such evolutionary and genetic reductionism. These take two seemingly incompatible forms. On the one hand, it is argued that human differences – in tendencies to aggression or drug addiction, religiosity, marital success or sexual orientation – are the results of genetic differences. This is the terrain of behaviour genetics. On the other, it is claimed that alleged human universals – male preferences for multiple younger sexual partners or for killing their stepchildren, female choices to mate with older men, cheat detection, morning sickness, love of green landscapes, and children's dislike of spinach – are evolutionary adaptations laid down in the Pleistocene. Evolutionary psychology claims

that these universals, while gene-driven, are mediated through the human mind, a modular, innate information processing machine. My non-random sample of behaviour geneticists and evolutionary psychologists indicates that there is little love lost between the two groups, albeit (like Trotskyists and Communists in the last century) their ideological and methodological commonalities far outweigh their differences. It is with the claims of evolutionary psychology that I am most concerned here.

The goals of evolutionary psychology

The declared aim of evolutionary psychology is to provide explanations for the patterns of human activity and the forms of organisation of human society which take into account the fact that humans are animals and, like all other currently living organisms, are the present-day products of some 4 billion years of evolution. So far, so good. The problem is that, like its predecessor, sociobiology, evolutionary psychology offers a false unification, pursued with ideological zeal. In order to achieve this vain goal it misspeaks and impoverishes modern biology's understanding of living systems, in three key areas: the processes of evolution, of development and of neural function. Underlying all of these are two major conceptual errors: the misunderstanding of the relationship between enabling and causal mechanisms, and the attempt to privilege distal over proximal causes. It is on these shaky foundations that prescriptions for how humans do and should behave, and for the social policies that flow from this, are based.

Evolutionary psychologists go to some lengths to insist that, unlike exponents of earlier versions of social Darwinism, they are not genetic determinists, or as they sometimes put it, nativists. Rather, they argue that the nature/nurture dichotomy is a fallacious one. Instead, they seek to account for what they believe to be universals in terms of a version of Darwinian theory – a version which in practice owes more to Dawkins' reductive fundamentalism than it does to Darwin's own more pluralistic and observation-rich insights.

Selfish genes

In the version of evolutionary theory popularised by Dawkins (1976), the fundamental unit of life is a gene, a conceptual abstraction clothed in the biochemistry of the nucleic acid DNA. The purpose, or telos, of this gene is replication – to make copies of itself – copies which because of random chemical and physical processes may be more or less accurate. The particular chemical structure of DNA provides a mechanism whereby such faithful copying can readily occur – as James Watson and Francis Crick pointed out

in the famous finale to their 1953 paper in *Nature* describing a proposed molecular structure for DNA.[2] Genes are thus naked replicators, and in their struggle to achieve the maximum numbers of identical copies, find themselves, mainly in competitive, sometimes in co-operative, relationships with other genes. However, genes cannot achieve replication by themselves; to do so, they need to be embedded in cells, which are in organisms. These external manifestations of the work of the genes are formally known as *phenotypes*, or, to use Dawkins' now famous – or infamous – phrase, are the 'lumbering robots' programmed and set in motion by the genes they contain, whose function is to enable more copies of these genes to be achieved. That is, to reproduce.

Genes within an individual organism share 'an interest' in that organism's successful reproduction and hence may co-operate. However, genes in different individuals within a species are not necessarily identical, and hence produce non-identical organisms. These organisms may be more or less 'fit', and hence may be more or less able to survive to reproduce in their turn. As a result, genes which contribute to the 'fitness' of the lumbering robots in which they are embedded are themselves more likely to survive and spread in the population of such organisms. This variation and spread is the mechanism and process of natural selection. Fitness is, of course, a relative term – it refers only to the specific environment in which the gene and their robot-organisms are located; in different or changing environments, different genes and their robots may be advantaged.

This is, in essence, the 'modern synthesis' of Darwin and Mendel achieved in the 1930s by Ronald Fisher and J. B. S. Haldane. Based on a series of relatively straightforward equations, it also took the study of evolution out of meticulously observed natural history and located it within a more abstract mathematised theory. Indeed, evolution itself came to be defined not in terms of organisms and populations, but as the rate of change of gene frequencies within any given population. One consequence has been a tendency for theoretical evolutionists to retreat further and further into abstract hypotheticals based on computer simulations, and to withdraw from that patient observation of the natural world which so characterised Darwin's own 'method'.

The additional refinement to the theory, which is essential for the full flowering of evolutionary psychology, was suggested in an often recounted 'pub comment' by Haldane in the 1950s, that he would be prepared to sacrifice his life for two brothers or eight cousins. Because he shared genes in common with his kin, the proportion varying with the closeness of

[2] 'It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material' (Watson and Crick, 1953).

the kinship, then 'his' genes would serve their interest in replication not only by ensuring that he himself had offspring (which to his regret he did not; he appears to have been infertile), but by aiding in the replication of the identical copies of themselves present in his relatives. This insight was formalised by William Hamilton in the 1960s by redefining fitness as 'inclusive fitness' (i.e. referring to the ability of the genes possessed both by you and your genetic relatives to spread in the population) (Hamilton, 1964). This is kin selection, and in the 1970s became the core theory of E. O. Wilson's 'new synthesis' of sociobiology, which in due course mutated into evolutionary psychology. The mathematical syllogism that this version of ultra-Darwinism provides is, within its own framework, irrefutable, which is why Dennett is able to refer to it as a 'universal acid' which eats through all other understandings of not merely biological, but cultural phenomena (Dennett, 1995).

The central aspect of evolutionary theory upon which evolutionary psychology builds is that of adaptation. Because genes can only survive via the capacity of the organisms they inhabit to survive and replicate, the products of gene action – their phenotypes – must be 'designed' by the honing force of natural selection to achieve that replication with maximal efficiency. Hence, every feature of the phenotype, from the protein structures within its cells to its behavioural responses to environmental contingencies, must be considered as adaptations to achieve this goal. In less fit organisms, the adaptations may not work so well, or, because of genetic mutation, may be positively dysfunctional, resulting in disease, incapacity to reproduce, or early death.

Nativism?

Because humans are as subject as any other organism to evolutionary processes, we should therefore expect to find such adaptations among our own kind just as much as among the others we study. Individual aspects of being human – from our body shape to our eyes and capacity for binocular vision – are clearly evolved features, and fit us for the environment in which we live. However, an important aspect of being human, which distinguishes us from other living forms, is our unique social organisation, achieved by virtue of our large brains and the minds they constitute (or at least enable). According to evolutionary psychology, we must consider these too as evolutionary products. The 'architecture' of our minds, and our forms of social organisation, must be seen as adaptations shaped by natural selection to achieve the goals of the optimal replication of the genes of individual humans and the increase in inclusive fitness predicted by the theories of kin selection.

It is here that, despite their disavowals, the nativism of the evolutionary psychology enthusiasts becomes clear. When the anthropologist Laura Betzig writes, as she does in her introduction to her edited collection *Human Nature* (Betzig, 1997) that everything from pregnancy complications to the attraction of money can be explained by invoking Darwinian mechanisms, the conclusion is inescapable: genetic mechanisms underlie these human problems and proclivities. More sophisticated evolutionary psychologists finesse the argument by maintaining that they are not really saying that there are specific actual genes – lengths of DNA – for being attracted sexually by symmetrical bodies, or for disliking spinach while a child but liking it as an adult, to take but two of the explanatory claims of evolutionary psychology. Instead there are mechanisms, ultimately encoded in the genes, which ensure that we *are*, on average, so attracted, albeit the way in which the genes ensure this is mediated by more proximal mechanisms – by, for instance, creating modular minds whose architecture predisposes this type of behaviour. The spread of such theoretical pseudo-genes, and their putative effect on inclusive fitness can then be modelled satisfactorily *as if* they existed, without the need to touch empirical biological ground at all. Dawkins is particularly prone to this type of stilt-walking, although at least he is open about the 'as-ifness' of the exercise in which he is engaged.[3] For others who join the evolutionary psychology bandwagon not from zoology, like Dawkins, but as psychologists like Steven Pinker or philosophers like Dennett, the disclaimers merely serve as ritual invocations before they get down to the real determinist/nativist business.

Enabling versus causing; proximal versus distal explanations

A consistent feature of this mode of explanation is to mistake enablement for causation. Clearly, all aspects of our existence – and indeed those of any living organism – are made possible by the framing limitations of physical and chemical processes (such as the requirement for energy-providing biochemical reactions, or the structural limitations of calcium phosphate in bone for load-bearing). They are also made possible by the specificities of the organisation of our cells and the multitude of macromolecules of which they are composed. These specificities have themselves been formed during evolution and development. However, this does not entitle one to say, for any observed behaviour, that it is *caused* by such processes; rather, they have made it possible – along with many alternative possibilities. Thus, the creation and perception of visual art is dependent on evolved human

[3] See, for instance, his discussion in the first two chapters of *The Extended Phenotype: The Gene as the Unit of Selection* (Dawkins, 1982).

capacities – having sense organs (eyes) which can respond differentially to wavelengths within a given, relatively limited range, having hands which can wield instruments with which to depict, specific brain structures enabling painting technique and production of pigments to be learned – and a social organisation which makes such production and appreciation possible and valued. None of these capacities is directly causal of the art that is produced, however.

Characteristically, however, evolutionary psychology theorists have argued the reverse. Thus Pinker, in *How the Mind Works*, claims that (with the engaging exception of what he describes as 'great art') humans show a universal propensity to prefer pictures containing green landscapes and water. Pinker speculates that this preference may have arisen during human evolution in the African savannah, the so-called Environment of Evolutionary Adaptation, (or EEA), The grander such assertions, then the flimsier and more anecdotal becomes the evidence on which they are based. Has Pinker ever seen savannah, one wonders? Is this so-called universal preference shared by Inuits, Bedouins, Amazonian tribespeople .... Or is it, like so much research in the psychological literature, based on the samples most readily available to US academics – their own undergraduate students? It is hard not to be reminded of the argument once made by an ophthalmologist that El Greco's characteristic elongated figures were the result of his astigmatism.

The point is that there are much simpler proximal explanations for such preferences should they occur – that in Western urban societies, as Simon Schama points out, 'the countryside' and 'the wilderness' have become associated with particular arcadian and mythic qualities of escape from life's more pressing problems (Schama, 1995). Such proximal mechanisms, which relate to human development, history and culture, are much more evidence-based as determining levels of causation, should these be required, than evolutionary speculations. It is surely an essential feature of effective science and of useful explanation to find an appropriate – determining – level for the phenomenon one wishes to discuss. As an example, consider the flurry of attempts, particularly in the US, to 'explain' violent crime by seeking abnormal genes or disordered biochemistry, rather than observing the very different rates of homicide by firearms between, say, the US and Europe, or even within the US over time, and relating these to the number and availability of handguns.[4] Despite the implicit and sometimes even explicit claim that if we can find an evolutionary explanation for a phenomenon, this will help us fix it (Betzig, 1997), it seems highly doubtful that evolutionary

[4] For a discussion of the US Violence Initiative, see Breggin and Breggin (1994).

psychology or behaviour genetics will ever contribute anything useful to either art appreciation or crime prevention. The enthusiasm in such cases for proposing biological causal mechanisms owes more to the fervour of such ultra-Darwinians to achieve what E.O. Wilson calls 'consilience' than to serious scholarship.

Evolutionary time

A further characteristic feature of the evolutionary psychology argument is to point to the relatively short period, in geological and evolutionary terms, over which *Homo sapiens* – and, in particular, modern society – has appeared. Forms of behaviour or social organisation which evolved adaptively over many generations in human hunter–gatherer society may or may not be adaptive in modern industrial society, but have, it is claimed, become to a degree fixed by humanity's evolutionary experience in the palaeolithic EEA. Hence, they are now relatively unmodifiable, even if dysfunctional.

There are two troubles with such claims. The first is that the descriptions that evolutionary psychology offers of what human hunter–gatherer societies were like read little better than 'Just-So' accounts, rather like those museum – and cartoon – montages of 'hunter-dad' bringing home the meat while 'gatherer-mum' tends the fireplace and kids, so neatly decoded by Haraway in *Primate Visions* (Haraway, 1989). There is a circularity about reading this version of the present into the past, and then claiming that this imagined past explains the present.

However, the more fundamental point is the assertion by evolutionary psychologists that the time-scale of human history has been too short for evolutionary selection pressures to have produced significant change. The problem with this is that we know very little about just how fast such change can occur. Evolutionarily modern humans appeared some 100 000 years ago. Allowing 15–20 years as a generation time, there have been some 5000–6600 generations between human origins and modern times. While it is possible to calculate mutation rates and hence potential rates of genetic change, such rates do not 'read off' simply into rates of phenotypic change. As Gould and Eldredge have pointed out in developing their theory of punctuated equilibrium, the fossil record shows periods of many millions of years of apparent phenotypic stasis, punctuated by relatively brief periods of rapid change (Eldredge, 1985). This is simply because there is not a one-for-one relationship between gene and organism, or even genotype and phenotype. The many levels of mediation between them means that genetic change can accumulate slowly until at a critical point it becomes canalised into rapid and substantial phenotypic change.

A 'Darwin' is the term used to provide a measure of the rate of evolutionary change. It is based on how the average proportional size of any feature alters over the years and is defined as 1 unit per million years. Laboratory and field experiments in species varying from fruit flies to guppies give rates of change of up to 50 000 Darwins. Steve Jones describes how English sparrows transported to the south of the USA have lengthened their legs at a rate of around 100 000 Darwins, or 5 % a century (Jones, 1999). So we really have no idea whether the 6000 or so generations between early and modern humans is 'time enough' for substantial evolutionary change.[5] We don't even know what 'substantial' might mean in this context. However, granted the very rapid changes in human environment, social organisation, technology and mode of production that have clearly occurred over that period, one must assume significant selection pressures operating. It would be interesting in this context to calculate the spread of myopia, which is at least in part heritable, and must in human past have been selected against, once the technological and social developments occurred which have made the almost universal provision of vision-correcting glasses available in industrial societies. What is clear, however, is that the automatic assumption that the palaeolithic was an EEA in which fundamental human traits were fixed, and that there has not been time since to alter them, does not bear serious inspection.

Beyond ultra-Darwinism

However, there are more fundamental problems yet. Even before we get to the human condition, each of the foundational premises of evolutionary psychology is at best only partial, at worst in error. While it is the case, as the population geneticist Theodosius Dobzhansky put it, that nothing in biology makes sense except in the light of evolution, his claim requires extension. Nothing in biology makes sense except in the light of history – the evolutionary history of the species, the developmental history of the individual living organism, and, for humans, of course, social, cultural and technological history. To this must be added the history of our own sciences, which provides the framing assumptions within which we attempt to view and interpret the world. The ontogeny of evolutionary psychology's ways of thinking about the living world – its roots in sociobiology and before that eugenic and social Darwinist thinking – goes a long way towards explaining both its current agenda and its biological misconceptions.

[5] The geneticist and ethologist, Hans-Peter Lipp, informs me that he has found substantial changes in the brain structure of laboratory mice released into the wild under the pressure of natural selection within four generations (Lipp, 2000).

The following sections summarise the central inadequacies of the biological theorising on which evolutionary psychology is based.

Naked replicators are empty abstractions

One of the central features of DNA as a molecule is that it cannot simply and unaided make copies of itself; it cannot therefore 'replicate' in the sense that this term is usually understood. It is a relatively inert molecule (hence, the possibility of preservation in amber and the plot of the film, 'Jurassic Park'). What brings DNA to life, so to speak, is the cell in which it is embedded. Replication – using one strand of the double helix of DNA to provide the template on which another can be constructed – requires an appropriately protected environment, the presence of a wide variety of complex molecular precursors, a set of protein enzymes, and a supply of chemical energy. All of these are provided in the complex metabolic web within which the myriad biochemical and biophysical interactions occurring in each individual cell are stabilised (Kauffman, 1995). Despite the constantly recurring metaphors of DNA as a 'master molecule,' a 'blueprint', and so forth, there are no such master molecules in cellular processes. Even the metaphor of the cellular orchestra, which I have used previously, is not adequate, as orchestras require conductors. Better to see cells as marvellously complex versions of string quartets or jazz groups, whose harmonies arise in a self-organised way through mutual interactions. This is why the answer to the 'chicken-and-egg' question in the origin of life is not that life began with DNA and RNA but that it must have begun with primitive cells which provided the environment within which nucleic acids could be synthesised and serve as copying templates.[6]

The relationship between genes and phenotypes is not linear

Neither cells nor organisms – still less their behaviours – spring fully formed from DNA, even with the richer account of its synthesis and replication described above. There isn't even a direct relationship between a strand of DNA ('a gene') and a particular protein, which is the immediate gene product. Most of the DNA in the human genome plays no known functional role in the survival and reproduction of the organism, but gets copied nonetheless. Hence, it is described disparagingly either as 'junk DNA' or, in the continuation by Crick of the metaphor made notorious by Dawkins, as 'selfish'. By contrast, the picture which modern biochemistry provides is of

[6] For a fuller discussion of this view of the origin of life, see Rose (1997).

complex processes of so-called 'editing', 'splicing' and otherwise working on the original DNA sequence before the fully formed protein is generated. In addition, the pattern of these editing processes is itself environmentally shaped. To put this in the language of genetics rather than development, and to use Dobzhansky's terminology, how genes are expressed reflects a *norm of reaction* to the environment.

Beyond the cellular level, there is the little matter of development, the processes that transform the single fused cell of a fertilised ovum into the thousand trillion cells of the human body, hierarchically and functionally organised into tissues and organs. Developmental processes have trajectories which constitute the individual lifeline of any organism, trajectories which are neither instructed by the genes, nor selected by the environment, but constructed by the organism (a process described by Humberto Maturana and Francisco Varela as *autopoiesis*) out of the raw materials provided by both genes and environment (Rose, 1997; Oyama, 1985; Maturana and Varela, 1998).

The unity of an organism is a process unity, not a structural one. All its molecules, and virtually all its cells, are continuously being transformed in a cycle of life and death which goes on from the moment of conception until the final death of the organism as a whole. This means that living systems are open. They are never in thermodynamic equilibrium. In addition, they are not mere passive vehicles, sandwiched between the demands of their genes and the challenges of their environments. Rather, organisms actively engage in constructing their environments, constantly choosing, absorbing and transforming the world around them. Every living creature is in constant flux, always at the same time both *being* and *becoming*. For instance, a newborn infant has a suckling reflex; within a matter of months, the developing infant begins to chew his/her food (Bateson and Martin, 2000). Chewing is not simply a modified form of suckling, but involves different sets of muscles and physiological mechanisms. The paradox of development is that a baby has to be at the same time a competent suckler, and to transform himself/herself into a competent chewer. To be, therefore, and to become.

Being and becoming cannot be partitioned into that tired dichotomy of nature versus nurture. Rather, they are defined by a different dichotomy, that of specificity and plasticity. Consider the problem of seeing, and of making sense of the world we observe, processes subserved by eye and brain. The retina of the eye is connected via a series of neural staging posts to the visual cortex at the back of the brain. A baby is born with most of these connections in place, but during the first years of life, the eye and the brain both grow, at different rates. This means that the connections between eye and brain have continually to be broken and remade. If the developing child

is to be able to retain a coherent visual perception of the world, this breaking and remaking must be orderly and relatively resistant to modification by the exigencies of development. This is *specificity*. However, as both laboratory animal experiments and our own human experience show, both the fine details of the 'wiring' of the visual cortex, and how and what we perceive of the world are both directly and subtly shaped by early experience. This is *plasticity*. All living organisms, and perhaps especially humans with our large brains, show both specificity and plasticity in development, and both properties are enabled by our genes and shaped by our experience and developmental contingency. Neither genes nor environment are in this sense determinant of normal development; they are the raw materials out of which we construct ourselves.

Thus, the four dimensions of living processes – three of space and one of time – cannot be read off from the one-dimensional strand of DNA – nor yet the modular minds it is supposed to generate. A living organism is an active player in its own destiny, not a lumbering robot responding to genetic imperatives while passively waiting to discover whether it has passed what Darwin described as 'the continuous scrutiny of natural selection'.

Individual genes are not the only level of selection

Central to the theoretical structure of evolutionary psychology is the concept of the individualistic, 'selfish gene' as not only *the* replicator, but as *the* only level at which selection operates. It was this assumption which lay at the core of the Fisher–Haldane synthesis, and which envisaged genes rather as individual beads on a string – a view disrespectfully described as the 'bean-bag' model by other population geneticists. The present-day understanding of the fluid genome in which segments of DNA responsible for coding for subsections of proteins, or for regulating these gene functions, are distributed across many regions of the chromosomes in which the DNA is embedded, and are not fixed in any one location but may be mobile, makes this simple view untenable. However, it always was. To play their part in the creation of a functioning organism many genes are involved – in the human, some hundred thousand. For the organism to survive and replicate, the genes are required to work in concert – that is, to co-operate. Antelopes that can outrun lions are more likely to survive and breed than those that cannot. Therefore, a mutation in a gene which improves muscle efficacy, for instance, might be regarded as fitter and therefore likely to spread in the population. However, as enhanced muscle use requires other physiological adaptations – such as increased blood flow to the muscles – without this concerted change in other genes, the individual

mutation is scarcely likely to prove very advantageous. In addition, as many genes have multiple phenotypic effects (pleiotropy), the likelihood of a unidirectional phenotypic change is complex – increased muscle efficacy might diminish the longevity of the heart, for example. Thus, it is not just single genes which get selected, but also genomes. Selection operates as the level of gene, genome and organism.

Nor does it stop there. Organisms exist in populations (groups, demes, etc.). Back in the 1960s, V. C. Wynne-Edwards argued that selection occurred at the level of the group as well as the individual. He based this claim on a study of a breeding population of red grouse on Scottish moors, and argued that they distributed themselves across the moor, and regulated their breeding practices, in a way which was optimum for the group as a whole rather than any individual member within it. It may be in the individual's interest to produce lots of offspring, but this might overcrowd the moor, which could only sustain a smaller number of birds; hence it is in the *group's* interest that none of its members over-breed. Orthodox Darwinians, led by George Williams, treated this claim with as much derision as they did Lamarck's view that acquired characteristics could be inherited, and group selection disappeared from the literature for three decades.

Today, however, it is clear that the attack was misjudged. The work of one of the leaders of current evolutionary orthodoxy, John Maynard Smith, itself indicates that stability in a population of social animals, may require the mutual interactions of members with very different types of behaviours – so called evolutionary stable strategies. Maynard Smith gives as an example a population in which some individuals are aggressive towards others in the group, whereas others are more pacific – he calls them 'hawks' and 'doves'. He goes on to show mathematically that populations with all hawks or all doves are unstable, whereas a mix of both behavioural types at appropriate ratios will be stable (Maynard Smith, 1982). An evolutionary stable strategy like this can be modelled as if it was based on either individual or group selection; the distinction is more semantic than 'real'. However, there are an increasing number of examples of populations of organisms whose behaviours can most economically be described by group selectionist equations. Recently Elliott Sober and David Sloan Wilson (Sober and Wilson, 1998) have published a major reassessment of such models and shown mathematically how even such famously counter-intuitive (for ultra-Darwinians) phenomena as altruism can occur, in which an individual sacrifices its own individual fitness, not merely for the inclusive fitness of its kin but for the benefit of the group as a whole.

Finally, there is selection at even higher levels – that of the species, for example (Jay Gould, 1998). Natural selection may be constantly scrutinising

and honing the adaptiveness of a particular species to its environment, but cannot predict the consequences of dramatic changes in that environment, as, for example, the meteor crash into the Yucatan believed to have precipitated the demise of the dinosaurs. Selection also operates at the level of entire ecosystems. Consider, for example, a beaver dam. Dawkins uses this example to claim that the dam may be regarded as part of the beaver's phenotype – thus swallowing an entire small universe into the single strand of DNA (Dawkins, 1982). However, if it is a phenotype, it is the phenotype of many beavers working in concert, and indeed of the many commensal and symbiotic organisms which also live on and modify for their needs the structure of the dam. As Sober and Wilson point out, selection may indeed occur at the level of the individual, but what constitutes an individual is very much a matter of definition. Genes are distributed across genomes within an organism, and they are also distributed across groups of organisms within a population. There is no overriding reason why we should consider 'the organism' as an individual rather than 'the group', or even 'the ecosystem.'

Natural selection is not the only mode of evolutionary change

Darwin was a pluralist. He was very careful to state that natural selection is not the only motor of evolutionary change. He invented the concept of sexual selection, the only addition to natural selection which evolutionary psychology theorists are prepared to include in their pantheon. We need not be Lamarckian to accept that other processes are at work. The existence of neutral mutations, founder effects, genetic drift, exaptations and adoptations (Dover, 2000) all enrich the picture.

Not all phenotypic characters are adaptive

A core assumption of ultra-Darwinism is that if not all, then most observed characters must be adaptive, so as to provide the phenotypic material upon which natural selection can act. However, what constitutes a character – and what constitutes an adaptation – is as much in the eye of the beholder as in the organism that is beheld, as Gould and Lewontin pointed out in their famous paper on spandrels (Gould and Lewontin, 1979). Natural selection's continual scrutiny does not give it an *a la carte* freedom to accept or reject genotypic or phenotypic variation. Structural constraints insist that evolutionary, genetic mechanisms are not infinitely flexible but must work within the limits of what is physically or chemically possible (for instance, the limits to the size of a single cell occasioned by the physics of diffusion processes, the size of a crustacean like a lobster or crab by the constraints

of its exoskeleton, or the impossibility of genetically engineering humans to sprout wings and fly because of the limits to the possible lift of any conceivable wing structure). Webster and Goodwin (1996) have extended this argument further, arguing that there are exact 'laws of form' that ensure, for instance, pentadactyl (five-fingered) limbs. Gould (1989) takes a contrasting line, arguing that much evolutionary change is contingent, accidental, and that, as he puts it, if one were to wind the tape of history backward and replay it, it is in the highest degree unlikely that mammals, let alone humans, would evolve. It is not necessary to adjudicate between these positions to appreciate the limits to the automatic assumption that all phenotypic characters are the honed consequences of natural selection at work.

Yet this is exactly what evolutionary psychology theorists do, again and again. Consider Martin Daly and Margo Wilson's search for evolutionary explanations to support their claim that stepfathers kill their adopted offspring more frequently than do natural fathers, ignoring the much more obvious proximal causal processes, of the complexity of multiple relationships with their attendant economic and social insecurity. As Hilary Rose (2000) has pointed out, social science's proximal explanations are much richer and explanatory. In addition, such examples manifest themselves repeatedly in the assemblage of papers on human sociobiology and evolutionary psychology that now fill the pages of the evolutionary psychology group's house journals, web sites and academic or popular books.

'Architectural' minds

Unlike earlier generations of genetic determinists, evolutionary psychologists argue that these proximal processes are not so much the direct product of gene action, but of the evolutionary sculpting of the human mind. The argument, drawing heavily on the jargon and conceptual framework of artificial intelligence, goes as follows: the mind is a cognitive machine, an information processing device instantiated in the brain. However, it is not a general-purpose computer, rather it is composed of a number of specific modules (for instance, a speech module, a number sense module[7] a face-recognition module, a cheat-detector module, and so forth). These modules have, it is argued, evolved quasi-independently during the evolution of early humanity, and have persisted unmodified throughout historical time, underlying the proximal mechanisms that traditional psychology describes in terms of motivation, drive, attention and so forth. Whether such modules

[7] For an example, see Dehaene (1997).

are more than theoretical entities is unclear, at least to most neuroscientists. Indeed evolutionary psychologists such as Pinker go to some lengths to make it clear that the 'mental modules' they invent do not, or at least do not necessarily, map on to specific brain structures. (In this sense, they are rather like Dawkins' theoretical genes.) However, even if mental modules do exist they can as well be acquired as innate (Ellman *et al*., 1996). In addition, even one of the founders of modular theory, Jerry Fodor, has taken some pains to dissociate himself from his seeming followers, in a highly critical review of Pinker (Fodor, 1998).

For evolutionary psychology, minds are thus merely surrogate mechanisms by which naked replicators enhance their fitness. Brains and minds have evolved for a single purpose, sex, as the neuroscientist Michael Gazzaniga rather bluntly puts it (Gazzaniga, 1985). However, yet in practice evolutionary psychology theorists, who are not themselves neuroscientists or even, by and large, biologists, show as great a disdain for relating their theoretical constructs to real brains as did the now discredited behaviorist psychologists they so despise. Although many brain processes – such as visual analysis, for example – do take place in distinct 'modules' or cell assemblies (Zeki, 1993) – the coherent result of brain activity unifies these distinct processes through distributed, non-hierarchical mechanisms.[8]

The insistence of evolutionary psychology theorists on modularity puts a particular strain on their otherwise heaven-made alliance with behaviour geneticists. For instance, IQ theorists, such as the psychometrician Robert Plomin, are committed to the view that intelligence, far from being modular, can be reduced to a single underlying factor, *g*, or crystallised intelligence (Plomin and Craig, 2001). A similar position has emphatically been taken in recent years by Herrnstein and Murray in *The Bell Curve* (Herrnstein and Murray, 1994), who argue that whatever intelligence is, it cannot be dissociated into modules!

Modules or no, it is not adequate to reduce the mind/brain to nothing more than a cognitive, 'architectural' information processing machine. Brains/minds do not just deal with information. They are concerned with living meaning.[9] In *How the Mind Works*, Pinker offers the example of a footprint as conveying information. My response is to think of Robinson Crusoe on his island, finding a footprint in the sand. First he has to interpret the mark in the sand as that of a foot, and recognise that it is not his own. However, what does it mean to him? Pleasure at the prospect of at last another human being to talk and interact with? Fear that this human may be dangerous? Memories of the social life of which he has been

[8] See, for example, Singa (1998).

[9] See, for example, Rose (1992, 1999) and Freeman (1999).

deprived for many years? A turmoil of thoughts and emotions within which the visual information conveyed by the footprint is embedded. The key here is emotion, for the key feature which distinguishes brains/minds from computers is their/our capacity to experience emotion. Indeed, emotion is primary – which may be why Darwin devoted an entire book to it rather than to cognition.

Emotional mechanisms, and indeed their expression, are evolved properties, and several neuroscientists have devoted considerable attention to the mechanisms and survival advantages of emotion (Damasio, 1994, 1999; LeDoux, 1996). So it is therefore all the more surprising to find this conspicuous gap in the concerns of evolutionary psychologists – but perhaps this is because not even they can speak of a 'module' for emotion. Rather, affect and cognition are inextricably engaged in all brain and mind processes, creating meaning out of information – just one more reason why brains aren't computers. What is particularly egregious in this context is the phrase, repeated frequently by Pinker, 'the architecture of the mind'. Architecture, which implies static structure, built to blueprints and thereafter stable, could not be a more inappropriate way to view the fluid dynamic processes whereby our minds/brains develop and create order out of the blooming buzzing confusion of the world which confronts us moment by moment.

On free will

There is an ultimate contradiction at the core of evolutionary psychology theory. Whatever the claimed evolutionary honing of our every intention and act, evolutionary psychologists remain anxious to insist on at least their own autonomy. 'If my genes don't like it,' says Pinker, 'they can go jump in the lake' (Pinker, 1997). Rather less demotically, Dawkins insists that only we as humans have the power to rebel against the tyranny of the selfish replicators.[10] Such a claim to a Cartesian separation of these authors' minds from their biological constitution and inheritance seems surprising and incompatible with their claimed materialism. Where does this strange free will come from in a genetically and evolutionarily determined universe?

The problem is indicated even sharply by the reprinting of a series of classical anthropological and sociobiological papers in the collection entitled *Human Nature* (Betzig, 1997). The editor's view is that these show the way that Darwinian insights transform our understanding of social organisation. The papers were largely published in the 1970s and 1980s, and, for their republication in 1997 each author was asked to reflect in retrospect

[10] See the concluding sentences of *The Selfish Gene* (Dawkins, 1976).

on their findings. What is interesting is that when the anthropologists go back to their field subjects, they report rapid changes in their styles of living. Kipsigis women no longer prefer wealthy men (Borgerhoff, Mulder), the Yanonomo are no longer as violent as in the past (Chagnon), wealth no longer predicts the number of children reared (Gaulin and Boster), and so forth. Each of these societies has undergone rapid economic, technological and social change in the last decade. What has happened to the evolutionary psychology predictions? Why have these assumed human universals suddenly failed to operate? Has there been a sudden increase in mutation rates? Have the peoples they had studied taken Dawkins to heart and decided to rebel against the tyranny of their selfish replicators?

There is a simpler explanation. The evolutionary path that leads to humans has produced organisms with profoundly plastic, adaptable brains/minds and ways of living. Humans have created societies, and invented technologies and cultures. We, the inheritors of not merely the genes, but also the cultures and technologies of our forebears, are profoundly shaped by them in ways that make our future as individuals, societies, and species, radically unpredictable. In short, the biological nature of being human enables us to create individual lives and collective societies whose futures lie at least in part in our own hands.

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QUESTIONS AND DISCUSSION

Armando Aranda: May I ask you, do you have any kind of key differences in your notion of autopoiesis and the one proposed by Maturana and Varela?

Steven Rose: No, it's very close, Maturana and Varela argued this. I haven't heard them argue it in quite this sort of way but the concept is close.

Michel Morange: You criticise the concept of gene of behavioral geneticists, but in fact when one looks at the criticisms you were addressing, the same concept of gene was used by classical geneticists, and still today it is chosen by many population geneticists. I think there is something in the concept itself which raises problems.

Steven Rose: There are at least two different ways in which the concept of genes is used. One is by population biologists in which, as I said, the gene becomes a theoretical entity. It's something that you infer in order to track evolutionary change in some sort of way. The second is the way that behaviour geneticists use genes in which they attempt to calculate heritability or, nowadays to isolate individual genes which have individual protein products. As you, and other people, were discussing yesterday, what we know about genes or strands of DNA is that they encode the proteins. We also know that they are labile, they are edited, they are transcribed, there are multiple ways of transcribing genes, and we also know that what brings a strand of DNA into existence as an active player within the cell, you Michel know very well, is not simply the DNA but it's the cellular environment in which it is embedded. So all those metaphors of genes as master molecules, as controlling what is going on in the cell, are a misunderstanding of the ways in which cellular processes operate. When geneticists refer to a gene 'for', most geneticists will say yes this is a shorthand slang expression and we understand, as it were, that it is not really a gene 'for', at best it's a gene in whose absence particular processes do not occur. That is, it's an absence of a gene rather than the presence of a gene which most people are referring to. But nonetheless, it is a widely misunderstood use of the term 'gene', and I agree with you that if I think this is the way that you were going, but many of my comments on genes in relationship to behaviour could apply to genes in other contexts. It's particularly in the context of claims in relationship to behaviour, that I think that many of the problems emerge at least in the sorts of terrain which interest me. There are clearly, for other people, other areas of problems.

Sahotra Sarkar: Let me make a comment, only partly tongue in cheek, which you probably will think completely unfair. There is virtually nothing that you said that I disagree with except for some of the religious terminology of autopoiesis and stuff like that. The comment I want to make is, yes we all say that there is this complicated developmental process where there is an

attraction between your heredity and environmental factor, the history of the environment matters and all of that. It's also true that these organisms don't just react to a passive environment – they create their environment and all of that. Beyond just accepting these things as true, and I do accept them as true, where does this new vision that you have date you in terms of designing research programmes?

Steven Rose: Well, it depends whether we are talking about me personally or research programmes in general. It wouldn't take me into funding a study of the routes of human aggression by the Law Enforcement Agency in the US. I'm not convinced that it would have taken me in favour of funding the Human Genome Project, though I was more critical of that at the beginning than I think I am now, partly because of the diversion of resources, but nonetheless I think that's a debatable area. Let me tell you where it takes me in terms of my own subject which is learning and memory, and that is understanding that, despite 30 years of research in this area, we are not going to find either memory molecules or stable patterns of ensembles of cells in which memory is encoded in that sort of way. The interesting thing about memory is that it is for all of us a subjective experience which shapes our own lives. For a laboratory researcher on memory it's also a process that we try to study objectively in the laboratory. Trying to bring those two parts of the experience of memory together, which has occupied me increasingly over the last few years, actually changes the nature of the research programme one engages in, but it also changes profoundly the models that one has of the nature of memories in the brain. No longer, if you like, fixed ensembles of cells, but dynamic and shifting patterns of connections which are recreated each time we recreate the memory. Now that it is a dynamic perspective which is very different from the one that you find that I was referring to yesterday, the doyen of memory research in the US, Eric Kurdel, for instance. So it does shift a research programme quite practically as well.

Ken Schaffner: To comment on your reference to schizophrenia genetic work, I think that the investigators in that area, and they are worldwide as you know, are sensitive to difficulties of characterising the disease. They deal with narrow definitions from DSN and then they find that they need to have broader definitions and then still broader definitions including things like schizotypal personality and so forth, so I have tended to see at least three clusters that have been investigated. The claim is that there are statistically significant linkages to various chromosomes like 6 and 13 and the like. The problem is that there is so much looseness in the methodology that the investigators seem to pick whatever classification they want to use in order to get the statistical significance and there haven't been terribly

useful replications. I think there is sensitivity to it, but I don't think that the science is yet very good. It may be, I wouldn't want to use the word 'dishonest' with this much flexibility, but there are I think some serious problems with the methodology.

Steven Rose: I think there are serious problems with the methodology, with the definition of what constitutes schizophrenia, which is particularly why some clinicians in this area argue that you should actually not deal with labelling but deal with symptoms. But there are peculiar features of it: one is that the diagnosis of schizophrenia is beginning to disappear in Britain over the last few years, but the other (and I tell this story because I think it is very reflective on the reductionist mindset that behaviour geneticists have) one of the sharp features of schizophrenia in the UK is that there is a far greater incidence of the schizophrenia diagnosis amongst people of Caribbean origin than there is of people of white origin in Britain. But also there is a far greater incidence, a sixfold greater incidence, of schizophrenia in the children of black/white relationships in the US than there is in any of the parent populations. Now, I thought there was no conceivable way in which you could account for this in genetic terms, and it seems to me much clearer accounted for by the existence of someone with two different types of ethnic origins in a profoundly racist society, and that seemed a potential explanation to me. I put this to a leading behaviour geneticist concerned with schizophrenia in the US and he thought for two minutes and he said 'Of course there's a genetic explanation. It's assortative mating; you have to be mad to marry and have a child across a colour boundary like that'. And that simply reflects, I think, what several people said yesterday – there is no conceivable distribution of a phenotype of the population that you cannot account for by partial penetrance, incomplete dominance and assortative mating. It's a completely self-contained and therefore unrefutable research programme in this context.

Ken Schaffner: I don't know the data that relates to the specific problems that you're talking about, but I think there are always difficulties about diagnosis in this area, and there's likely to be biases of all sorts with respect to trying to determine whether or not an individual fits a diagnosis or not. I think one has to be eternally vigilant and careful with respect to those kinds of diagnoses, but my question was about the Brunner study that you had mentioned, the MALA study. I had read Brenner's paper in the CIBA volume that you showed, and it looked to me as if he was actually backing away from the results of that study. One, he said, it was very limited, it wasn't going to be replicated, it didn't have any extrapolability. I couldn't tell whether or not this was under social pressures because I had read some things in *Science* that indicated that he had come under a lot of criticism,

from his University for pursuing this kind of research, or whether he felt that it was so methodologically limited and the phenotype was just as you say bizarre that it just hasn't gone anywhere.

Steven Rose: You're absolutely right, and he was much more cautious about the interpretation than the US members of the team who were the majority authors in the paper, who were much more 'gung-ho' in the terms of the way it's interpreted. Also, as you know, the question as to whether you can employ a genetic defence against a criminal charge, for example, of violence, as in the Stephen Mobley case, has now come to the fore in the US and is still, I think, unresolved. But, yes, Brunner did, I think – it was quite interesting the way he backed away from that in that CIBA meeting, but the original paper and the way it has been interpreted remains, I think, a much more conspicuous landmark in the literature than does a bit of discussion in a slightly obscure book, unfortunately.

Ken Schaffner: I agree with that. People haven't noticed the CIBA volume, but they have continued to notice the *Science* paper.

Panayiotis Tsakalis: I generally agree with you and I found your speech very interesting and instructive to me, but let me pretend to be devil's advocate for a while. I want to pose two questions. First, you mentioned 'free will', and you said that we have the ability to overcome what DNA determines or something like that. If we assume that 'free will' is a psychological term, someone could say that it is related, or it is reduced to a biochemical equilibrium. In order to see that, think of someone who is drunk, or someone who gets a more lenient sentence just because he was recognised to be 'not in full control' of his actions, when she/he committed a crime. I want your comment on that. My second question is this – what do you exactly mean by 'meaning', when you say that mind is not dealing with information but with meaning? Somebody else could suggest that we are just Turing machines that read printed characters on a tape and that later we produce a kind of calculation or 'thinking' endowed with meaning. We could have a Turing machine reading Dennett's footprints and connected to a gun to have him shot, as somebody has meaningfully wished!

Steven Rose: I'm not likely to shoot Dan – I think he's a good protagonist. Other people here may disagree, but the quotations on 'free will' I gave at the beginning from Pinker and from Dawkins were designed to show what seemed to me to be a conceptual flaw. They weren't designed to say that these were positions I supported, and that is I cannot see how on the one hand you can argue that you are a lumbering robot designed for the propagation of your genes, and then say that you have the power to overcome the tyranny of the selfish replicators. In some way, the power to overcome the tyranny must be embedded in the replicators themselves

on this argument. So a thoroughly materialist position cannot allow this sort of dualism of escape, and therefore a thoroughly materialist position doesn't make a dichotomy between the power of the genes and the nature of the living processes, but tries to understand how they are integrated in the complex of choices and determinisms within which all living organisms are faced all the time. And that seems to me to be a more thoroughly materialist position, and a more complicated position than the Dawkins or Pinker one. On meaning, I guess what I'm trying to argue is precisely against the computer metaphor for the way that brain processes operate. There's a long literature on this and I've written about it elsewhere, and I'll take too much time if I try and expand on that here. Let me just do it very briefly by saying that 'information processors' imply, as it were, a neutral assessor and absorber of information – that's what they mean when they talk about the computation of architecture of the brain. What I'm trying to argue is that information is never neutral, it's never simply cognitive architecture. It's always imbued with affect, with emotion, with the experience of past history, and so on. It's well demonstrated in Tony Damasio's books, *Descartes Error* and his more recent *Feeling of What Happens*, and that's the sort of argument that I'm making, where I'm insisting on meaning which has relevance to the history of the organism and is not neutral in this sort of way. The other arguments about whether brains are computational Turing machines and so on, which I am absolutely sure they are not, take us again outside the terrain that we are discussing. We can talk about it later.

Bob Richards: Fred offered a little earlier, the model of what happens in sickle-cell anaemia case where there's a huge sequelae of different kinds of what might be regarded as symptomatic clusters. In the case of the mouse pup macao genes, would you say that model that has sickle-cell is a fair model in a general sort of way for what happens with the mouse pups who displayed various kinds of behaviour, including some that were labelled aggressive.

Steven Rose: You mean it's the pleiotropic consequence of the deletion of that particular gene? Yes, but I think in a sense that pleiotropy has almost lost its meaning in this particular context. We do not know the routes in any of these cases between the deletion of the gene and those complex forms of behaviour. We do not know (it's the same as the argument about spandrels, in a sense) which are secondary and which are primary aspects of the behaviour that we're talking about. We don't know the cellular routes. The main problem with the knock-outs in this consequence is the same as the lesion study. What you're doing is investigating the properties of the system in the absence of that particular gene. You're not studying the effect of that particular gene. The analogy was made many years ago by Richard

Gregory, and it still applies – if you take a radio and delete a transistor from it and the result is that instead of a symphony you get a howl, you can't conclude that the function of the transistor was a howl suppressor. That is one of the major problems of knock-out studies, that they are compounded by the fact that if you take a transistor out of a radio it can't self-repair. In a developing animal, if you take out a gene, then what you get is compensatory plasticity, other processes taking over as well. So the interpretation of any of those knock-out studies is immensely complicated.

Chapter 15

Reductionism and Social Policy[1]

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At the annual meeting of the American Society for Cell Biology in 1999, Paul Sternberg of the California Institute of Technology announced – 'To me the challenge for the year 2000 and beyond is [to understand] the genetic control of behavior and to reduce behavior down to problems in cell biology'.[2]

Gregory Simon, a psychologist who uses brain imaging to study multiple chemical sensitivity, asserts that 'Beliefs are chemical events in the brain. They must be'.[3]

Stephen S. Hall imagines a day 'when the MRI machine replaces the couch, when the therapist uses words or odors or pictures to excite and pinpoint circuitry and then the neuroanatomist translates the images into explanations of behavior' (Hall, 1997).

Science popularizer Matt Ridley sums it all up – Genes are 'recipes for both anatomy and behavior' and the body is but 'the victim, plaything, battleground and vehicle for the ambitions of the genes' (Ridley, 1999).

Reductionist theories of human behavior are hardly new. During much of the Nineteenth and Twentieth centuries man has been constructed as an evolutionary product, the brain as biochemical, and the body as hormones or genes. The Nineteenth century sciences of craniometry and phrenology reduced social, moral, and intellectual differences to physical manifestations.

[1] The assistance of Aaron Panofsky is much appreciated. So too are the contributions of Susan Lindee in our book, *The DNA Mystique: The Gene as a Cultural Icon* (Nelkin and Lindee, 1995).

[2] Quoted in *Science*, **283**, 171 (1999).

[3] Quoted by Joseph Dumit in 'Doing things with evidence: living ill in a risk society', paper presented at CASTAC Meeting, Columbia University, New York, June 11, 1999.

Promises and Limits of Reductionism in the Biomedical Sciences
Edited by M.H.V. Van Regenmortel and David L. Hull

The bodies of criminals, wrote anthropologist Henry Boies, 'Diverge in some essential respect from the normal type of mankind'.[4]

During the eugenics movement, scientists saw the 'germplasm' as the source of intelligence or feeblemindedness, special talents or criminal tendencies, industriousness, pauperism, alcoholism, laziness, poverty, harlotry and vagrancy (Kevles, 1985). The physical markers so important in the earlier classification of human behavior became less meaningful as real differences moved from gross to hidden body systems. Behavior and personal character were reduced to the germplasm. Today, they are reduced to the genes.

Reductionist views of behavior have become so pervasive, so well integrated into the way we think, that they pass as self-evident and unproblematic. When exploring the mass culture media for our book, *The DNA Mystique*: *The Gene as a Cultural Icon*, historian Susan Lindee and I found an extraordinary range of behavior attributed to the genes, including aggression and violence, homosexuality, exhibitionism, addiction, arson, intelligence, learning disabilities, tendency to tease, propensity for risk-taking, family loyalty, religiosity, social potency, tendency to giggle, traditionalism, happiness and zest for life (Nelkin and Lindee, 1995). Recently, a Scottish investigator has claimed to have found a 'laziness gene' that 'explains Scotland's poor health record'. He is looking for therapies that would increase his countrymen's desire for exercise.[5]

The scientific and philosophical problems of such reductionist claims have been extensively debated.[6] This paper will not deal with questions of scientific validity, but rather with some of the policy implications and applications of reductionist modes of thinking about the body and behavior.

Today, reducing behavior to molecular substrates has remarkable appeal. By providing tools for predicting future health and behavior, genetic explanations have become a scientific basis for policy decisions (Nelkin and Tancredi, 1995). Framing the way we think about individual success or failure, sources of social problems, and questions of blame and responsibility, reductionist ways of thinking, I will argue, bear on legal and institutional practices. Offering visions of moral (that is, natural) order, they convey a message about workable social policies. In addition, driven by economic and social agendas, reductionist theories are translated into moral guidelines and justifications of prevailing beliefs about appropriate behavior, effective policies, and even the nature of the person.

[4] Boies (1893) – quoted in Rafter (1997, p. 118).

[5] August 24, 1999.

[6] See, for example, Lewontin *et al*., 1984.

Social context

Historical experience has demonstrated the cultural importance of scientific ideas when they coincide with current social preoccupations and support existing beliefs. The scientific illumination of what is 'natural' has long served to justify social policies. The sciences of craniometry and phrenology were used, for example, to assess predispositions to criminal behavior, suitability for immigration, and social and physical fitness for work. The reductionist theories of the eugenics movement were a way to justify – as natural – the policies to reduce the number of unproductive members of society through reproductive controls. Premised on the notion of human improvement, eugenics appealed in the cultural context of social reform in the United States during the 1920s. Fiscal conservatives, Social Darwinists, and anti-immigration nativists all used eugenic ideas to support their political goals.

The value placed on efficiency and predictability, and the institutional pressures for cost-containment, accountability and measurability are enhancing the appeal of reductionist theories. They fit with the tendency to locate social problems in individual pathology. They suit the actuarial mentality that places faith in statistical information as a means to predict and minimize future risk.[7] Genetic and evolutionary explanations have become a way to address the issues that trouble society – the perceived decline of the family, the problems of crime and persistent poverty, changes in the ethnic structure of the population, and the pressures on public schools.

Patterns of research funding since the 1980s have both reflected and encouraged interest in reductionist approaches to social problems. If one looks back to the 1960s, the National Institute of Mental Health (NIMH) had sustained the Great Society Programs through its support of studies of the influence of poverty and urban blight on behavior. However, President Reagan gutted the NIMH budget and redefined its authority to emphasize its scientific mission. The new plan, according to Steven E. Hyman, former Director of the NIMH, was 'to bring biology to center stage in the efforts to understand human behavior' (Hyman, 1998). This increased focus on the biological components of behavior provided an apparently more straightforward research agenda and also allowed co-ordination with the biotechnology and pharmaceutical industries. However, the reductionist approach has foreclosed other possibilities for research. The important questions about human behavior and social problems such as crime and poverty are increasingly addressed from biological rather than social perspectives – with deep and sometimes problematic policy implications.

[7] For a discussion of the actuarial mentality and its institutional implications, see Nelkin and Tancredi (1994).

Addressing crime

'Evil is embedded in the coils of chromosomes that our parents pass on to us at conception', writes a *New York Times* reporter (Franklin, 1999). Media references to violence genes or criminal genes are ubiquitous. When geneticist Xandra Breakfield associated the high incidence of impulsive aggression among the men in a Dutch family with an extremely rare mutation in a gene for the MAO enzyme, her preliminary study of a single family became a media event. Even war, despite its extraordinary political complexity, has been reduced to genes by evolutionary psychologists who regard conflict as an adaptive strategy for males to acquire the resources to mate and to produce offspring that will carry on their genetic endowment. Their theories, they claim, can yield tools for identifying regions that are ripe for conflict before trouble actually breaks out.[8]

The pervasive tendency to reduce aggressive behavior to the genes has opened the way to speculations about risk-management measures that might help to prevent crime more efficiently by identifying and circumscribing the rights of those thought to have criminal predispositions. Preventive models call for calculating risk probabilities. These calculations are based not on individual dangerousness implied by a person's actions, but on predictions that might indicate potential risk. Preventive measures could include identifying the purportedly predisposed or keeping certain groups under surveillance. The idea holds media appeal. 'Rape could be reduced greatly' wrote a journalist for the American Airlines magazine, *The American Way*, 'if we had a way to determine who was biologically predisposed to it and took preemptive action' (Keehn, 1992).

Though shocking in terms of civil liberties, the concept is consistent with recent trends in the criminal justice system. British criminologist Nikolas Rose has described the increased employment of preventive models in the United States in the efforts to control crime (Rose, 1999). Sexual predatory statutes in some states, for example, require 'propensity hearings'. Megan's law requires those convicted of sexual crimes to register the fact with local police after they have served their time.

Reductionist explanations of behavior may also influence legal decisions for they bear on concepts of moral responsibility and free will. In Georgia, the lawyers appealing against the death sentence of a murderer, Stephen Mobley, used a genetic defence to argue that their client was not responsible for the crime because his genes predisposed him to violence. In this case, a biological defence was used to argue for mitigating punishment. However, biology-based arguments can be appropriated for other ends. The perception

[8] C. G. Mesquida and N. I. Weiner – quoted in Saltus (1998).

that genetic conditions are hopeless and immutable could call for permanent incarceration or the death penalty for those with 'bad' genes. Criminologist Norval Morris argues that linking behavior to genetic predisposition will tend to augment the severity of society's response to criminal behavior and increase punitive control (Morris, 1994).

Writing on behavioral psychology, science popularizer Robert Wright argues that the idea of moral responsibility underlying the current legal system is unrealistic because it is grounded on the premise that individuals can freely choose how they will behave. However, people, says Wright, cannot control what they do because they are driven by their genes. Policies must change accordingly – 'Tortured legal doctrines that defy ... our emerging comprehension of human nature are unlikely to withstand the test of time' (Wright, 1944, p. 203).

However, reductionist explanations of violent behavior follow less from science than from political ideas about punishment and prison reform. Disillusioned with the failure of past rehabilitation schemes and pressed to save money, criminologists are leaning toward 'selective incapacitation' of prisoners instead of efforts to rehabilitate them (Jeffery, 1985, p. 82). Theories of behavioral genetics have become convenient ways to justify these trends. Significantly, research funding in the field of criminology is increasingly directed towards studies of the biological cause of violent behavior.[9]

Opposing immigration

Genetic arguments also enter policy debates over immigration. Biology-based theories influenced the restrictions on immigration from Central, Southern, and Eastern Europe that were imposed in the United States by the 1924 Immigration Act (Kraut, 1994). They appealed at that time in the context of economic concerns – the public cost of supporting the poor, and the threat of a new and endless supply of cheap immigrant workers. After World War 2, eugenic arguments virtually disappeared from public discourse, but they are reappearing today in the arguments of nativist groups (Nelkin and Michaels, 1998). Directed mainly towards Hispanic immigration, their rhetoric reduces behavior, skills and IQ to biological differences.

Nativists contend that genetically determined traits are characteristic of specific racial groups and that cultures themselves can be reduced to biological characteristics. Extremists have opposed immigration with arguments that the inferiority of some races is a 'biological fact' based on evolutionary

[9] The US Department of Justice (1999) seeks to support the 'Application of principles of science and technology to understand problems of crime', and in particular has developed a five-year plan to 'encourage development of cutting-edge molecular biology methods and tools'.

history. However, such views also appear in mainstream media as race theorists promote their views about genetic differences. In *The Bell Curve*, Richard Herrnstein and Charles Murray argued that economic inequities are a ratification of 'genetic justice' and insist that immigration policy must consider that Latino and Black immigrants 'are putting downward pressure on the distribution of intelligence' (Herrnstein and Murray, 1994). A psychologist, J. Phillipe Rushton presents a gene-based theory of racial differences in brain and genital size based on evolutionary adaptations. Such differences, he says, call for racial selectivity in immigration.

In order to deny the possibility of assimilation, these writers reduce culture itself to a biological phenomena. Peter Brimelow, in an anti-immigration book called *Alien Nation*, writes that the process by which nations are created 'is not merely cultural, but to a considerable extent biological (Brimelow, 1994). This means that cultures develop through evolutionary changes expressing the genetic characteristics of their people. Based on a Darwinian model of world history, this view posits that some people are intrinsically backward and some nations intrinsically poor. They 'possess differing degrees of evolution'. Rushton too argues that cultures express genotypes – that questions of order, socio-political attitudes, and variation in skills can all be reduced to genetic makeup. In addition in France, Bruno Megret, Secretary General of the Front National, said in 1991 that 'True Ecology goes hand in hand with the defense of identity ... Why fight for the preservation of animal species and accept at the same time the principle of the disappearance of the human races due to widespread miscegenation?'. He claims, as mentor, the eugenicist and Nobel Laureate, Alexis Carrel.[10]

Reductionist views enter policy discourse through anti-immigration lobbying groups. In the US, the most influential of these, the Federation for American Immigration Reform (FAIR), receives support from the Pioneer Fund, an organization with an explicitly eugenics agenda. FAIR's director, Dan Stein, has tried to dissociate himself from the explicitly eugenic framework of the European rightists such as Le Pen, but he too worries about race suicide and the future 'quality of the nation' (Stein, 1995).

Such beliefs are drawing respectability from the tendency to reduce human behavior to evolutionary explanations. Neo-Darwinist theories seem to explain why some people thrive in the competitive world of the 1990s and others do not. Promoting these theories, some scientists argue that genetics is important in selecting people with superior skills. Says, Daniel Koshland, molecular biologist and former editor of *Science* – 'As society

[10] Quoted by Andre Reggianni, at The New School, March 6, 2000.

gets more complex, perhaps it must select for individuals more capable of coping with its complex problems' (Koshland, 1988).

Explaining social inequities

The paradox of persistent poverty in an affluent society is another troubling issue calling for explanation. Reductionist theories are convenient: people are simply driven – and limited – by their genes. This again is a time-worn idea. Eugenicists, for example, had explained 'pauperism' as 'in the blood'. In retrospect, it is easy to see the fallacies in such formulations, but similar beliefs have re-emerged in public discourse, appearing in a preoccupation with what makes people different.

Gender differences, for example, are often explained in reductionist terms. Evolutionary psychologist Robin Baker believes that moral evaluations and realistic policies must take into account the differences between men and women that have evolved from the need to ensure that the fittest genes are carried to the next generation (Baker, 1996). This means that women's natural abilities will lead them to prefer child care to work outside the home. Richard Dawkins takes this idea further to claim that women have a disproportionate biological stake in children because of their 'investment' of both time and cytoplasm (the egg, after all, is larger than the sperm) (Dawkins, 1976). Women will therefore naturally be more interested in infants than men. In the mid-1990s, some political candidates from the religious right appropriated Dawkin's argument to oppose the Equal Rights Amendment.

Reductionist explanations of social differences conflict with the most basic assumptions underlying the democratic experiment in America – the belief in the improvability, indeed the perfectibility of human beings. They represent a remarkable change in the 'bootstrap ideology' that once pervaded American folklore; for neither individual actions nor social opportunity really matter if fate can be reduced to genes. The rich and powerful are what they are because of their genes – and so too are those who are dysfunctional. Opportunity becomes less critical than predisposition; for belief in genetic destiny implies there are natural limits constraining the individual. The moral? No possible social system, no possible educational or nurturing plan, can change the *status quo*. This is especially useful to those seeking to reduce the costly social services provided by the state. Why, asks Herrnstein and Murray, support job training, welfare, or child care programs when those targeted are biologically incapable of benefitting from the effort? (Herrnstein and Murray, 1994).

A statement proposing new guidelines for philanthropy from private organizations suggests the influence of reductionist explanations. Private

philanthropy has been based on the conviction that, given the opportunities provided by money, people can change. However, according to this statement, evidence ('widely accepted by experts') about the heritability of intelligence and other behavioral characteristics is challenging this conviction. 'Philanthropic efforts to help disadvantaged groups may well be thwarted to the extent that their differences are hereditary' (Lemkowitz, 1994).

Explaining educational failures

During the 1960s, explanations for academic failure had centered on the social environment – family, teachers, the organization of the classroom. However, today, behavioral and learning problems are located less in a student's social situation than in the biological structure of the brain. These ideas have been reinforced by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), published by the American Psychiatric Association. An influential document for establishing classification and diagnostic criteria in schools and mental health institutions, the DSM has reduced an increased number of problems – even telephone scatalogia – to developmental disturbances.

Educational institutions face demands for accountability and pressures to establish rigorous classification standards. In this context, genetic assumptions have strategic value. They offer, for example, apparently predictive indicators that can serve as a basis for categorizing students. They can be used to justify the expansion of special education programs. However, in the climate of cost containment, this is less likely than proposals that would support political efforts to abolish affirmative action, and to limit costly special education programs. For example, members of a taxpayers association in a Long Island, New York community, used genetic arguments in their effort to reduce local school taxes. They campaigned against their school district's program of special education classes for learning-disabled children by arguing that such disabilities are of genetic origin. That being the case, they concluded, responsibility should fall on the medical system, and not on the schools.

Interests and implications

These examples suggest how reductionist explanations of behavioral are translated into a moral rhetoric and a guide to social policies. The message, as one writer put it, is that 'Moral codes and policy prescriptions that don't acknowledge human nature are doomed to fail' (Flint, 1995). Many interests

are involved. Just as Wright argued that the legal system must acknowledge biological explanations of behavior, so Nigel Nicholson, a professor at the London Business School, claims that Chief Executive Officers (CEOs) have an interest in evolutionary principles. In an interview with *Fortune* magazine, he argues that certain companies are more successful than others because they follow a model 'for which we were designed' (Colvin, 1998).

The use of reductionist explanations may serve economic and business agendas in quite explicit ways. The Ernest Gallo Clinic and Research Center supports research to identify the biological causes of alcohol abuse. In 1993, the Center's scientists identified what they claimed to be a gene responsible for alcoholism. They hypothesized that this gene produced a protein that 'jams the signals', thus warning a person to stop drinking. Those who lack this genetic warning system are prone to become alcoholics. Learning about their condition allows them to take precautions. However, genetic explanations of alcoholism also serve the commercial goals of the wine industry that supports the research; for it locates responsibility for alcoholism not on their product, but on the vulnerable individual's DNA (Miller, 1994).

Similarly, the tobacco industry is supporting research on the molecular basis of the causes of lung cancer, hoping, according to critics, to sow doubt about the dangers of smoking (Cohen, 1996). Cancer is, of course, a genetic disease in the sense that it involves gene mutations. However, environmental influences are responsible for many mutations. The recent emphasis on the genetic basis of cancer and, indeed its redefinition as a genetic disease, can shift responsibility away from industry and regulators as the focus turns to individual predisposition.

The economic stakes in shifting blame can be seen in the courts. Defendants in some toxicity court cases are arguing that the plaintiffs are genetically predisposed to susceptibility to toxic exposure. In a products liability suit, for example, a plaintiff blamed his birth defects on *in utero* exposure to toxics at the plant where his mother worked. The defendant, however, claimed that a genetic disorder had caused the defects, not exposure to toxics.[11] In another liability case, a company tried to compel a plaintiff to take a test for Fragile-X Syndrome, insisting that his disability was not caused by toxic substances, but by his genes (Billings, 1996). I earlier quoted Gregory Simon, the psychologist, who defined that belief as a 'chemical event'. He is employed by Boeing Corporation and his statement, made at a conference on Multiple Chemical Sensitivity, was presumably intended to minimize the importance of toxic exposure as a cause of chemical sensitivity (see Footnote '3' above).

[11] Severson vs. Markem Corporation, No. 698517, February 26, 1990.

Reducing problematic behavior to biological causes calls for pharmaceutical solutions and here too powerful corporate interests foster such explanations. The redefinition of hyperactivity as 'Attention Deficit Disorder' (ADD), for example, has significantly benefitted the pharmaceutical industry. The use of Ritalin as a treatment for ADD has doubled since 1995, and it is prescribed to over 4 million children in the US. Production of the drug is up 700% since 1990, and 90% of the production is consumed in the US where pharmaco-genomics is a burgeoning field. Europeans have been more cautious, and the International Narcotics Control Board of the UN has expressed concern about the growing tendency to redefine behavior as amenable to pharmaceutical modification.

Managed healthcare systems also have interests in reductionist definitions of disease. The payment and reimbursement structures of Health Management Organizations (HMOs) require that conditions be identified and coded in terms of a predefined list of syndromes with pre-established measures of cost and risk. Calling for 'evidence-based medicine', HMOs are more likely to reimburse conditions that are defined as biological because diagnosis appears objective.

The hegemonic appeal of reductionist explanations is having important implications for the medical profession. It has, for example, led to the dominance of bio-psychiatry over earlier Freudian and community-based mental health approaches to mental illness, changing the role of the psychiatrist and the nature of many treatments (Brown, 1987). Attributing pathological behavior to biological causes has turned psychiatrists into psycho-pharmacologists as drugs have become the predominant therapeutic tool. The change is partly driven by increased scientific understanding of mental illness and the real therapeutic effectiveness of certain drugs. However, it is also a response to economic pressures for rapid and cost-effective treatment brought about by new reimbursement strategies and the need to control costs.

Perhaps more important, reductionist definitions of the body and behavior are effecting perceptions of the person. Supported by many interests, these definitions are, in effect, reconstructing the person in terms of economic categories. This, however, is not the first time. In 1970, a commission met in London to measure the affect of the proposed Third London Airport. The Commission assumed that people have a cash value and their worth could be reduced to a price. They calculated this at £9300. However, following the logic of the calculation, a critic discovered that because women and old men consume more than they produce, they are a net drain on the economy so they have negative value (Adams, 1971).

In the biotechnology age, the body really does have cash value as a potential source of valuable patents, marketable products and useful

information (Andrews and Nelkin, 2000). Body tissue is valued today by scientists seeking research information, companies needing material for pharmaceutical products, and institutions seeking predictive information about individuals. The body in this entrepreneurial culture is reduced, in effect, to a commodity. It is, writes anthropologist Margaret Lock, 'reified, isolated, decontextualized, and abstracted from real time, actual location and social space' (Lock, 1993).

The value of the human body in the biotechnology age is encouraging the reduction of persons to objects. In the language of contemporary science, the body has become a 'project' – a system that can be divided and dissected down to the molecular level'. Science texts are permeated with a commercial language of supply and demand, contracts, exchange and compensation. Body parts are extracted like a mineral, harvested like a crop, or mined like a resource. Tissue is procured. Cells, embryos and tissues are banked, placed in repositories, marketed, patented, bought and sold. A baby, conceived to supply bone marrow for a sister, was called 'a biological resupply vehicle'. 'Donated' eggs are sold at values up to $50 000 if they meet certain specifications.

Donna Haraway observes that bodies are portrayed not in terms of their essential properties but as strategic systems or information-processing devices. People, she says, are described in terms of 'design, boundary constraints, rates of flows, system logic. ... Persons can be reasonably thought of in terms of disassembly and reassembly'.

Molecular biologist Leroy Hood anticipates that people will carry credit-card type strips that contain computer readouts of their personal genome. 'Your entire genome and medical history will be on a credit card'.[12]

Concluding remarks

Drawing from several different policy areas, I have suggested the appeal of reductionist explanations in the context of social, political, and economic agendas. Individual behavior and even cultural traits are being reduced to biological mechanisms, leaving little place for human agency and public responsibility. Clothed in the neutral garb of scientific discourse, such explanations, easily appropriated, are becoming embedded in institutional practices and social policies. They can be used to justify biases and to reinforce social divisions. They can deflect blame for social problems on to the individual while exonerating the individual as blameless in the face of

[12] Interview with Leroy Hood by Laurie Garrett in *The Dots are Almost Connected ... Then What? Mapping the Genetic Code*, Los Angeles Times Magazine, March 3, 1996, p. 49.

biological predispositions. Genetic explanations can be used to absolve the state from responsibility for providing social services, but also to absolve the individual from responsibility for his or her actions – 'It's all in the genes'. Reducing behavior to genetics can express a sense of fatalism – 'the luck of the draw', or a moral judgment – there are good and bad genes.

Reductionist theories today – as in the past – are also leading to proposals for reproductive controls. Claiming that negative traits can be reduced to genes, psychologist David Lykkens notes that 'We wouldn't let a crack addict, a teenager, or a criminal adopt a child. Why not make the same minimal requirements for people having children biologically?'. He proposes that biological parents be licensed. A Minnesota legislator is trying to write a version of this view into law (Anon, 1998).

While reductionist theories of body and behavior are useful in clinical and research settings, they also provide justification for social policies and legitimation for political goals. It is interesting that, at a time when government funding of many areas of research is drastically declining, the field of genetics is enjoying expanding Congressional support. It is revealing to follow the uncritical and unquestioned adoption of genetic language and assumptions in the popular media. In addition, it is remarkable to observe the commercial attraction to reductionist theories – 'Want to be Happier? It may be in your Genes!! Happiness is no different than hair color ... Receive our free self test to determine your genetic happiness level. Call 1-800-875-3177'.

As reductionist assumptions become broadly accepted, they are influencing the decisions of schools, courts, healthcare professions and other institutions because they serve short-term economic and administrative needs. Indeed, the power of the gene as a biological entity is being outpaced by its social power, commercial possibilities, and policy significance. This is likely to increase as an expanding science meets the shifting policy agendas of the new millennium.

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QUESTIONS AND DISCUSSION

Stanley Shostak: I'm reminded of Huxley's response to Wilberforce. You've used your enormous intellect to reduce the subject to humour. I object, and I think we have a very serious crisis in our culture, and while we might find it amusing it's going to be devastating unless we have an alternative. So let me be reductionist for a moment and remind you that in 'Code of Codes' Watson explains that he appealed to Congress for support because he knew that the politicians wanted to be able to advertise that they

were doing good. So what is the good that you can offer, the alternative to the reductionist approach, what is the good that comes out that we could use to advertise the non-reductionist approach?

Dorothy Nelkin: Well, first of all as a social scientist I feel that humour is serious. It is also a pedagogical device to get people to listen at the end of a long meeting. Studies of the sociology and psychology of humour suggests that it's serious, as social commentary and an indication of public attitudes.

Speaker: Is there a gene for humour?

Dorothy Nelkin: Is there a gene for humour? There's a gene for happiness – there must be one for humour. You know the only way I can figure out how to counter the impact of reductionism is to make people aware of the absurdity of what is happening, because certain assumptions become so embedded in culture and the way we think about things that they are not raised to the level of consciousness. Once people are aware then there's hope of thinking more seriously about the policy consequences.

Armando Aranda: What you say is actually deadly serious indeed, and I wonder whether the problem comes from the science and the scientists or is it the political and social system that then takes the science that is useful for its purposes? Or is it an interactive situation, a certain attitude or ideology breeds a certain kind of science or do they feed back each other?

Dorothy Nelkin: Well, it's a complex picture. There's a belief among scientists – I'm only talking of the United States because this is where I have done research – that increased media publicity is going to help their funding, both from private industry and from Congress. And therefore scientists and their institutions have become extremely adept at packaging information for the media. They are familiar with the soundbite, they use colourful metaphors – Steven went through some of them, the Bible, the Book of Man. Whether scientists really believe that they are developing a Bible or a Holy Grail, I don't know, but they certainly use this language in their public communication and in their interviews with journalists. This is the message that gets conveyed to the public and to people responsible for policy. You can be sure that people involved in policy decisions are not reading the *New England Journal of Medicine* or *Cell* or any of the other technical journals. These get filtered through public relations. I've argued in other contexts that scientists really should be rather careful in their public communications, that they should be aware of how their work is interpreted and the effect of their own pronouncements, their own promotion, their own hype.

Lisa Lloyd: I guess this is the same question. There are several sets of groups involved in the set of stories that you were talking about. There are Washington policy makers, although there are also local policy makers, and then there are all kinds of media. I would like to talk about the general

educated public for a moment. I guess my question was about where the possibilities for action lie for someone who wants to resist what's going on? I talk to my sister-in-law, who is very highly educated, and she's as genetic determinist as they come, and it doesn't matter how many times I have dinner with them and carefully explain to them what's up with the biology and what's wrong with that, she just believes in genetic determinism and because she reads about it all the time she believes what she reads more than she believes me. I have an agenda, they don't, and so on and so forth. Where is the access that you see to what is most effective in action?

Dorothy Nelkin: This is a very difficult question. I have been interested for many years in the interaction between science and the public, and studied this by looking at disputes. Then I went to look at science in the news media. Then I realised – and this was the origin of the book that I wrote with Susan Lindee – that we're bombarded with reductionist messages from talk shows, from child care books, from television, its all in the genes. With the Kennedy plane crash, he had risk-taking genes. Once you become aware of this in popular culture, you begin to see it everywhere. I'm not sure what the solution is except for scientists themselves to be extremely careful in their reductionist communications, because they still have a certain kind of authority in the society when it comes to scientific matters. I have written elsewhere on genetics and dismantling the welfare state. I think genetic reductionism appeals in the context of efforts to place blame and responsibility on the individual instead of the society.

Lisa Lloyd: The scientists you are talking about, it's against their own self-interest.

Dorothy Nelkin: I think in the long run it's disastrous for science, yes, absolutely.

David Hull: We keep placing the onus on scientists – they must do their job better – but how about us? What should we be doing? One possibility is to get really good with sound bites. Beat them at their own game.

Ken Schaffner: Some of the blame though does lie with the media. I've done nothing like Art Caplin does – he makes it is major activity in life to dialogue with the media. I've done it a few times, and they ask me to do soundbites, they say give us a soundbite, and then what I find out from having talked fairly extensively with a reporter of the *The New York Times* or some other publication, that they'll shop around, they'll go from one person to another, until they get the soundbite that they want that fits into their prescribe. So it's a little bit of an uphill battle with at least some of these people because I think they have their own agenda.

Dorothy Nelkin: They clearly do, and I've made a kind of a personal policy to be receptive and to talk to journalists, but not necessarily to give them soundbites but to elucidate the background issues. I'm not very good at soundbites.

Fred Tauber: I was struck by the comment that you made and which I've thought about also in regards to putting the onus of responsibility on the individual. One can turn the table and look at it in another way that the individual in fact is biologically determined and so is not responsible, and therefore social constraints, social policy, etc., then have to be imposed in order to adjudicate the biological bad effect, if you will, on culture.

Dorothy Nelkin: The gene is a malleable image. It has appeal because it can be interpreted in many different ways, but at a time with cost constraints on institutions and demands for accountability, for categorisation, then biological explanations are convenient. As I mentioned when referring to the criminal justice system, they can be used to mitigate punishment or to put people up for ever – it depends on policy agendas.

Steven Rose: Three things, firstly about soundbites. One of the problems about soundbites is that it is much easier to make a soundbite claiming simplicity than claiming complexity. If we are claiming complexity, it is much harder to compress this into a phrase which immediately captures the imagination. Dot, I thought you were a bit unnecessarily kind to scientists because the implication is the transmission belt between scientists who ought to have a better sense of responsibility and it's the media and everything else which is transforming it. Yet, you know better than most of us, that a lot of this emerges from the scientists themselves, from the press releases which are put out by the universities, the press releases which are put out every week by *Science* and *Nature* which actually compete with one another in the terrain to actually magnify the claims that are being made. But also, above all, the fact that science is a commercial enterprise, and many of the scientists who are making these claims have financial stakes in what is being said. The best example from my own terrain comes from the field of memory research where a distinguished colleague in the field has set up a company to produce a drug which is supposed to enhance memory. He made a claim at the American Neuroscience Society that he had now got a drug which would give 'a 70-year-old the memory of a 20-year-old'. I am told that the share value of his company shot up by 50% overnight, and we are not innocent.

We should dislike Jews and Blacks, but this was not because we were inferior but actually because we were different. And it's quite interesting the way they pick up the subtle changes that are going on in there.

Dorothy Nelkin: The race issue raises other questions. If you take a look at the Human Genome Diversity Project the search is for genes that are particular for different ethnic groups. There are ads now for people with Jewish genes to study breast cancer and colon cancer; there are efforts to find genes for differences, that I would argue can reify notions of race differences. So, on the one hand, you have this discourse that everybody's the same, but on the other hand there are efforts to point out diversity. The risk is the reification of race stereotypes.

Steven Rose: Anyone who talks about Jewish genes should bear in mind that the genetic profile of Polish Jews is much more similar to Polish non-Jews than it is to Spanish Jews, for example. There's been some hanky-panky going on here.

Dorothy Nelkin: Yes, of course.

Bob Williams: I would like to bring up Steven's point more strongly. I think what has happened in the universities – this is the only ground you're going to get for criticism of this system as far as I can see – is that they have become locked into the political game now. When I started that was not the case, if anything we stood aside and criticised all the time. Now you find that, especially say biochemists, you need so much money for your work that you are bound to hype what you are doing, and if you don't do that you won't get the money. You are bound to associate the thing with social objectives like disease, manufacturing goods or something, and you are doomed to do that. The point is that we ought to try to think, how do we get the universities or at least part of the universities back into the situation that they can be independent? This came about particularly strongly in the States, and now it's come strongly into England. If you take a research grant application now, at the bottom it says 'and what use is this research?'. Unless you can say something like 'OK, if I follow this course of study of genes I will be able to look after something or other', then what's the use of it?

Dorothy Nelkin: Current industry/university relationships developed in the United States following 1980 legislation. One problem is that universities have lost their ability to stand back and be critical. And of course, conflicts of interest are inevitable.

Chapter 16

Reductionism, Complexity and Molecular Medicine: Genetic Chips and the 'Globalization' of the Genome

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Introduction

This paper has two parts. Part I is somewhat historical but includes material from the history of philosophy of science, while Part II deals more with current scientific developments but within a philosophical perspective. The historical–philosophical part begins with a brief account of reductionism that sees molecular biology as moving from a period of simplicity and linearity to one involving complexity and global approaches. I then turn to the philosophy of science literature for a more personal view of the relationship between reductionism and genetics in the 1960s, 1970s, 1980s and 1990s, touching on the emergence of the antireductionist consensus in philosophy of biology, and the subsequent reaction that defended a reductionist *anti*consensus in biology. Some comments follow describing a reappreciation of complexity by geneticists in the 1990s, including references to Lander and Schork's fourfold way. Here, I also discuss examples from cystic fibrosis and cancer genetics, and the shift from what Plomin has termed a 'one gene–one disorder' (OGOD) view to a more recent 'many-genes–variable range of disorders' (MGVRD) perspective.

The second part of this paper considers genetic chips or microarrays as one recent tool developed to deal with the reappreciated complexity of

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biological organisms, including their *genetic* complexity. Gene chip technology also resonates with many geneticists' perceived need to move beyond a focus on the DNA *sequence* and understand genes in simultaneous complex interactions – what are called 'global views'. I sketch two examples in which gene chips have been used to implement this global approach, including analysis of a metabolic shift in yeasts and the metamorphosis of flies, and then touch briefly on the classification and treatment of human cancers. Finally, I consider some lessons, limitations, and prospects for further work in a variety of directions, including nascent developments in proteomics.

Part I: Some historical and philosophical developments relevant to reductionism: 1960–2000

Some themes in molecular biology

One can look at the past fifty years of molecular biology from many different perspectives, but the one that I think is most germane to this conference's themes sees biology moving from a period emphasizing simplicity and linearity to one that has become more focused on complexity and global approaches. The Watson–Crick structure for DNA, discovered in 1953 (Watson and Crick, 1953), was a simple and essentially linear representation of genomic information, and the genetic code deciphered in 1960 was also linear (albeit redundant) (Crick, 1968). Early reductionistic strategies such as Benzer's 1956 identification of the 'corrected' classical gene with segments of a Watson–Crick DNA sequence were essentially a one–many identification (more specifically, one (Mendelian) gene → three sequence lengths (muton, recon, cistron, etc.)) (Benzer, 1956; Schaffner, 1967). The process of gene-directed protein synthesis, encapsulated in the 'central dogma' of molecular biology (gene → RNA → protein), was similarly simple and linear (Judson, 1996), and the genetic code was thought to be universal. Even the Jacob–Monod operon model of 1959–1961, although more reticulate and involving feedback and control genes, underscored the prospect that the diverse complexity found in biology would be explicated by using simple on–off interactions at the molecular level.

Developments in the mid-1970s began to cast doubt on simplicity at a molecular level, as recombinant DNA studies and the emerging diversity of protein sequences revealed a rapidly growing multiplicity of molecules and pathways. Successive editions of Watson's well-known textbook, *Molecular Biology of the Gene*, first appearing in 1965, and then in 1970, 1976 and 1987, are a microcosm reflecting this increasing developing complexity.

Although molecular genetics was rapidly increasing in complexity at the time, the Human Genome Project (HGP) that was born in the late 1980s

represented the apotheosis of a view of simplicity and linearity of genetics in the project's early forms (Cooke-Deegan, 1994). Obtaining the s*equence* of DNA for humans was to be a 'Holy Grail' that would enable the diagnosis and cure of human disease (Gilbert, 1994). However, ironically, just as James Watson, the first director of the National Institutes of Health component of the HGP, was implementing this huge scientific project in the early 1990s, additional tools for interpreting the genetic code were heralding the need for considerably more complex analyses, tools typified by Lander and Schork's 'fourfold way' (Lander and Schork, 1994), a topic to which I shall return to again shortly.

Some themes concerning reduction in philosophy of science and biology

The general reduction model and the antireductionist consensus During the early period of modern molecular biology, essentially its first 25 years from 1953 through to 1978, a thesis that molecular biology would provide simple, general and unified explanations of biology was eminently defensible. One approach to reduction that generalized the classical Nagel model of *theory* reduction (Nagel, 1961) and incorporated insights of Popper, Feyerabend and Kuhn was introduced and defended by this present author in several papers (Schaffner, 1967, 1969, 1974, 1977) against the criticisms of Hull (1974) and Wimsatt (1976); for a summary and extensions see Schaffner (1993). In a prescient way in his 1974 book, Hull identified some of the complications standing in the way of any simple mapping between Mendelian (transmission) genetics, taken to be typical of biology, and molecular genetics, seen as paradigmatic of a physicochemical reducing science (Hull, 1974). He argued that the relations between Mendelian and molecular genetics were not one–many, as Benzer had suggested in his modification of the classical concept of the gene in the light of the Watson–Crick model of DNA, but much more bizarre and reticulate – a 'many-many' relationship that would defeat any simple mappings between those sciences. Hull's important criticisms were accepted and elaborated by Kitcher (1984) and Rosenberg (1985),[1] and with the backdrop of the biology of the 1980s providing *prima facie* supporting details for an emerging complexity, this view of the nonreducibility of Mendelian to molecular biology had achieved the status of an 'antireductionist consensus' by the 1990s (Dupré, 1993; Rosenberg, 1994).

The antireductionist consensus has been concisely and evenhandedly discussed recently by Sterelny and Griffiths (1999),[2] and the reader is

[1] Rosenberg, in particular, points to biology's emerging complexity as vitiating any simple reduction model; he dates the turning point to recombinant DNA in the late 1970s (Rosenberg, 1985).

[2] See in particular, Chapters 6 and 7.

encouraged to examine their account of the back-and-forth arguments that were involved in the discussions (also see Waters' reductionist defense (Waters, 1990) and Sarkar's analysis (Sarkar, 1998). From my own perspective, the most salient issues involved in the antireductionist consensus involved three intertwined theses, namely (1) replacement of Mendelian genetics, (2) autonomy of Mendelian genetics, and (3) mind-boggling many–many complexity interrelating Mendelian and molecular genetics. ('Mind-boggling' is Pat Churchland's term for this kind of view of the complexity of relationships, although she introduces the term in connection with mind–brain relations see Churchland, 1986)).

In his 1974 book, Hull advanced a curious *replacement* thesis as part of his argument that molecular genetics could not reduce Mendelian genetics. Since there were no simple connections between the entities (such as genes) and predicates (like dominant) in the two domains (molecular and Mendelian genetics), a reduction could not be occurring. Plus, if a reduction were not occurring, the only relationship could be that of replacement. This aspect of Hull's thesis was intriguing, but was accepted so far as I am aware, by virtually no one (more on this below). However, his arguments regarding the difficulties of mapping between entities and predicates did take hold, and were further amplified by Kitcher in his influential 1984 article (Kitcher, 1984), and were there used to support a thesis of the partial *autonomy* of Mendelian genetics. For Kitcher, cell biology, and the process of meiosis in which an account of gene segregation and linkage was given, provided a reduction of sorts of Mendelian genetics, but no further lower level of analysis was needed or obtainable. Hull's and Kitcher's accounts were largely accepted by Rosenberg who underscored the difficulties of providing workable connections between Mendelian genes and molecular entities (see both his 1985 (Rosenberg, 1985) and his 1994 (Rosenberg, 1994) books). Many others joined this debate, mostly on the antireductionist side – for a summary and references see Schaffner (1993) (in particular Chapter 9).

The Reductionist anticonsensus Although biology was becoming more complex throughout the 1980s and 1990s, and thus providing encouragement for the philosophical antireductionists' thesis of non-connectability of Mendelian (transmission) genetics and molecular genetics, most molecular biologists themselves perceived of their methods and results as supporting reductionist rather than antireductionist claims, whether this be in genetics or more broadly. In 1987, Eric R. Kandel, a neuroscientist and a recent (2000) Nobel laureate, wrote in the Preface to a volume on *Molecular Neurobiology in Neurology and Psychiatry* that:

> *This volume reflects the impact of molecular biology on neural science and particularly on neurology and psychiatry. These new approaches have accelerated the growth of neurobiology. The resulting increase in knowledge has brought with it two unanticipated consequences that have changed the ways in which clinical researchers and practitioners can now view the findings that came from basic science. The first consequence is a new unity, a greater coherence, in biology as a whole, as studies move from the level of the cell to that of the molecule ....*

(The second consequence was that 'as science becomes more powerful, it becomes more ambitious – it becomes bolder .... In addition, some biological researchers are so bold as to see their ultimate interest as the function of the human mind (Kandel, 1987).

Furthermore, as Sterelny and Griffiths note, in a highly critical review of Rosenberg's book, molecular biologist Gunther Stent wrote that:

> *What geneticist could take seriously any explication of 'reductionism' which leads to the conclusion that molecular genetics does* not *amount to a successful reduction of classical genetics (Stent, 1986).*

(This short account of the emergence of the antireductionist consensus and the counterview of the reductionist anticonsensus oversimplifies the issues but to examine them in the depth needed would take us beyond the scope of this present article. A more extensive analysis can be found in Schaffner (1993), while more recent reflections on the topic will be provided in a forthcoming book.)

What really *went on in* biology *from 1975–2000 (a personal perspective)?* There are different visions among philosophers and biologists, and the following is primarily my own personal perspective on developments from 1975 to 2000. In my view, most biologists saw Mendelian (better Mendelian–Morganian/transmission) genetics as a limiting case of cellular/subcellular/molecular genetics, but adopted various differing strategies to deal with the relations. Watson and his co-authors of the 1987 edition of *Molecular Biology of the Gene* (Watson *et al*., 1987) took the approach of discussing Mendelian genetics in its Chapter 1, then getting on with the real stuff, molecular biology, with virtually no further mention of Mendel or the approaches of transmission genetics. On the other hand, Alberts and co-authors in their influential 1995 edition of *Molecular Biology of the Cell* do not define the classical gene concept until p. 423, and then they modify it

on p. 457 to handle alternative RNA splicing, well after simple and complex molecules and DNA, as well as protein synthesis, are introduced (Alberts *et al*., 1974). In a 1998 book which is much less molecularly oriented, Lynch and Walsh in their *Genetics and Analysis of Quantitative Traits* see both quantitative transmission genetics and molecular genetics as 'two levels of organization that will ultimately have to answer to each other, and it is likely they will soon do so' (Lynch and Walsh, 1998, p. 7). They also add 'An ultimate understanding of the mechanisms responsible for expressed variation in quantitative characters requires information at the molecular level' (Lynch and Walsh, 1998, p. 321).

I read the history as represented by these three texts as indicating that no biologist (seriously) bought the *replacement* thesis, although those who were more molecularly oriented thought and increasingly wrote largely in molecular terms. I also think that no one accepted the *autonomy* thesis (although Mayr (1982), Lewontin and Levins (1985), and others argued for various kinds of emergence notions that asserted biology goes beyond purely molecular accounts). We also see a kind of quasi-autonomy thesis in Lynch and Walsh's views above. However, increasingly everyone embraced a *complexity* (or many–many) thesis, even *within* molecular genetics, as additional mechanisms and families of mechanisms and pathways rapidly emerged from a triumphantly advancing science with its new and more powerful instruments for deciphering sequences and studying structural interactions. (I say 'even *within*' molecular genetics because so many varied mechanisms for related processes were discovered, e.g. multiple ways of regulating DNA translation at the molecular level, even in *E. coli*.)

However, having acknowledged this complexity, biologists began to explore better ways to analyze complexity – no boggled minds here! Some moved to explore 'complexity theories' – a term that has several different senses. Excellent introductions to several of these senses can be found in Goodwin (1994) and in Liebovitch (1998), which address these perhaps 'sexier' methods, including chaos theory and fractals, but I will not focus on them here. In this paper, I consider what I view as more mainstream approaches to working with increasingly complex genetic systems. A paradigm essay in genetics that represents this development is Lander and Schork's article that appeared in the special 1994 genome issue of *Science* (Lander and Schork 1994).

Complexity in genetics and the fourfold way

The 1994 article by Lander and Schork was a landmark essay signaling the reappreciation of genetic complexity. In the abstract for their article,

they noted that 'medical genetics was revolutionized in the 1980s by the application of genetic mapping to locate the genes responsible for simple Mendelian diseases' (Lander and Schork, 1994, p. 2037). However, they cautioned that:

> *Most diseases and traits, however, do not follow simple inheritance patters. Geneticists have thus begun to take up the even greater challenge of the genetic dissection of complex traits. Four major approaches have been developed: linkage analysis, allele-sharing methods, association studies, and polygenic analysis [including QTLs] of experimental crosses (Lander and Schork, 1994, p. 2037).*

Lander and Schork added that 'this article synthesizes the current state of the genetic dissection of complex traits – describing the methods, limitations and recent applications to biological problems'.

The Lander and Schork article is far too long, and complex in its own right, to summarize in this paper. Suffice it to say that this present author did write, with the help of Irving I. Gottesman and Eric Turkheimer, respectively a genetically oriented psychologist and a behavioral geneticist, a summary that was intended to be accessible to policy makers interested in complex trait genetics. That paper was presented orally at a national meeting of the American Society for Bioethics and Humanities in 1997, and in updated form it is due for publication in a volume being put together by the American Association for the Advancement of Science and the Hastings Center (Schaffner *et al*., 2001).[3]

For the purposes of the current paper, it is sufficient to note that Lander and Schork found they needed to address the *reasons* that very few genetic markers show perfect cosegregation with a complex trait. The reasons included incomplete penetrance and phenocopies, genetic heterogeneity and polygenic inheritance, the confounding effects of a high frequency of disease-causing alleles, as well as other transmission mechanisms (e.g. imprinting and anticipation). Lander and Schork's overview of the 'four major approaches' cited above was a *tour de force* in communicating ways that geneticists could get purchases on complex traits. A review of the genetics literature of the 1990s clearly shows how all of these methods were utilized, as well as further extended after 1994, to begin to deal with the re-appreciation of complexity.

Lander and Schork's article was written against the backdrop of related investigations by 1990s geneticists, who also found that 'single-gene disorders' were not so simple, even when inherited in a Mendelian way. Cystic

[3] Preprints can be obtained from this present author on request.

fibrosis turned out to have many more mutations than was expected, and some of those that were predicted to cause the disease did not because of a difference in genetic background of the host (Mickle and Cutting, 2000). Breast cancer genetics that was revolutionized by the identification of the BRCA1 and BRCA2 genes has had to become much more sophisticated in reckoning highly variable risk and in advising patients who have a history of breast cancer about their mind-numbingly complex options. (See Garber (1999) for an excellent patient case illustrating the complexity of clinical decision making and moral dilemmas involving BRCA1/2 testing.)

Writing in the same year as the Lander and Schork article appeared, one of the most vigorous advocates for a genetic approach to behavioral disorders in the 1990s, Robert Plomin, stressed that the field of behavioral genetics had to move away from its older paradigm of 'One Gene–One Disorder' (called the OGOD model) to a new one appreciative of the new complexity (Polmin *et al*., 1994). This new paradigm was one Plomin termed a 'Many Genes–Variable Range of Disorders' perspective (with the less pronounceable acronym of MGVRD). The MGVRD perspective was eager to seize on the various methodologies summarized in Lander and Schork's fourfold way to make headway in behavioral genetics. Unfortunately, even over one year into the new millennium, the application of these sophisticated fourfold way methodologies to human behaviors have yet to result in a clear replicable consensus identifying any 'gene for' serious mental disorders or even 'for' 'normal' personality genetics (Schaffner *et al*., 2001). (The devastating Alzheimer's Diseases are the one exception in the human behavioral genetics area where the clearest advances have been made, but even here the story is seriously incomplete – see Schaffner (2001) and Schaffner *et al*. (2001). for a discussion. Even more surprising is the virtual absence of 'genes for' specific behaviors even in so 'simple' an organism as the 959 cell nematode, *C. elegans*, with its 302 neurons (see Schaffner (1998) for details).

The upshot of the recognition of complexity in genetics is a realization that identification of a gene is not easy, nor when accomplished is only the first step in a 'reduction' of the biological entity, trait, or process of interest, including a disease (compare Tauber on sickle cell anemia in this volume, see Chapter 13). This complexity highlights the multiplicity of pathways between gene and trait, as well as the variability of the trait, and provides support for a many–many view of the relation between genes and traits. Such complexity also supports a view that virtually all 'reductions' are, in point of fact, *partial* reductions (Schaffner, 1993).

Part II: Genetic chips – A solution via globalization?

This present author has frequently been told that his frustration over his inability to find a clear replicable consensus identifying a 'gene for' serious mental disorders, or even such a gene in the promising area of personality genetics (Schaffner, 1999), will be relieved shortly by new advances in technology. Now, the optimists proclaim, since a draft of the entire human genome sequence exists (two drafts to be more precise (Anon, 2001a, 2001b)) gene searching will be more efficient. Furthermore, the optimists add, the problems of gene identification and the better tying of genes to their function(s) will be solved by a new technology, variously termed the genetic chip, the DNA chip, or more technically and accurately, the *DNA microarray*, that has become available to examine many genes' actions simultaneously. (Readers will also encounter the term 'GeneChip®', with that spelling and internal capitalization; this term has been registered by Affymetrix, the pre-eminent biotech company that produces commercial microarrays – hence the ® suffix.) This microarray technology is of quite recent vintage (mid- to late-90s) and has generated considerable excitement in the molecular genomics community. For reasons that will become clearer below, it is seen as permitting a 'global view' of gene processes. The remainder of this paper examines whether the optimists seem to have a good case that this technology will solve major problems in the area of complex genetics and perhaps achieve something like reductions in biology.

Part I of this paper concluded with a brief discussion of Lander's article, co-authored with Schork, which summarized the powerful 1990s gene identification methodologies. Thus it is appropriate to cite Eric Lander again on the promise, as well as some limitations, of the new gene chip technology. Lander's January 1999 *Nature Genetics* essay is a useful introduction in which he models his interpretive approach on an analogue of the Periodic Table in chemistry. He notes that gene sequencers are now obtaining gigabases of structural information and thus genomics needs a way to 'discern the underlying order,' and he suggests that perhaps a *k*-dimensional 'periodic chart' analogue might be one such approach. More specifically he wrote:

> *The next great challenge is to discern the underlying order [in the genome]. The Periodic Table summarized chemical propensities in its rows and columns, and thereby foreshadowed the secrets of sub-atomic structure. Understanding biological systems with 100 000 [since revised downward to 30–40 000] genes will similarly require organizing the parts by their properties. The Biological Periodic*

> *Table will not be two dimensional, but will reflect similarities at diverse levels: primary DNA sequence in coding and regulatory regions; polymorphic variation within a species or subgroup; time and place of expression of RNAs during development, physiological response and disease; subcellular localization and intermolecular interaction of protein products. The traditional gene-by-gene approach will not suffice to meet the sheer magnitude of the problem. It will be necessary to take 'global views' of biological processes: simultaneous readouts of all components. Arrays [or genetic chips] offer the first great hope for such global views by providing a systematic way to survey DNA and RNA variation. They seem likely to become a standard tool of both molecular biology research and clinical diagnostics. These prospects have attracted great interest and investment from both the public and private sectors (Lander, 1999).*

This *k*-dimensional periodic chart metaphor is one Lander has employed before in describing the results of the HGP (Lander, 1996), and although suggestive at capturing both complexity and an image of an approach to handle that complexity, to this author the metaphor is missing the typical functional and dynamic dimensions associated with molecular genetics. Later, I will explore some alternative metaphors after we have examined the details of gene chip results.

Making and using genetic chips

First, I will describe genetic chips generally, and then move on to specific examples. The reader unfamiliar with genetic chips may want to scan this general section first, then look at an example or two, and then re-read the general description of the technology immediately below.

A typical genetic chip is about one inch square in size but has thousands of systematically arranged very tiny (~200 micron) dots deposited on it. Each dot is a piece of probe DNA (or in the Affymetrix GeneChip® technology, a short stretch of synthetic DNA called an oligonucleotide or 'oligo') that replicates a unique sequence identifying a gene. To determine which genes have been expressed in a sample, researchers isolate messenger RNA from the samples, convert it to complementary DNA (cDNA), tag it with fluorescent dye, and run the sample over the chip. Typically there are two samples per slide, i.e. a test and a reference sample, dyed 'red' and 'green', respectively. The reference sample may be cells at 'time 1', and the test sample cells at 'time 2'. Each tagged cDNA will stick to a probe or oligo with

a matching sequence, lighting up a spot on the wafer where the sequence is known.

A detector, often an automated laser scanner microscope, then scans the slide and determines which probes or oligos have bound, and hence which genes were expressed. The data then may be statistically reduced (summarized) and represented in a matrix, plotting sample experiments or temporal stages of a process horizontally and the different genes of interest vertically (usually 'red' is used for increased expression and 'green' for decreased expression). These are the Christmas-colored sets of squares most readers will have noted in genetic chip articles. A caveat that needs to be kept in mind is that the genetic chip data may sometimes be presented as a picture of the *array or* as a data-summarizing *matrix*, but the data matrix is not a picture of the array. Typically, genetic chip articles present data in matrix form, although some articles provide a picture of the array itself.

Genetic chip data interpretation

The amount of data that genetic chip experiments can generate is extraordinary. One of the articles discussed below, that reports on seven stages in yeast, produced 43 000 expression-ratio measurements (DeRisi *et al*., 1997). A series of experiments on the simple roundworm, *C. elegans*, that is being deposited in a Stanford University archive is estimated to amount to over a *tera*byte of data per year. Thus, a major issue in genetic chip technology is *data interpretation*, and the development of the appropriate tools for data summary and detecting meaningful patterns in the data. (There are other problems of standardization of data, mistakes in chip construction, and probe contamination that cannot be discussed in this article. See Lander (1999), as well as the website for Genetic Analysis Technology Consortium (GATC).[4] More recently, there have been concerns expressed in *Nature* about reported error rates of up to 30% as well as about Affymetrix's problems with its mouse GeneChips® (Knight, 2001).) Lander (1999) refers to a 'dizzying assortment of techniques' that includes *clustering* algorithms – the most highly favored approach – which search for similarities, as defined by using various similarity metrics, and also decision tree searches to help classify genes into clusters. Many articles reporting genetic chip results use prior knowledge of existing biochemical pathways (e.g. the glycolysis pathway and the Krebs TCA cycle) as an interpretive framework or guide. Known genes acting in these pathways can be identified and unknown genes

[4] See http://www.gatconsortium.org/about.html (accessed 30-03-01).

that are active at about the same time can be associated (termed 'guilt by association' by some) with these existing pathways and investigated further.

Microarray data cannot be analyzed by purely brute force techniques to generate a causal model of a set of biological processes because the data represents gene expression patterns that are only *correlated* with temporal processes of interest in the organism. Lander (1999) comments on this problem as follows:

> *How well can causation be inferred from correlation? The problem is akin to inferring the design of a microprocessor based on the readout of its transistors in response to a variety of inputs. The task is impossible in a strict mathematical sense, in that the microprocessor layout could be arbitrarily complicated, but is likely to prove at least somewhat tractable in a more constrained biological setting, especially when combined with ways to cut specific wires in biological circuits using antisense and related techniques.*

Further below, I will refer to a Bayesian causal network approach that does attempt to infer causation from microarray data. Furthermore, as Lander suggests, the microarray data, suitably constrained, may be used to generate causal hypotheses that can then be tested in other experiments and contexts. Thus, there are strategies that *may* be able to address this difficulty of determining causation.

Two examples: yeast and flies (plus comments on cancer)

Later in this article, I will return to the question of data interpretation. First, however, it will be more useful to sketch several examples of genetic chip application to illustrate the issues. A favorite organism to test the power and utility of genetic chips is the yeast, *Saccharomyces cerevisiae*. The complete genome of yeast is known and has been sequenced (~6000 genes), and the small genome allows for the detection of low levels of gene expression. Fundamental biological processes in yeast have been explored by using microarray technology, including a popular study of cell cycle genes involved in sporulation (Spellmann *et al*., 1998). A good and easily accessible example is the earlier (1997) analysis by DeRisi and co-workers (DeRisi *et al*., 1997) of the 'diauxic shift' in which yeast changes from feeding on sugar to living on alcohol, when the sugar supply runs out. The organism employs well-known metabolic pathways in the two stages, and these pathways and their known involved genes can serve as an interpretive framework to begin to analyze the global expression patterns of the yeast

genome. The diauxic shift example is particularly useful pedagogically, since an animation of a very simple microarray experiment involving this shift is available as an Internet movie[5] that is an excellent introduction to the technology for those readers unfamiliar with it.

It is worth quoting DeRisi and co-workers' Abstract *in toto* to give the reader a sense of this type of investigation. They write:

> *DNA microarrays containing virtually every gene of* Saccharomyces cerevisiae *were used to carry out a comprehensive investigation of the temporal program of gene expression accompanying the metabolic shift from fermentation to respiration. The expression profiles observed for genes with known metabolic functions pointed to features of the metabolic reprogramming that occur during the diauxic shift, and the expression patterns of many previously uncharacterized genes provided clues to their possible functions. The same DNA microarrays were also used to identify genes whose expression was affected by deletion of the transcriptional co-repressor TUP1 or overexpression of the transcriptional activator YAP1. These results demonstrate the feasibility and utility of this approach to genomewide exploration of gene expression patterns (DeRisi* et al *., 1997).*

DeRisi and co-workers prepared DNA microarrays with about 6400 different DNA sequences and then obtained mRNA from their yeast samples at seven successive two-hour intervals following an initial nine-hour period of growth. The yeast went from an exponential, but essentially stable, growth phase during the availability of glucose, to an anaerobic phase during which there were significant changes in the patterns of gene expression. Over two thousand genes altered their expression patterns during this shift, with about 400 by a factor of four. Half of the genes involved had no recognized function. De Risi and co-workers used those genes of known function and mapped them on to a framework involving well-known classical metabolic pathways including the glycolysis/gluconeogenesis pathway and the TCA cycle (see Figure 3 in their article (DeRisi *et al*., 1997)). In two other experiments, they also employed two modified yeast strains, one with a deletion mutation of TUP1 and another with a plasmid adding a YAP1 gene that affect known regulatory pathways. The purpose here was to examine the effects of these interventions on the general expression

[5] An animation of how to run a simple experiment using a microarray (this is like the DeRisi experiment) by A. Malcolm Campbell of Davidson college is available at: http://www.bio.davidson.edu/courses/genomics/chip/chip.html (accessed 13-04-01).

patterns of the organism, and they obtained useful direct and indirect effects (see DeRisi *et al*., 1997, for details). They conclude their experiments suggesting that the technology is not costly and not difficult for a small laboratory group to develop and apply to other organisms and processes, and that the experiments can yield vast amounts of global information. They acknowledge, however, that 'perhaps the greatest challenge is now to develop efficient methods for organizing, distributing, interpreting, and extracting insights from the large volumes of data these experiments will provide' (DeRisi *et al*., 1997, p. 685).

Other investigators have, in fact, utilized this genetic chip technology in different and more complex model organisms. For example, White and co-workers examined the important process of fruit fly metamorphosis during which the larvae develop into pupa (White *et al*., 1999). This set of experiments is the beginning of a complex long-term project that has as its major goal 'to define the gene expression patterns of every gene in the genome that can be detected in whole animals using DNA microarrays'. Elsewhere, White adds that 'the complete *Drosophila* life cycle will be analyzed'.[6] In the fly, metamorphosis is initiated by a strong hormonal pulse of ecdysone (a steroid). During the process, a number of the organism's tissues undergo cell death and histolysis, and other organs are restructured and developed, including the nervous system. White and co-workers devised a microarray consisting of some 6240 samples including cDNA expressed sequence tags (termed ESTs) and ecdysone-regulated control genes, and then examined pupal formation prior to metamorphosis and at six additional time points during the process (thus at seven data-gathering time points). They looked at elements that were highly fluctuating during this time course, and identified 534 structural (ESTs) and control genes. These genes were then grouped using criteria for similarity of expression patterns employing two clustering methods. For a matrix summarizing the expression data of these 534 genes, see White *et al*. (1999). The bar spectrum under the figure in that paper provides an interpretation of the colors in terms of expressed ratios.

White and co-workers closely examined muscle tissue development and central nervous system (CNS) remodeling. The latter process involves new nerve growth and nerve placement. Two genes known to be involved in neurogenesis are *neurotactin* and Plexin A, and both are induced during metamorphosis. Other genes that are new candidates for neural outgrowth have also been determined by these experiments. A considerably more simplified matrix depicting the results of these neurogenesis analyses is also

[6] See http://quantgen.med.yale.edu/ (accessed 30-03-01).

presented. In the latter, green indicates the genes are repressed (2 to 4 × ratios) prior to metamorphosis, while black represents a midpoint of gene expression. The most strongly late-expressed gene (8×) shown in red in this matrix, *shortsighted*, is involved in fly photoreceptor development. Again, a bar under the figure color codes the expression ratio magnitudes.

These results are first steps in the use of this technology to simultaneously track all genes that are expressed during fundamental biological processes. Again, however, the *interpretation* of these results, that are still only correlations, is a key problem. White and co-workers argue that although much is known about the genetic networks that control fly development, the usual representations using 'stick diagrams' must be incomplete, since 'inactivation of a majority of the genes does not result in obvious mutant phenotypes' (White *et al*., 1999, p. 2183). Microarray technology could expand these diagrams to include all functional genes, but 'integrating and visualizing data derived from genomic studies present a substantial challenge'.

From a clinical point of view, the most useful results that are likely to arise from genetic chip investigations in the near term may be in the area of disease identification. This is the case particularly in cancer classification and diagnosis. An excellent study by Golub and co-workers that appeared in 1999 in *Science* developed a general approach for identifying new cancer classes (Golub *et al*., 1999). That approach was able to discover the distinction between two types of leukemia, i.e. acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), without previous knowledge of these two classes. Furthermore, a method for assigning new tumors to the two classes was derived from this approach, and usefully applied to a clinical case. Surprisingly, the analysis also had some implications for cancer pathogenesis and pharmacology. More recently in this field, an essay in the *New England Journal of Medicine* reported the ability of genetic chips to differentiate between inherited breast cancers caused by mutations in the BRCA1 versus the BRCA2 genes (Hedenfalk *et al*., 20001). Application of the method to an existing tumor sample suggested that the patient had been misdiagnosed as BRCA2 as opposed to her actual BRCA1-related tumor. (Follow-up testing with this patient, needed because the therapies for the two tumor types are different and she had not been tested for BRCA1, generated an ethical conundrum because of the need to re-contact the patient. She had been promised donated-sample anonymity. Remarkably, it turned out that this patient's tumor was *not* associated with the BRCA1 gene, per se, but had the promoter region of her BRCA1 gene methylated (silenced)).

Data interpretation and genetic chips, redux

In this part of the article I have described the new genetic chip technology for dealing with biological complexity and sketched two representative examples from the biological literature, as well as alluded to others. Both of these examples illustrate the vast amounts of data that this new technology can provide, and both point towards difficulties of proper interpretation and conceptually summarizing the data. Earlier I cited Lander's model of a *k*-dimensional periodic chart in terms of which one can understand the results generated by the human (and other model organism) genome project, but suggested that it might be an incomplete model. I want to return to this point again now in the context of some of the results generated by microarray technology, and ultimately relate this discussion to the themes of reductionism surveyed in Part 1 of this essay.

There are two problems we encounter in dealing with complex biological processes – problems that we can distinguish, at least to the first approximation. The first we have encountered explicitly in the microarray data results; namely the problem of *data reduction*. *This* sense of 'reduction' has little to do with the levels and disciplines discussed in Part 1, but it is related to a notion of summary and simplification, and identifying salient patterns in noisy data measurements. The second problem is the proper mode of *conceptual representation* of biological processes. Biologists frequently use the terms 'model' and 'mechanism' to refer to their conceptual representations. There is a vast literature in philosophy of science dealing with various senses of model (see Schaffner (1993, pp. 97–101) for some of those senses), and more recently there have been some interesting discussions of the notion of 'mechanisms' as well, that this paper cannot examine (Machamer *et al*., 2000). Suffice it to say that models are rough and idealized summaries of biological processes which identify causal entities and modes of interaction over the course of the process. Often these are represented in diagrams or 'cartoons' in research articles and textbooks. A good example of a fairly simple model is the operon model of genetic regulation for the *lac* region of *E. coli*. A more complex model of post-synaptic neuronal response is provided in a recent article by Weng *et al*. (1999). Models (or better *families* of models) serve as surrogates for theories for the most part in contemporary biology (see Schaffner, 1993, Chapters 3 and 5). Models permit the interpretation of experiments and suggest additional experiments, and can serve as the basis for other types of interventions in nature.

On this view that emphasizes the importance of models, Lander's metaphor of modern genetics as summarizable in a *k*-dimensional periodic chart involving many thousands of genes falls short. It does so because it does not recognize the temporal/causal processing dimension of molecular

genetics that models capture. However, *something* like what Lander was grasping for is needed to take us beyond a mere listing of models, since we will need to represent the models in interaction and appropriately organized for different species and strains. The features of the appropriate metaphor are not yet clear to me. Morowitz (1985) has suggested the notion of a biological 'matrix' in which complex models can be represented along with partial analogies among them, but the overall structure of the matrix and its key substructures and relations are not yet evident, nor has this metaphor to the best of my knowledge actually been used to organize and extend actual biological systems. More likely, the models will be complex networks best expressible in computer simulations and difficult for humans to represent well in working memory. Modularization of the networks will help (Hartwell *et al*., 1999), as will the use of the anchoring prototypes such as we find in *model organisms*' research results (Brown and Botstein, 1999).[7] However, those modules and prototypes will need to have pointers to similar but not identical models with all the diversity that evolution appears to have produced. Moreover, for the foreseeable future, the models will be interlevel and not purely molecular. The 'Divine' here will be both in the details and in the capturing of broadly conserved mechanisms and pathways in the same representation(s).

These two problems of data reduction and conceptual representation are only independent to the first approximation, since one of the tasks of biology is to infer representations (models) from data, and use data to test models. A review of four current general approaches to data interpretation may help to make this interdependence clearer, as well as indicate the promise and limitations of microarray technology. I group these four approaches into clustering, expression analysis, Bayesian causal modeling, and artificial intelligence (AI) categories.

Of these four approaches, *cluster analysis*, in its generic sense, is the most widely used and most developed. Cluster analysis, as I have mentioned briefly earlier, organizes the genes into related subsets that are termed clusters. Usually a biological process of interest, such as the diauxic shift or metamorphosis described above, has a series of temporal stages at which expression data has been gathered. The highly expressed (or repressed) genes at each stage are then clustered by using a computer-implemented algorithm. Typically, the clustering is done on the basis of their similarities in the temporal expression of gene expression profiles – what some have termed 'guilt by association'. Automated sorting requires some means of assessing similarities and needs to assume some metric for defining

[7] See also Chapter 13 (Tauber) in this volume.

strength of similarity. Correlation coefficients (where unknown and known genes expression ratios are correlated) have been used, as has similarity employing a Euclidean metric for log-transformed expression ratios (Hodor *et al*., 2001).

A related approach that uses similarity analysis applied to gene chip data, but with some added intriguing twists, might be called 'expression profiling'. In this approach recently applied to yeast, a reference database or 'compendium of expression profiles' corresponding to some 300 different known mutations and chemical treatments was constructed. A new unknown mutation's effects can then be interpreted by comparing its gene chip profile with the existing profiles in the compendium (using a similarity measure based on correlation coefficients), and from the best fit, some suggestive hypotheses about the unknown mutation's function may be inferred. Hughes *et al*. (2000) report results of a series of deletions of genes with unknown function to which this method was able to assign functional roles. These included the genes' roles in sterol metabolism, cell-wall function, mitochondrial respiration, and protein synthesis. Hughes and co-workers also apply expression profiling to determine what the target may be of an exogenously administered drug agent. In comments on this method of expression profiling, Young (2000) states that their results 'provide an important proof-of-principle for new approaches to pharmacological research and development'.

Cluster analysis and expression profiling depend on the assumption that similar expression patterns correlate with similar causal roles of the expressed genes. Some pre-existing causal models are thus assumed, as we encountered, for example, in the DeRisi and co-workers' experiments on yeast and their interpretation by using existing model pathways such as glycolysis/gluconeogenesis and the Krebs' cycle. However, a third approach to interpretation of gene chip data takes a different tack and looks for ways of inferring causal patterns from the raw data without using similarity to pre-existing mechanisms. This approach relies on Bayesian network modeling strategies similar to those developed by Pearl (2000) and Cooper and Glymour (1998) for causal modeling generally. Friedman and co-workers write in their recent article that 'It is important to note that our learning algorithm uses *no prior biological knowledge nor constraint*s. All learned networks and relations are based solely on the information conveyed in the measurements themselves' (Friedman *et al*., 2000).

Friedman *et al*. (2000) tested this approach on a data set for yeast cell cycle expression patterns provided by Spellman and co-workers (1998), writing that 'This data set contains 76 gene expression measurements of the mRNA levels of 6177 *S. cerevisiae* ORFs. These experiments measure six

time series under different cell cycle synchronization methods. Spellman *et al*. (1998) identified 800 genes whose expression varied over the different cell-cycle stages'. Some causal graph orderings of causal effects in a gene network were obtained by Friedman and co-workers from these data and are summarized in their article. Although the results that Friedman's group obtained are interesting and make some biological sense, the authors themselves admit that these are based on many assumptions and the results are quite preliminary ones. One problem that will probably have to be solved is that Bayesian networks assume that there is no feedback in the system they are modeling. If samples could be obtained in very small time periods that condition might be met (Pearl, 2001), but this does not seem to be satisfied in current microarray experiments. The proof of the applicability of this method in the microarray area waits on some novel predictions of causal dependency that then can be confirmed in other contexts. Glymour and his colleagues have in point of fact just recently turned their attention to analyzing yeast microarray data provided by Leroy Hood's laboratory using their approach (Cooper and Gilmour, 1998) and some results are anticipated soon (Glymour, 2001).[8]

A fourth and final approach to microarray data interpretation is being explored by Jeff Shrager and his colleagues (Shrager *et al*., 2001). I characterize this as an artificial intelligence (AI) perspective, since it draws on tools developed in the AI branch of computer science to represent theoretical biological processes and interpret genetic chip data. The general framework is a biological representation and reasoning system called BioLingua, which works with partial and abstract biological knowledge, as well as with concrete exemplars. Various stages in an abstract biological process, such as photosynthetic adaptation, are 'conceptually-annotated'. Conceptual annotation means the stages are assigned to general categories termed 'views', for example, 'transcription regulation' or 'signal transduction'. Then, a forward search strategy can be used to find various abstract pathway solutions and make qualitative predictions by simulation. Those predictions can then be used to selectively regress genetic chip data and assign likelihoods to the paths based on the fit of qualitative predictions to the regressions. This project is in its very early stages, but it offers considerable promise for systematically dealing with information in a complex domain such as microarray data analysis. It is highly likely that other AI

[8] Glymour and his group were recently funded by an $\sim$ \$1M grant from NASA to pursue this research. In addition, see Spintes, P. Glymour, C. and Scheines, R. (2001), 'Constructing Bayesian network models of gene expression networks from microarray data', to appear in *The Proceedings of the Atlantic Symposium on Computational Biology, Genome Information Systems and Technology*.

approaches will also be developed to assist in the interpretation of genetic chip data, some perhaps involving adaptations of other existing biological discovery programs, and some possibly creating 'expert systems' based on the knowledge of leaders in the microarray field.

The missing prince: proteomics

My account thus far has dealt with reductionism through the lens of genetics. However, it is important to recall that biology is more than about DNA. Naked DNA does not have many interesting biological properties; it requires the conjoint actions of proteins (plus the proper aqueous environment, chemical co-factors, etc.) to have its effects. In the days of 'simple' linear molecular biology discussed earlier in this paper, the central dogma of protein synthesis and one-to-one links of genes and enzymes provided hope that genetics and DNA sequences would illuminate biology generally. I have already indicated that genetics realized it had to grow in complexity, and recognize many genes interacting in complex ways as causative of interesting biological (or pathological) effects. Gene chips are but the latest development of a technology developed to capture this complexity. However, the story thus far is like a version of Hamlet in which the Prince of Denmark has not appeared – or has not appeared in a recognized central role. Here, the prince is proteins. In addition, biology in general is increasingly recognizing that protein structure and function are more likely the sources of biological insight and biological interventional control than is genetics, even though it is the DNA informational sequence that plays a key role in determining protein structure.

A new buzz word in biology is 'proteomics' – a term that is patterned on 'genomics'. A recent review article on the subject illustrates the significance of proteins and the incomplete nature of what could be inferred functionally from genomics pure and simple, noting that 'researchers are realizing that merely having complete sequences of genomes is not sufficient to elucidate biological function . . . . There is no strict linear relationship between genes and the protein complement or ''proteome'' of a cell' (Pandey and Mann, 2000). Proteins can be modified in ways not discernable in the DNA sequence per se (isoforms and post-translational modifications) and protein regulation takes place at the level of proteins and not genes. The recent surprise at the numerical paucity of the human genome has given rise to a realization that the explanation for such a comparatively simple genome (after all, *C. elegans* requires 19 000 genes) may be a *dramatic* increase in humans of transcriptional and translational complexity. Thus, the key to understanding the genome may be 'regulation, regulation, regulation',

involving proteins playing key central roles. New computational strategies for analyzing protein function are being developed (Eisenberg *et al*., 2000) and two types of protein chips are becoming available to pursue proteomics in a high throughput manner (Kodadek, 2001). This quite recent increase in interest in proteins and their role resonates well with the Developmental System theorists' perspective that a strong focus on DNA and genetics alone can be most misleading (Oyama *et al*., 2001).

Conclusions: beyond 'genetic' reductionism

The science of genetics has occupied a prominent place in this paper on reductionistic themes in biology, but it has served two somewhat different roles. First, attempts to reduce classical transmission genetics using molecular genetics, and ultimately the effective criticisms of that effort, were based on the *prima facie* simplicity of molecular genetics that then unraveled into a complexity of context: the many–many problem. Secondly, an earlier sense in biology that molecular *genetics* is the key to molecular *biology* has begun to be tempered with a realization that what in part *underlies* the many–many problem are the proteins and the pre-existing complexes of DNA and proteins that themselves embody a complex *history* (of billions of years).

The account of gene chips provided above also holds several lessons for reductionistic biology. First, a purely gene's eye view, in which the differing expression over time of a vast number of genes is tracked, will likely not be very informative about the genes' functions per se. Genes and mRNA levels may be too indirect a measure of the protein-based phenotype, which is where the action is. Gene chip data so far also seems to need traditional models of causal function to yield interesting interpretations of that data. Those models of causal function, such as the glycolysis pathway, are actually and typically interlevel in their constitution and are contextualized as contributions to cell maintenance and survival, even though they can be abstractly represented as simple chemical flow diagrams involving elementary chemical constituents. That simple pathways are, in fact, quite localized and well-regulated is nicely reviewed in the text by Alberts and co-authors (Alberts *et al*., 1994, Chapter 2). (Again, for an account of the generally interlevel nature of molecular biology see Schaffner, 1993). Secondly, additional work of an integrative and multilevel sort will likely be required to make biological sense out of the enormous amounts of data being generated from gene chip experiments now and in the future.

Nevertheless, even with these caveats it is likely that mRNA microarray technology will play an increasing role in biological science. The technology

has just recently begun to be applied in the neurosciences, and also in psychiatry to schizophrenia research, with preliminary but exciting results (Sandberg *et al*., 2000; Mirnics *et al*., 2001). In addition, as Young writes:

> *Two features of expression profiling make it the most productive approach to study biological systems for the immediate future. First, the present efficiency with which investigators can obtain global and quantitative information with DNA arrays exceeds that of proteomic techniques. Second, RNA expression profiles provide an extremely precise and reproducible signature of the state of the cell that probably reflects albeit indirectly, the functional state of all proteins (Young, 2000, p. 13).*

Genetic chips will play a very important role in the advance of biology in this new millennium, but they will not in and of themselves be magic chips solving the mysteries of biological life.

Reductions in biology, as in other sciences as well, such as they exist, are partial and fragmentary in the sense that they are rarely unilevel and applicable across a broad domain. Partial reductions are powerful augmentations of our understanding of biological processes, but they do not support a dream of the logical positivists of a totally unified science. Rather, even these successful partial reductions are reminders that we have a purchase on cells and organisms that is incomplete and multifaceted, and that for the foreseeable future will not be unilevel but rather multilevel. The realization that genetics is complex, and in addition, critically involves pre-existing regulating proteins (at least pre-existing to the regulated cycle) points to the partial nature of a purely *genetic* reduction. Although computer representations of genetic data may permit chemical level predictions and explanations of all organic properties at some point in the distant future, even then pre-existing constraints, typically represented in protein molecules (both free and complexed with DNA) and thus in the genetic *environment*, will be a critical part of those predictions. Although I see no in-principle argument against this form of molecular reductionism, it is not here and now. Finally, although complex genetic methods and new technology such as genetic chips, complemented by new ways of analyzing proteins as well, will advance us toward this reductionistic goal, it is *many many* years away.

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QUESTIONS AND DISCUSSION

Stanley Shostak: Larry Holmes said that Krebs was the worst commentator on his own history, he's totally unreliable about everything he ever accomplished.

Ken Schaffner: Larry also says that Krebs kept enormously detailed books and notebooks and so forth, and he was able therefore to do a very good reconstruction of the work from laboratory books. At least, that's what I remember Larry told me.

Armando Aranda: You show the data about the leukemia study. There is a much more recent paper by an American group published in *Nature* in February, in which they work with B-cell lymphomas and use actually a microarray which is devised just to test the expression of genes which are known to be associated with immune responses, so they have a range of thousands of genes there. They have checked 96 different patients, all have the same diagnosis of exactly the same kind of diffuse large B-cell lymphoma and when they did this they found out that basically no two tumors are equal. So even though they are using this complex but novel methodology, the thing is that they are discovering the real complexity behind it which may lead eventually to the need not only to find tools as has been proposed by Michael Ashburner and other scientists in *Nature* recently, in order to deal with this very large amount of data so as to reach a common ground. For example, to calibrate experiments in order to make comparisons between experiments from different labs, but it may be the case that eventually this technique may really lead to applying a real complex systems approach, for example, a notion of causality that cannot be directly related to this single factor causality.

Ken Schaffner: Well, certainly multiple causality and multiple pathways that are involved in these systems. I've not read that particular *Nature* article but my sense is that we are likely to find a lot of diversity and that's apparently what they have found in these circumstances, and then the question is when you find that much diversity, how do you do classification in a useful way?

Armando Aranda: That was pointed out by the scientists doing the study, that really the problem is classification, it becomes the problem.

Ken Schaffner: It may be that the proper regimen for different variants is different, and it will be difficult to actually have an easily available catalogue because you would have to have so many patients to study.

Steven Rose: Of course this is the claim of pharmacogenetics now – that you will be able to use this with the SNPs, with the polymorphisms to interpret appropriate pharmacological regimes. There's obviously some case for that in broad classifications. If you look at anti-hypertensive drugs, for example, and it may become feasible really to use this sort of analysis to classify patients who will respond to ACE inhibitors versus beta-blockers versus calcium channel blockers. The concern that people have with that approach is what about that large category of patients who may very well turn out to drop through the middle and will simply be excluded from any pharmacological treatment because the DNA diagnosis doesn't allow it to be there. That's one point, but the more theoretical point is some of that diversity may not matter. It may be contingent diversity because

the outcomes may be the same, and that's true at every level of biological analysis. The final point is that what those chips are measuring is essentially the gene expression, but what you really need to know for network analysis (and I'll put on my classical biochemist's hat in this particular context as someone who was taught by Krebs), is that you actually need metabolic flowcharts, that is, you need the flow of the metabolites and therefore you need a network analysis to try and actually understand that. Understanding the proteins doesn't tell you, as it were, the dynamics for the throughput and I'm not sure how you go from the first to the second.

Ken Schaffner: I'm not sure what the next stages are going to be to get to that point. You can see a sort of feedback – I'm not sure I should use that word – but an interpolation of the known pathways and such into this in order to make sense of even as much as they've got, which are just mNRA expressions lining up.

Armando Aranda: I think the next stage is actually the protein microarrays. Scientists got behind the times and they thought of it too late, but they are busy developing them and I think within eighteen months there will be several protein microarrays on the market.

Ken Schaffner: I would think that people were developing those, but I don't know that. But you know of developments that are going on?

Steven Rose: That still won't tell you the metabolic flow – it will be one step better than this – but it won't tell you the flow.

Armando Aranda: The publication of papers dealing with the problem of the metabolome using high-throughput techniques which are not related to micro-arrays – it is basically biophysics, but at a larger scale. They are addressing this problem, of how big metabolic networks interact and also measuring on a timescale, changes in a large number of metabolites and products.

Speaker: What are the instruments they use?

Armando Aranda: For example, mass spectrometry and things which I am not really familiar with, but that kind of thing. For example at Los Alamos National Laboratory they have a group, because they are concerned – you have the genome, you have the transcriptome, you have the proteome and then you have the metabolome.

Ken Schaffner: Are there any results yet?

Armando Aranda: What I know is that the papers are basically about to be published this year. They have been working on this for some time.

Ken Schaffner: I have heard of the group, the Proteomics group and so forth, and it sounds right and the question is do you know whether or not the technology is there to begin to deliver or whether mass spectrometry is fine-structured enough to get the information?

Speaker: The problem I see is that it seems to be a kind of a circular logic because you put in what you know already, and this will interfere with the process you are studying.

Ken Schaffner: Well, there's a little bit of what some people call 'bootstrapping' involved here. But that isn't necessarily a bad thing if it can then be extended, and the question is whether or not there are appropriate ways to extend it. The claim is in some of these pathways that there are similar genes and they are being turned on at similar times, similar in structure. So they expect they will be similar in function and they'll have some kind of role to play, and these sort of point the way towards that and one can do whatever the additional experiments are. And data I didn't show you from some other experiments, there's an array which shows you something of the order of say 45 different experiments, and the experiments are different kinds of interventions that are done on the same organism, and then looks at the genes. You try to make sense out of having changed one input and gotten one response to what happens when you get another input and another response, but as Lander says, then you've got a 'back-inference', and that's where I think the field doesn't quite know where to go.

Michel Morange: I think that it changes the relationship between computers and biology. Before this new technology biologists used computers, databanks, but it was only a technique, a tool, nothing essential for the research activity. With this new technology, bioinformatics has a central place because you must be a very good programmer to try to see clusterings in these kind of studies. When you look at the authors of the articles, frequently you have computer science specialists among the main authors, and I think it's the first time in biology that you have this kind of very close interaction between computer specialists and biologists.

Ken Schaffner: This may be a new full employment technology for bioinformatics because of the need to have people do the interpretation. I have heard that people should be developing training programmes to be able to learn how to do this, but it looks to me as if it's relatively older mathematical technologies which are being used and employed in a new context. I don't know exactly which programmes are being used because I haven't delved into it. I would imagine you'd use Wiz and other kinds of programs to look for correlations and similarities.

Speaker: Just a small correction. I think if you think of computer specialists getting into biology, this might be the first time this is happening in molecular biology but a similar thing has happened in conservation biology and ecology about ten years ago when GIS based techniques began to be used extensively to try to simulate different kinds of ecotypes and things of

that sort. So this might be new in molecular biology but it's not really new in other contexts.

Ken Schaffner: I know at the Santa Fe Institute we would have a representative trying to do that kind of stuff in a large variety of biology including immunology and such for many years. In some sense, this seems a little bit different than any of that work. It seems to be so data driven which I think is maybe something that's good, but at the same time it seems at the moment so Baconian that I'm not sure where it's going to go.

Round Table Discussion 3: Chair – Kenneth F. Schaffner

David Hull: Speaking for those of us whose professions are parasitic on science, we can comment on science. We can complain about this aspect and promote that aspect, but in the process we are not actually doing science. If non-reductionist science is going to make a mark, non-reductionist scientists have to produce. They have to make (I hate to use the term) 'breakthroughs', make major contributions. Just criticizing reductionist science is not going to touch reductionist scientists.

Bob Williams: Can I just say, I don't think that any science is strictly non-reductionist. The whole mode of operation is reductionist, it's only the question of how far you can go sensibly. For instance, when Bob May is discussing with us things like the fish population of the North Sea, he doesn't say it's the cod fish, he doesn't try to reduce it to the properties of one cod fish. He knows that will be ridiculous and any property of that one cod fish is not very relevant to the problem of the ecology of the cod in the North Sea. Similarly, I think when a chemist is dealing with certain sorts of problems he realises that he can't go through the statistical mechanics of the system and all the rest. He has to stop somewhere, so he can only get at more global types of functions, but he still is reducing it to these functions to give him a quantitative interpretation. Somebody said earlier that scientists here, whoever they are, were anti-reductionist – that's absurd. We have no other method, and to think that we have some global methods, that's a nonsense. All our methods are reductionist in some sense, that's the way we have to be, and if you say OK we have to stop at certain levels, I will accept that. I think that the only question is where you can't go, and it may be because of complexity, it may be because of the inability to have a decent method at the present time. One of the things, for example, Steven Rose was saying, if you're talking about biological systems you probably have to get into definitions of flow, but there's hardly any definition of flow ever used

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by any biologist. He talks about energy and structure, he never talks about vectors in the problem, and if he doesn't talk about those then in a sense he is not going to get there. But we're all struggling to be reductionist and we all have to realise there will be a point at which you probably can't go any further, and that's what is sometimes confused as anti-reductionism. It isn't, it's just an inability to get any deeper, and the inability can come about through the fundamental nature of the system or just from incompetence, or just from complexity, but you may not be able to go there.

David Hull: So it sounds as though holists are all temporary holists and everyone ultimately is aiming to be reductionists.

Bob Williams: That's right.

David Hull: Notice the reductionist Lander co-opted global.

Lisa Lloyd: I disagree with what Professor Williams just said. I think that every time you use the word 'reductionist', I would have used 'analysis'. I think that it is correct that scientists use analysis to break systems down, but I think of reductionism as being something else which is the complete description of entire systems in terms of entities at a lower level. That's the sort of standard philosophical definition of reductionism which has a lot more metaphysical and epistemological bite than does the kind of analytic method that you are describing. So I would want to distinguish between analysis as a method, a set of approaches that all scientists do use, and reductionism as a set of commitments about what the ultimate aims of science or of a scientific theory would be, which is explanation at the lowest possible level. Does that make sense to you?

Bob Williams: Yes, all it needs for me to ask you is to amplify that with an example, so that if you give me a real example I could see more easily what you are actually saying.

Ken Schaffner: I think what Lisa is saying is that the analysis is what some of us call partial reductions or being able to find a mechanism that accounts for part of what's going on in the cell, whereas complete reduction would be in effect the potential replaceability of all of the language at the higher level with the language at the lower level.

Bob Williams: Well, if one may just stay with that, it may be that there are some things where, in fact, even if they wanted to scientists couldn't interfere. It may be that we could say that there are some things which are not reducible in scene, but then the scientist is no longer engaged. For instance, this morning when talking about what a doctor might do opposite a person, if he is going to try to take the person as a whole, which I think is a very sensible thing for a doctor to do, I don't see how he can use reduction methods at that phase of investigation. The molecular scientist's part is the reductionist part where he looks for something at a lower level,

as you call it. Doing the opposite, looking at the subjective thing, at the whole organism, that is not his realm. He is not a medical practitioner.

Steven Rose: I have deep problems with the concept of level in this particular context because I think there are many different ways one is using the word. I have eventually come to decide it is much easier to talk about discourse. To give you an example, consider, as it were, the physiological discourse of the muscle twitch, the biochemical discourse of the sliding of the actin and myosin filaments across one another. Clearly, we can have an almost complete translation between the languages of biochemistry and the languages of physiology in this context. But what does describing the muscle twitch in biochemical terms actually provide – is that a reduction? It's a different description using a different language and we can translate between the two of them, but we can't replace one by the other to use, as it were, what Lisa and Ken were just suggesting because they both serve different sorts of functions, depending on the language and the problem that one is asking, so I have a problem with the concept of level. I just wanted to come back to some examples that David was asking for, and let's take your metabolic flowchart. I was taught as a youngster (indeed I wrote it in my own little biochemistry textbook) about flowcharts like that, that what one should look for in terms of the regulatory process was the slowest enzyme in the entire sequence. So that was the bottleneck and where feedback operated, so you controlled a sequential flow of metabolites through a metabolic pathway by feedback control at the initiation point which tends to be the slowest enzyme. We now know that's actually not true, the stability and control of the path is embedded within the pathway as a whole and that is not reducible to any of the individual enzymes or the pathways through it. It's what Henry Kacser called 'molecular democracy' in a paper analysing the mathematics. Now that I would regard as a non-reductionist description of a metabolic pathway. Of course, it has been amplified by the Santa Fe people and Stu Kaufmann in terms of metabolic networks and so on. That's one example, I think, where reductionism to single molecular processes cannot explain the stability of a system that you are observing. The other comes, I think, from an example I was hinting at this morning, which is my own work in the field of memory, where it's perfectly clear that, despite the arguments that have existed in the field for a long time, that memory exists in the encoding of changes in a single synapse or a single small ensemble of synapses which stably represent the memory for a long time, you cannot understand it that way. You have to understand it as a dynamic flux across a whole range of synapses and different brain regions shifting in time and space and reconstituting each time, as it were, the processes activated. And again, (a) that's not reducible to the properties

of single molecules, although we can analyse single molecules and single synapses, and (b) I think that it represents a conceptual breakthrough in asking what it is that we have to understand even if we can't mathematicise it yet. I don't know if that satisfies you, but it's the direction I would go in.

Ken Schaffner: If Fred and Alex were here they would probably say that this is still reductionistic – it's just not single-molecule reductionism, it's more complex molecule reductionism.

Marc Van Regenmortel: Yes, I would agree with one of the earlier speakers who put the emphasis on analysis. As I mentioned, analysis is a matter of dissection and in that sense you have to be reductionist. You can't dissect without being a reductionist but the only thing you are achieving is a description of the constituent parts. Whether you like the word 'level' does not matter. Physiology will never be transformed into biochemistry. The same phenomenon can of course be described at different levels, or you could say in terms of different contexts, but whether the description is relevant depends on the question you ask or the problem you want to solve.

Science, I think, tries to do two things, one is to achieve understanding, the other is to solve problems. These are two separate aims and activities. Some people manage to do both but some specialise in one or the other. When looking for explanations, it's an infinite regress – you never ever find the ultimate explanation. You can go on forever, and for pragmatic reasons you have to decide to stop at a certain stage. In that sense, explanations cannot be reductionist in the final analysis. Descriptions, on the other hand, often are, but eventually when you get an explanation it will not be in terms of reduction, at least not in biology, mainly because of complexity.

The second aim which is problem solving is also a respectable scientific enterprise. It often does not require a considerable amount of understanding – a certain amount obviously, but not necessarily very much. When you tackle a medical problem, like developing a vaccine, or a sociological problem, as we discussed this morning, a limited amount of understanding may suffice. I think that analysing sociological phenomena in terms of genetic predispositions is beside the point since you are simply replacing a sociological question by a genetic one. Little understanding of sociology is obtained in this manner and few social problems are likely to be solved along the reductionist path. For instance, it seems hopeless to want to decrease the amount of aggression manifested in modern urban societies on the basis of our knowledge of the genetic predispositions of certain individuals. I suspect most of us agree on that. Does anybody want to counter the view that problem solving cannot be achieved by a reductionist approach that ignores the importance of context and higher-order interactions?

John Dupré: Well, to pick up on problem solving/multiple discourses in cancer, I actually don't want to question at all (I'm not competent to do so) the kind of science that you've been explaining. It may well be wonderful science and basically reductive as you suggest, but I guess that one thing that we sometimes should focus on is that there are many different approaches to cancer as a problem and solving the problem of cancer. One, of course, is understanding the processes which go on when cancer tumours grow, and that's what you are talking to us about. But, of course, there are also questions as to why people get cancer and they are addressed by questions about the sources of industrial pollution, smoking, the way people live. There were questions that were raised this morning about how you should treat cancer patients, which may have a lot to do with how effectively we deal with the problem of cancer. I guess what I am suggesting is that, even if you think that the way to solve that first kind of problem is as reductive as you can possibly imagine, it seems to me that the enthusiasm we have for reductionism tends to channel resources towards this kind of discourse about the processes by which cancer cells grow and divide and so on, rather than the questions about why people get cancer and how to deal with people who have cancer that in some ways hold out more hope of solving problems than the first. Of course, I am not suggesting we should abandon those, because there are therapies that develop and so on, but I'm just suggesting maybe reductionism should also be seen as a real distorter of the way we invest resources and effort in problem solving.

Ken Schaffner: That can happen, and Steve has made a similar point in his article in *Nature* several years ago about tilting the development of medicine in the wrong kinds of directions. I should say very briefly that that so-called seven-plus hit theory that I mentioned that colon cancer had gone to has to do with all the things that happen to go wrong. Some of them are environmental kinds of carcinogens, other kinds may have to do with genetic factors or they may have to do, for all we know, with psychological kinds of factors. Exactly how that interacts with the immune system is under study, but not everything is completely known about it.

Stanley Shostak: I want to disagree with my host. It is not really understanding and problem solving – that's, of course, where we claim our legitimacy – it's also synthesis, putting things together and changing things. I feel that we are claiming as a group to be vastly ignorant, but the future is the only thing that is certain, the past is, of course, a myth. I'm being very Deleuzian here but the reason is I want to attack the binarism that I think is so generally assumed. I think that although we might agree that we are living in a thermodynamical world there is no reason to take Hawking so seriously, because when I begin this sentence with 'I begin this sentence', I already

know at some level how the sentence is going to end. Now the fact that the future can impinge upon my sentence, and it's only a few seconds into the future that impinges on the sentence, there is the possibility of extending that future and understanding in a more synthetic way how adaptations are moulded, how life will evolve. I can say with confidence that longevity and immortality research that is going on now is going to impact on the future, and that the choices that we as scientists are making available to people will determine human life in the next decade, and we are like Einstein saying to Roosevelt 'Yes we can make an atomic bomb' and then ignoring the consequences. The Manhattan Project goes ahead and Szilard then rings the bell and says 'No, no, no, you don't want this to happen', and no-one here, although we are talking about curing cancer, is looking at the consequences of what we are doing. Now, maybe that's too hard a judgement, but if we break down the linearity and see the synthesis as scientists I think we have to make some decisions.

Lisa Lloyd: I was just wondering how you can convince other scientists of any of what you said. I think there's a huge amount of interest in anti-reductionist and complexifying approaches to research in this room, and it makes me wonder what happens when everybody goes home. So if we go home and you think that what happens in the next ten years is going to have a huge influence, how exactly does the influence go? This is an activist kind of question.

Stanley Shostak: Let's take just one example. There's a popular science writer, Ben Bova – he's an MD, and he considers himself an Asimov spin-off – and he's writing on immortality right now. There was a piece of his in *Nature* a few weeks ago and what he's predicting is that in a very few years people will have available longevity treatment that will restore you to the condition of a 24-year-old and prolong your life indefinitely. Space travel, for instance, to the next planetary system in our galaxy may take 320 years, which we might consider impossible but, when you live forever, 320 years, what's that, a night's sleep. This is going to have an effect. So let's take one example, not cancer research because I think it will probably be successful, but longevity research and examine how that will impact on society much like the atomic bomb impacted on society. 80 % of the electricity in France is made by atomic power, isn't it? The Deleuzian point is, of course, that the future is the only thing that is predictable; we must deal with the future and stop mythologising about the past.

Marc Van Regenmortel: Some humorists have said that the only thing you can predict is the past; in biology, you may be successful at 'predicting' past adaptations but the future course of evolution will for ever remain unpredictable.

David Hull: A question – is there anybody here who wants to live for ever? By 75, I'm going to be so bored I don't know what I'm going to do. Are there people who really want to live forever?

Marc Van Regenmortel: We have been totally incapable in the past of predicting the technological innovations achieved by human design. Biological systems are considerably more complex than human artefacts or weather patterns and predicting biological evolution or the future of human society is clearly not possible.

Stanley Shostak: I'm talking about synthesis.

Marc Van Regenmortel: How are you going to synthesise? It's just impossible. When something is complex enough you have no idea how all the various elements in a particular context are going to interact to produce a certain result.

Stanley Shostak: We have no alternative to the linearity of reductionism, and I'm saying there must be an alternative – let us be synthetic, let us be creative. What is the alternative if you are saying there is no synthesis? There must be an alternative that is non-synthetic.

Marc Van Regenmortel: I think the synthesis that is relevant is a non-linear synthesis. Linear synthesis and push–pull causality have been given up, because complexity cannot be analysed using linear mathematical tools.

Bob Williams: As a scientist I would say, that as far as reductionism is concerned, we could think how far physics has got. Now physicists would say that given the Big Bang at a tenth of minus fiftieth of a second, they can come all the way forward to the present time as far as most dead things are concerned, and they've achieved that conclusion over a very long period of time. I don't know how far this reductionist game will go as far as living things are concerned. What I worry about is, if I am not allowed to say that all the scientific activity is in some way reductionist, what does holistic research mean. What is it exactly? If somebody could answer what is holistic research, I would be very interested.

Lisa Lloyd: I thought that Steven Rose gave a very vivid description of holistic research.

Bob Williams: Not for me, no way. It is to a level, that's all – you're down to a level. He's only describing a set of enzymes.

Steven Rose: I'm not sure that I actually quite understand your question, Bob. What I was describing was systems which when you tried to reduce them you lost the sense of the system – you couldn't actually do it. Now that's an irreducible aspect of a particular form of living system, and it's one that you and I agree on. I don't care whether it's called holistic research or not, it's an example of finding the right level and finding the right type of description for the phenomenon that you want to study, and that seems to

me to be the crucial issue. But I wanted just to come briefly back to what Stan was saying because he was moving us out of the terrain of science itself into the embedding of science within the social order. I wanted to reflect firstly on the fact that nuclear power has had a huge impact on vast numbers of people through society. I don't think that longevity genes are going to do that. Indeed, they may affect those unlike David, among the super rich who actually do want to try to live for ever, like those idiots who have their heads cut off and put in cryogenic machines in California. But the control of science after all primarily, as we know, is in the hands of the funders of science, and those funders of science are the military, they are big business, the State in various shapes or forms, and they are shaping the direction in which this research is going. I don't think one can get away from the social forces which shape and direct it. On the other hand, we can also point out that an awful lot of what we've been discussing over the last couple of days, which is of intellectual and theoretical and scientific interest, is going to have damn all to do with the fact that we live in a world in which there are gross inequalities of wealth and of poverty, of splits in life expectations and social justice between classes, between races and between genders. Those are the great defining facts of the world in which we live, and the great shapings that science and technology in its development are bringing on that – issues such as global warming and utilisation of the earth's resources are quite outside the terrain of the things that we have been thinking about now. But if one is going to answer Bob's question of what holistic research ought to be, picking up and expanding on what Fred was saying this morning, I would argue that the science that we do and the questions that we are asking need to be seen in the context of that much more global terrain than the ones that any of the little microbits that you and I and other people do around here. I suspect that a lot of the collapse in trust in science which we are all aware of, and the suggestion that scientific research is generating more problems than it is solutions at the moment, is coming precisely because we are actually not looking at that much broader context.

Bob Williams: Global warming is an easy thing to take, it's a marvellous example of the modest success so far of reductive analysis but it is still the way a scientist works. We've gone after finding out what could possibly cause it. Now at the moment there's a great argument about this, but you categorise the possibilities which is the typical way a scientist works. He reduces global warming to chemicals if he possibly can or to properties of the sun if he possibly can, and he describes the phenomenon – that's fine. What you do about it, which is much more the concern of the longevity research chappie, what you do about it, that's out of our hands

altogether, we can only supply the information or the data and say this is the conclusion. If you want global warming, boys, you can have it and we can't stop you!

Stanley Shostak: On global warming, I heard Hasselmann a couple of weeks ago from Hamburg, and the thesis of his talk was if you want to know what to do with your money send it to Hamburg. His modelling – he uses a Bayesian model and others do, of course, for climate prediction – was very much the sort of model that I had in mind when I talked about what kind of work we should do for evolutionary studies. It's going to be complex and it's going to be multivariate, and we have Bayesian modelling to work on variables simultaneously, so we're not bereft of ways going beyond reductionism to a kind of polyreductionism plus interactions. But that's not what I'm challenging you with because I think it's just more of the same, not an alternative, and I'll just spit it out – you may laugh – but what I'm talking about it is Lamarckism. I'm not talking about Lysenko – I think there's no way of talking about Lysenko because it was a different time and the circumstances were enormously different. Nevertheless, I am talking about perhaps a different kind of Lamarckism because Lamarck was aware of the future and he was trying to bring it within bounds.

Stanley Shostak: We're not engaging in self-fulfilling prophecies but in new ways of non-linear thinking.

Stanley Shostak: I'm not a holist, I've read Kessler and I've read the Frankfurt School and I dissociate myself from the holists.

John Dupré: I just wanted to respond to Bob William's last point. I think what I was trying to get to in my last comment, and then Steve Rose put much more eloquently, was what you might call the anti-reductionism about science rather than the content of science. It is precisely the attempt to persuade scientists not to see themselves as just one component in an atomistic society where scientists just provide bits of knowledge and then somebody else does something with it. The whole importance of what Steve says is that what science gets done isn't actually decided by scientists. I think scientists are on the whole deluding themselves if they think the content of science is determined simply by the logic of what's going on, what's being discovered and so on. Certainly some of it is, and I'm not trying to impugn the decency and well-meaning on both sides, but there's a huge amount of research that shows the effects of social institutions, just what Steve has been talking about, on what science gets done. So science is part of a complex system, and I think just to say we provide the facts, scientists provide the facts and somebody else deals with it is exactly the kind of extension of reductionist thinking on to the social level that is one of the things we should try to escape from.

Bob Williams: I am sorry, but I think you mistake my intention. What I mean by what the actual scientist does includes his publication of what he finds. The fact that what he does then has an enormous effect he is very well aware of. The fact that he is biased by all sorts of inputs he also is very well aware of. But what does he actually do as far as implication and application is concerned?

John Dupré: Perhaps he should be aware of what he is doing in a broader context.

Bob Williams: No, he is aware of what goes on outside himself, but what does he actually do? He does an experiment to find out something, and he does it I say in a reductionist mode, and the fact that he can't go very far I don't call that anti-reductionism, I just say he gets stuck. Now when you say take that into the context of society which people are now talking about, then, of course, he is muddled by every sort of thing. I sit on committees of all kinds, discuss these problems with all sorts of people. The discussion about basing society on scientific knowledge gets diluted out into education, into everything under the sun, but that doesn't help us to resolve what the attitude is inside the scientist to a problem. That's all. I would say that is basically reductionist. A scientist does not try to put things into the whole – he takes the whole and looks for the bits and draws conclusions about the whole.

Armando Aranda: Just a general question that is addressed particularly to the philosophers in the audience because in these talks the term 'gene' has been coming up all the time. We are all aware that with the Mendelian gene and the gene according to modern molecular biology there may be great discrepancies, and also Dorothy Nelkin pointed out that the gene term itself is subject to a great deal of manipulation. So do you believe it is useful for the future of science itself to have a sort of new modern definition of the gene, or is it worth spending time trying to get a common ground in order to find a new concept for the gene?

Ken Schaffner: I'm sure people can address that. My sense is that people have tried to get away from using the term gene because it is fractured so often, yet they tend to come back to it for some reason and maybe it's social, or maybe it's historical, or it may have an insight into that. I've not done a systematic analysis.

David Hull: There are at least three meanings of the word Mendelian genetics. Not all Mendelian genes are the same and there are different methods of determining a Mendelian gene. The evolutionary gene of G. C. Williams, is designed for evolutionary theory and does not coincide with any of the Mendelian genes. Then molecular biologists spot all sorts of genetic material, at least 20–30 different things, each one of which can be

called a gene. So it's the level of discourse, you just talk about genes. But in research you were probably limiting yourself to three different senses of gene. You can try and do away with the word gene; we have tried to do away with the word 'species' for exactly the same reason. But there are certain words that seem just to be needed and we do use them. They are highly ambiguous but the assumption is the ideal state is to express yourself with absolute clarity, no ambiguity, no vagueness, and that's impossible.

John Dupré: And conceivably not desirable. There is a school of thought at least in philosophy, that the fact that words have a certain kind of looseness may actually be advantageous in developing thought.

David Hull: Even though Alex Rosenberg played the hard-nosed constructivist, he wrote a paper on the necessity of vagueness in communication.

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