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TOWARD A HOLISTIC THEORY OF LIFE

by

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"The vital force directs phenomena that it does not produce; the physical agents produce phenomena that they do not direct" ... Claude Bernard 1839

Introduction

The following paper is intended as an introduction ... an overview... of a "revolution in biological science"; a revolution that is taking place in time present[2]. An attempt is made here to provide a non-technical description of the transition from the current view of life as a machine to a holistic view of life as a *creative force*. capable of ordering the great diversity of organismal design that we see everywhere. To the metaphysical and religious mind this transition sounds less like a revolution and more like a rather obvious fact. Nevertheless, it does represent a *scientific* revolution and the more we can understand the scientific failure of modern biology to explain "life as a machine" the more able will we be, if we are so disposed, to make the connection between our metaphysical and scientific understanding of life.

These two ways of understanding are irrevocably entwined. For example, the question of life's origin and evolution is once again at stage center in our public affairs and continues to divide us in our struggle to define ourselves, our spirtual goals, our relationships to one another and to a sustainable world. Evolution is a key element in all this because now, as in the past, how we think scientifically about the origin and diversity of life will govern our views of how we are to survive. Today's scientific theory of evolution is guided by a reductionistic, machine-like view of life and has no place for matters of the spirit or of human values and aspirations. These are all epiphenomonal to a random, mechanistic view unable to inform us of these deep human questions. Many scientists, however, hold the view that there are no necessary or inevitable conflicts between a spiritual and scientific view of the living world and in giving voice to their belief they support the possibility that life itself is not a machine; that life, while it obeys the laws of the physical world, also has laws (yet to be discovered) that are new and different from the laws governing the non-living realm. I take the view, with Nordenskiold, that life is indeed a wholly separate form of matter[3] embodying creative forces, choice, and non-random processes that implement the design that so clearly characterizes and sets apart all living things from the physical world to which they are so completely related and on which they are so utterly dependent. My view is that a scientific but non-

reductionistic understanding of the complexity of life and its proper relationship to the world will inform us of the futile nature of our quest to dominate nature and will provide a basis for the construction of a future world in which, as biologist Brian Goodwin puts it, "a science of values" emerges as our dominant paradigm[4].

Of course, I can only point in a general direction here and the best I can do is to outline some approaches to a holistic biology that is responsive to our deeper questions. I will not succeed but my attempt will be to show that modern reductionistic biology cannot *in itself* explain the key features of biological evolution and the recognition of this failure forces us to seek an alternative scientific world view. I have chosen to write this paper with a historical setting tracing the holistic revolution in biology back only to about 30 years ago. I believe that we can find embedded in this recent history a scientific concern and a basis for a new science of values.

Early attempts at holism

In 1966, amidst the clamor and expectations of a burgeoning molecular biology, a small group of biologists, physicists, and mathematicians ... and, from a reading of the proceedings, with at least one poet among them ... convened at the Villa Serbelloni in Bellagio, Italy to discuss the role of theory in biology. The meeting, supported by such diverse entities as the Rockefeller Foundation and the United States Office of Naval Research, would last for a week or so and would be reconvened again over the following three years so that ample time could be given to develop whatever consensus was possible on the question of a theoretical biology[5]. Why there should there have been a concern about theoretical biology in the first place will become clear as we go along.

One of the major questions was whether or not life could actually be explained using solely a basis in physics and chemistry. In 1966 most scientists had not yet become so thoroughly accustomed to the view that life was a machine or that life could be completely reduced to machine-like ways of operation. Some biologists, certainly, were not convinced of the machine analogy. However, they were also acutely aware of the vitalistic 'baggage' carried by the life sciences, and were anxious to move in a direction of progress so clearly in evidence in the physical sciences where reductionism, mostly through the theoretical structure of quantum mechanics and its penetration into

chemistry, had been so successfully applied. The progress in molecular biology had been rapid in the 1950s and 1960s. With DNA identified as the genetic material, the linkage of biological heredity with chemistry was forged. Watson and Crick supplied the structural mechanism essential for understanding hereditary coding and information replication. It was clear to most that it was only a matter of time and 'details' before the means were at hand for reducing life to mechanisms ruled by laws of physics and chemistry. The discovery of a veritable infinity of mechanisms had already begun by the time of the meeting, and this discovery process remains today as a major growth industry. We have biological pumps, electrical switches and conductors, energy generators and transducers, informational encrypting and storage systems, signaling devices, sensing receptors, mechanical lifters; one could go on. These mechanisms which apparently provide the basis for the life of a cell have been found everywhere. They are shared by all organisms in more or less the same design.

Still, the scientists we are about to describe were hesitant. Not only were some biologists uncomfortable with machine analogies but physicists, and especially the theoretical-minded among them, were dubious because of their own considerations having to do with uncertainty and complementary ... with the need for a "renunciation of knowledge". That is, their own experience had led them to realize that a point was reached where reduction of a complex system to further detail brought about a loss in the possibility of comprehending that system as an entire entity. For example, if one refines measurements to determine more precisely the momentum of a particle then one loses precision in defining that particle's location. The question in Bellagio was, therefore, whether the complete identification of biological sciences with reductionism was premature. If the nature of the organism was to be denatured (lost) in the search for detail then, indeed, biological reductionism was fatally flawed. As I will try to show , complex phenotypes, or features at the level of the organism, can not be completely described by elementary particles or even by genes. Genomes provide essential "maps" of working parts (proteins) all of which are assumed to obey the laws of quantum mechanics. However, directions for reading these maps are not in the genome alone. These directions are located at other levels in the organism.

As it turns out the question of the irreducible nature of the organism was not to enjoy much attention outside of these meetings. The feeling among biologists and scientists generally was that the answer to life was "surely in the details". Bellagio

was important because it represented a continuation of the scientific proposition that biology and the organism were special, and of the idea that one still could ask questions about the "secrets of life". One of the theoretical physicists there, Howard Pattee, put it this way[5].

> *"... if you ask what is the secret of life, you will not impress most physicists by telling them what they already believe - that all the molecules in a cell obey the laws of physics and chemistry. The real mystery, as in any machine, is in the origin of the highly unlikely and somewhat arbitrary constraints which harness these laws to perform specific and reliable functions. This is the problem of hierarchical control...".*

Pattee was arguing, not against reductionism, but in favor of reductionism coupled to higher (hierarchical) laws unique to living systems. In living cells reductionistic description rules over molecular machinery; in those same cells, he argued, molecular machines are constrained at the next level by rules and laws not only different from, but irreducible to, the laws of physics and chemistry. Living things, according to another theoretical physicist attending these meetings, Walter Elsasser, consisted of

" ... a set of centers where the coordination of causal chains is totally lost in complexity. These active centers are what we call organisms." [6]

Elsasser, who had made many fundamental contributions in physics, and who would receive the 1987 National Medal of Science U.S.A., was already embarked on a twenty five year effort to develop a theory of biology that would embrace the reductionistic aspects of biological mechanisms as well as the irreducible centers of living things. He died in 1991 while still at work on this problem. Both Elsasser and Pattee represented a small but highly informed group of physical scientists going back to Bohr[7] and Polanyi[8] who realized that biology, in its movement toward an upward causality from physics and chemistry, had neglected to develop any theory of its own that could account for the apparent ability of cells and organisms to impose a downward constraint on reductionistic mechanisms below. The rules of this downward causality were seen to be irreducible to the physical rules governing molecular motion; they were the rules unique to the organization of matter found in living systems.

Elsasser's and Pattee's arguments at the end of this era marks our beginning now. As we approach the year 2000, modern life sciences are struggling with the complexity of life revealed by 50 years of molecular biology. Most biologists, uninterested in holistic theory, expect that reductionism will prevail and that the

special features of life will eventually be explained by the laws of physics. Scientists with serious interests in theory think otherwise and the initial attempts made by the Bellagio conferences are important points of departure. The current interest in non linear dynamics and its derivatives, complexity and chaos, is evidence enough of a renewed search for laws that simplify and make useful the enormously complex ... even unintelligible ... picture that we now have of living systems. It seems clear that these dynamical approaches do, in fact, capture the essential complexity inherent in a multiplex hierarchical structure of life. Whether they provide the whole answer ... as in a master theory of life ... is hardly relevant. That they remain as candidates to parallel and contextualize genetic reductionism is of critical importance.

A third participant at Bellagio was Brian Goodwin who is now a professor of biology at the Open University, London. Brian is a theoretical biologist and one of the early leaders involved in bringing non linear dynamics to bear on the analysis of living systems. His papers at the meetings served to express possible answers, or approaches to answers, to the theoretical concerns of Pattee and Elsasser. The juxtaposition of (a) critical analyses of reductionism in biology from two theoretical physicists with (b) the description from a biologist who was also firmly grounded in the theory of complexity is one that provides a clear view into a brief, intermediate stage in the life sciences. This was a time when advances in molecular approaches were rapid but had not yet overwhelmed the field. It was also a time that allowed for pause and for reflection. It was a time of interdisciplinary work between biologists, physicists, and mathematicians. It was a time in which a pluralism of ideas, theories and experiments seemed to flourish. Of course, today in 1995, we see this mix all the time but we see it in a very different way. *In 1966, pluralism truly meant exploration of different possible interpretations or pictures of life; today it signifies only that workers of different disciplines are exploring the same mechanistic picture from different technological perspectives.*

The prime mover for the Bellagio meetings, which took place during 1966 thru 1970, was the developmental geneticist, Conrad Waddington. He had already made a profound impact in developmental genetics with his demonstration that embryological development could be altered by environmental influences and that these alterations mimicked those brought about by gene mutations (1953). Briefly, he showed that if the larva of fruit flies were exposed for 10 minutes or so to high temperature, some of these would give rise to adults with no veins in their wings.

Gene mutation could also produce this effect but in the Waddington experiments there was no reason then, or now, to suspect that mutations were involved. Temperature shock, somehow, induced a change in development to produce "crossveinless" flies. If these flies were mated with one another and the larvae again exposed to temperature shock, then a larger fraction of adults would become crossveinless. If this process were repeated for some 15-20 generations then, even without temperature shock, crosveinless flies were produced. The change had become heritable, and would last for many more generations.

These 'phenocopies' were the first experimental evidence for the idea of genetic assimilation which was itself heretical in the context of the current theory that genes controlled development. Rather than control vested in specific genes, the idea of genetic assimilation had been offered by James Baldwin in 1903. The idea was that embryological development (ontogeny) was dictated by a regulatory process (unspecified) co-extensive with the organism itself. Changes in ontogeny are produced, according to Baldwin, as a matter of normal variation and without mutation. These changes sometimes resulted in better or more fit performance by individuals in specific environments. Genetic assimilation was the process in which random gene mutations would later, over successive generations, become assimilated to the prior developmental changes. Without identifying this global regulatory process, Waddington's phenocopy experiments were consistent with a regulation of development in which genes played the subordinate but critical role of supplying parts (proteins) necessary to carry out the global plan at the level of the organism; a plan that while it included genes, was itself not in the genes. In other words, according to Waddington genes were controlled by higher levels of regulation; precisely what Walter Elsasser and Howard Patte were talking about from a theoretical perspective. (For an up to date discussion of Waddington's experiments and the cellular global processes by which the genome is regulated see reference 9).

Most of the time at Bellagio was spent talking about the kind of global regulation proposed by Baldwin and Waddington. There was, however, no body of consistent experimental evidence for hierarchical constraint on genetic process. The Waddington experiments were extremely difficult to do, were labor intensive, and ... worst of all ... there was no convincing theory available to explain how such hierarchical regulation could be visited "from above on the genes below". The meetings therefore turned to intensive discussions about theory. They dealt with levels of control beyond the gene and were clearly the prelude to much of what we

now hear under the description of complexity and chaos theory. However, there was also something quite special about Bellagio. Clearly absent was the modern impulse for hyperbole or for master theories. One gets the impression that the Waddington meetings were much closer to the organism as a fact of life disregarded by reductionism. The participants appear to be less interested in damning reductionism than in recognizing its limits. They attempt to conceive of a biological theory which at the same time would be consistent with reductionism, as far as it went, but also capable of supplying what was missing.

Finally, my own impression, as already stated, was that in this matter of building on reductionism while also moving to a more representative view of life, the physicists Walter Elsasser and Howard Pattee, and the biologist Brian Goodwin played leading and sustained roles. Many others were also present who have made enormous, sustained contributions to biology and to the necessity to break out a narrow genetic view of life. But the three I have selected to focus on here appeared, to me at least, to be more fully formed from the perspective of the need for a holistic biology.

Pattee's view of hierarchical structures in living things, far from polarizing discussions between scientists of different persuasions, attempted to bring them together to take a modest next step. That step was to examine how it might be possible to merge a mechanistic theory of life ... one based on the laws of physics and chemistry ... with a view that admitted non-random, adaptive behavior that, while it was not inconsistent with reductionism, was also not reducible to physics and chemistry. His view of hierarchical structures in life accomplishes such a merger. In addition, Pattee's papers provide a clear view of the difficulties inherent in any attempt to break out of a strictly reductionistic mode of thinking.

Walter Elsasser was a master physicist and theorist; his contribution was to begin a systematic search for a theoretical biology that would admit much of what used to be thought of as vitalism, but which he felt certain could be described in scientific terms not at odds with the laws of physics.

Brian Goodwin's papers provide a clear view into complexity and also provide a bridge from the expressed concerns - then and now - about the enormous

complexity of life to a future in which a theory of life adequate to that complexity might be put in place.

The essential duality in biology

In neo Darwinism, biology creates a fundamental split: it separates individual becoming from species becoming. Evolution, by standard theory, works through the operation of natural selection on random mutations. Over time, small differences are 'collected' as significant enough variation so that variant populations arise from initial populations. In this evolution of new groups the significant source of variation is natural selection. Mutation provides raw material but selection itself is the origin of all creative change in evolution. Ontogeny, the development of the individual, is thus made irrelevant to biology's main question, evolution. This schism, as we shall soon see, has had an unfortunate effect in biology at many levels. For example, one might logically conclude that developmental processes would have to be considered as the major source of individual variation and thus would be the leading science in evolutionary biology. But neo Darwinism, in separating development from evolution and positing natural selection as sole driving force, clearly says otherwise.

Howard Pattee

This essential duality is reflected everywhere in biology. But Pattee sees it as a particular instance of a general separation found in elsewhere in science. To him, as a physicist, the separation is quite familiar ... as are its profound negative consequences. He argues that structures per se do not determine functions. A lock and key relationship is too simple by far as a basis for developing understanding of most physical events. Function is determined by the context ... the state of organization ... in which the structure is embedded. The question now for Pattee is:

> *"What is the origin of the context which defines the structure/function relationship? "*

If we focus on the mechanistic details of structural changes associated with functional output we tend to loose sight of this question of a context defining structural change and the linkage between structural change and functional operation. The context defining the relationship between structure and function is a hierarchical interface in which the new rules arise which determine outcome.

This is a difficult concept so let's try an example. In complex human phenotypes ... take obesity for example ... many genes are involved; perhaps

hundreds or thousands, we really don't know. We may say that genes determine obesity and we would be partly correct; we would also be vacuous. The simple causative assertion that genes determine anything hides the deeper question of the context in which the genes contribute to obesity or any other trait. In this case let's imagine that 10 genes produce 10 enzymes that constitute a metabolic network linking sugar and fat metabolism to energy requirements and net fat storage. Ten genes defining 10 enzymes produces an interactive network of over one million possible interactions (10 genes, 2 alleles each or 2^{20}). The situation here is that the number of possible patterns of metabolic output vastly exceeds the number of patterns actually observed. Pattee concludes that some constraint must be present that provides order, persistence and reliability to the system as whole. Modern biology focuses on details of enzyme structure and function, substrate binding, reaction kinetics, and even feedback inhibition all of which gives us an informative map of interactive molecules related to fat metabolism and storage. That map will even include information related to rate limiting reactions so that some idea of overall regulation is also provided. What is absent is information concerning the origin of the network itself and the rules governing the network origin, stability, etc. Such rules, Pattee argues, can not be derived from the physical laws governing motion of constituent system molecules. And he is concerned because all of science's attention, while focused on the details, is missing the point of integrated activity. He is especially concerned at Ballagio that biology, in investing so much in reductionistic analysis, is making it more and more difficult to know anything about the origin of complexity and adaptive behavior so characteristic of life; in emphasis on detail we make it impossible to understand the organism.

Hierarchical relationships exist at all levels of biological structure. The following is directly from Pattee:

1. *"It is the central problem of the origin of life, when aggregations of matter obeying only elementary physical laws first begin to constrain individual molecules to a functional collective behavior.*

2. *It is the central problem of development where collections of cells control the growth or genetic expression of individual cells.*

3. *It is the central problem of biological evolution in which groups of cells form larger and larger organizations by generating hierarchical constraints on subgroups*

> 4. *It is the central problem of the brain where there appears to be an unlimited possibility for new hierarchical levels of description".*

As an addition to level 2 we may add may add a fifth.

> 5. It is the central problem of physiology where tissue and organ levels of organization constrain individual cells to particular patterns of metabolic and genetic expression.

Physiological and developmental constraints share much in common but while developmental constraints become progressively irreversible (differentiation), physiological constraints are reversible over time spans from seconds to years.

Pattee concludes this part of his discussion with an emphasis on the separation of the question "how a thing works" from the one of "what is the origin of constraints within a system". He uses a hypothetical debate between Francis Crick of DNA fame, and the physical chemist and philosopher, Michael Polanyi. The following quotation from Pattee shows the essential nature of this separation and its relationship to the separation between the two major areas of inquiry in biology evolution and development.

> *"In order to see the central problem of hierarchical organizatin more clearly, it is helpful to look at the difficulties which arise when the hierarchic interface is viewed from only one side or the other. Viewed from the loiwer side of this interface, the elementary laws (of physics) are regarded the given conditions and the problem is to see how the hierarchical constraints arise to perform integrated function at then higher level. Viewed from the upper side of this interface, the hierarchical constraints are regarded as the given conditions and the problem is to see if the integrated function is consistent with the elementary laws."*

Crick takes the view from above. He assumes the hierarchical rules are in place ... put there by natural selection. They remain and, presumably, will remain hidden from us for all time. In the simple language of natural selection ... things are the way they are because they got that way. Therefore, according to Crick, the only thing to do is to pursue the organism in terms of ordinary physics and chemistry. On the other hand, Polanyi looking from below, assumes that all molecules obey the laws of physics and chemistry but takes the position that:

"the origin of constraints or boundary conditions which result in hierarchical integration are irreducible to those laws" .

Crick is interested in how things work while Polanyi is looking for the origins of new rules or laws of constraint that speak to the special characteristics of life. These constraints are available to us by a scientific investigation of cells and organisms if only we had the theory and methodology adequate to the task. Polyani is saying that scientific laws unique to the living state are discoverable but not through the process of Cartesian reductionism. Biology represents for him, as it does for Pattee and Elsasser, a wholly new science.

Walter Elsasser

Walter Elsasser presented a paper on biological individuality in which he developed an approach to a theory of organisms that moves beyond reductionism. As far as I can tell it is the only attempt to date by a modern scientist, familiar with the broad concepts of biology and possessed of a deep knowledge of physical theory, to formulate such an approach. In 1987 he published his last account of this approach in which he was able to refine and clarify his thoughts[6] Below is a summary of this last account.

In his last book he begins at a place of great sensitivity for students of the modern university so deeply steeped in reductionistic science; he begins with a dialectical treatment of the historical polarization between reduction and holism. In many ways the entire book is a theory of holistic biology made acceptable by virtue of the fact that the author captures holism in purely scientific terms without all of the usual holistic metaphysical baggage. It is entirely useful, in my own experience as a university professor, to confront biology students with this dialectic. Since they are never made aware of holism in science, and since they have so little time to explore such "anti-reductionistic" philosophy elsewhere, they remain completely uneducated about the possibility of a science potentially able to combine the two approaches.

Holism means to perceive the organism as a dynamic, stable, coordinated center of activity that is difficult to interpret as being the sole result of physics and chemistry. It is important to note that Elsasser never holds against reductionism as a

powerful perspective in biological systems; his emphasis is that reductionism in itself is simply incomplete and requires additional theoretical and real considerations in order for life to be revealed in a more complete and useful manner.

The opposite view to holism was provided by Descartes in 1637. Now called Cartesian reductionism, what Descartes argued was that life displays a multitude of complex mechanisms all of which may be broken down and analyzed in terms of their parts. Here is the first startling conclusion drawn in plain language by Elsasser; biology is a non-Cartesian science. *The organism is first and foremost an organized center of enormous complexity.* We detect physico-chemical processes within this center but the coordination and stability of that center cannot be reduced to these processes. The proposition of "irreducibility of life" to physics and chemistry alone leads immediately to the conclusion that an entirely new science, one different from Cartesian reductionism, is necessary. Such a statement, in itself, has usually been thought to be scientific heresy. But things are changing and in 1997 we find many books from renowned scientists that come to the same conclusion. But Elsasser gives us the early vision of the requirements for this new science. As I have said above, perhaps because it was so early is the reason it contains these requirements stated in such a clear and jargon-free style. We can deal here only with Elsasser's introductory survey in which he provides a bare outline of the major points of his approach. They are presented in terms of three major principles as follows.

The first is the *principle of ordered heterogeneity* or "order over complexity". It is a statement based on a branch of mathematics known as combinatorics which allows calculations dealing with the different patterns that can be produced from an initial number of interacting components. His example uses chemical complexity inside a living cell, for example, and describes such complexity in terms of the number of possible arrangement of the atoms found just in organic molecules (carbon, oxygen, hydrogen and nitrogen) which make up 99% of all living material. The number of possible arrangements is larger by far than the number of atoms in the universe. In mathematics such a number is modestly described as 'immense'. We may put this example in terms of genetic probabilities just for another perspective. Here is the problem. A human genome of 100,000 elements, and 2 inputs (alleles) per element (gene) can produce $10^{30,000}$ different states. This is truly an immense number. How does a cell impose order on such a large number of possibilities so that, instead of a random production of states, we see an orderly

progression of states. The cell not only survives but produces different patterns of states to fit its circumstances... the cell adapts. In Elsasser's words[4],

> *"Under these circumstances there can be regularity in the large where there is heterogeneity in the small: order above heterogeneity. ... It is clearly a type of order that is completely foreign to the traditional thinking of the physicist and chemist. This kind of behavior, ordered heterogeneity, will here be used as a first step toward the construction of a holistic theoretical biology that does not violate the laws of quantum mechanics."*

The second principle is the one of *creative selection.* The combinatoric consideration provided above reveals that the simplest living cell will have a number of possible 'morphologies' vastly in excess of the number of cellular types actually observed or that could conceivably be accommodated in a finite universe. This observation that more possible cell types exist than actually do exist leads, in Elsasser's words to the following conclusion:

> *Hence a choice is made in nature among the immense number of possible patterns. I have become persuaded ... that the availability of such a choice is the basic and irreplaceable criterion of holistic or non mechanistic biology. ... If we postulate the existence of a choice we have opted for a holistic biology. At the same time, since all admissible patterns satisfy the laws of quantum mechanics, we have also arrived at a scientifically precise concept of creativity. In particular, those aspects of morphology that cannot be "reduced" to mechanistic causality appear here as direct expression of a scientifically justifiable form of creativity."*

The third principle is that of *holistic memory.* and refers to the criterion needed for creative choice. Holistic memory is, at the same time, most simple and most abstract. Elsasser defines it as follows:

> *"This principle says that the content of that which is created results from a selection, among the immense number of patterns available, of a pattern that resembles some earlier pattern of the same organism or of preceding (parental) organisms. The main point of the third principle is that no mechanism for the transmission of information over time is specified!" (Exclamation point added)*

Elsasser goes on to say that the idea of information transmission without a mechanism will certainly be viewed by most biologists with horror. However, in the language of chaos one does not need a storage mechanism in the usual sense.

The selection or choice by the organism is a process decided by the non linear dynamics of the system itself (see below). Elsasser predicts the presence of such a system:

> *"... we claim in effect that organisms make use of two separate and quite different processes for information transfer over time."*

As will be pointed out below, the first system is the genetic encoding of information that uses storage and transmission through DNA replication and Elsasser, of course, said as much. The second process, that he did not specify a mechanism for, is observed historically as epigenetic process and may now be described in the language of non-linear dynamic and chaos theory (see Figure 1). As just stated, in non-linear thinking, memory itself is not required but familiar patterns occur through the limited number of attractor states available in a highly conserved but dynamic living state. To make his position even more modern on this issue he adds the following:

> *"Here, we say that both processes, mechanistic storage and holistic memory, exist everywhere in the living organism and supplement each other rather than mutually excluding each other. In some cases one of these processes predominates at the expense of the other."*

FIGURE 1 HERE

Brian Goodwin

As one reads over the Bellagio papers what is particularly striking is the kind of questions asked. Pattee wants to know what are the secrets of life, and he asks about heirarchial levels of control and about the surrender of one level to another; life, it seems, is all about surrender even at a quantum mechanical level. Elsasser posits choice as a central scientific question and as a key element in the structure of life itself. For Brian Goodwin the questions have to do with the nature of self organization and self realization. All these are asked not from a philosophical point of view necessarily but from point of view that these are special qualities, are undeniably essential characteristics of life, and that no theory of biology is worth its salt unless it addresses them.

Why are these questions no longer asked is another question. Goodwin argues that it has to do with what he observes at the meeting as a polarization among

scientists along the axis of analytic rigor Vs synthetic process, or between strict deductive logic vs inductive logic. Those scientists more committed to a reductionist approach understandably preferred the tried and true analytic method so familiar in physics while others, surprisingly including most of the physicists, preferred the looser synthetic processes. The former were comfortable, says Goodwin, with a safer and narrower focus while the latter group:

"...appear to feel that intellectual freedom and creative insight are more important at this stage of development of biological concepts, and so prefer to conduct their discussion in a language much closer to the roots of experience, which necessarily borders on metaphysics and poetry."

The reason for the disappearance of these questions from our biological scientific world view perhaps has something to do with this perception and with the fact that the narrower view of Cartesian science has become the monolithic view dominating modern biology. Under this dominance there is no perceived need to develop new insights or, certainly, new concepts outside of the prevailing paradigm. Pattee and Elsasser represent those scientists with critical evaluations all pointing to the limits of reductionism in biology. Both see organisms as much too complex for reductive analysis, and both provide a general outline of a biological theory that, when developed properly, would augment an insufficient mechanistic approach.

Brian Goodwin joins this group but adds to it his own experience as an experimental biologist with working knowledge of an actual theory already in place that appears to him to be appropriate to the complexity actually observed. Brian's actual subject of investigation ... what he does as a working biologist ... corresponds to what Elsasser refers to as the second informational system in parallel with DNA. What for Elsasser is a theoretical necessity is for Goodwin an experimental reality. Goodwin is modeling biological processes as if the secondary informational system was already in place. He has already taken the inductive position that if 'this and that' are observed to happen then the system must work like 'such and such'. Such and such turns out to be a non linear interactive system (epigenetic system) with its own logic. Epigenetic logic emerges from the complex interactions of reductive elements -as Pattee would have it; in addition, it is a logic that cannot be reduced to those elements -as both Pattee and Elsasser would insist.

In his 1970 paper of the Bellagio proceedings entitled "Biological stability", Goodwin identifies the key to an enormous misunderstanding in biology; a misunderstanding that, in my mind stands squarely behind the most egregious class of mistakes in modern biology. It is a misunderstanding about genetic programs and how they work. We should go over this with some care. In his paper Brian, in his usual "friendly-combined-with-impeccable" manner of argument takes on a proposition made by another participant there, Christopher Longuet-Higgins who is a professor of Machine Intelligence at Edinburgh and a Fellow of the Royal Society. Longuet-Higgins had made the familiar argument, quite expected of a professor of machine intelligence, that DNA was the repository of all the information needed to produce the organism. What he said was:

> *"Not until we can interpret the DNA of a new species without actually growing an individual from it will we be able to claim a full understanding of epigenesis."*

The context of this assertion was one of program and the way it works in biological control. Now epigenesis, we all agree, is regulated by a program (set of instructions) which imposes some order or constraint on the process in question. Most people, including Longuet-Higgins, assume that the program under discussion is a DNA program, and that the biological system is completely analogous to a computer. Brian says no; the DNA program is not the same as a computer program. DNA, as program, is not directly referred to at the moment of cellular decision about state change as it would be if the computer analogy were correct. At the moment the cell switches from one state to another there is a change at what Brian calls switching points where the decision is taken to move into one or another alternative pathways of development, growth, metabolism, etc. In describing the misunderstanding he says:

> *"In computer terms the cell must at such a point obey some sub-routine which takes the form of a conditional instruction: if such and such conditions are satisfied, do such and such. The implication of the computer analogy is that the cell computes its own state, looks at the DNA program for further instructions, and then changes state accordingly."*

The mistake in this analogy is to leave out any definition of the actual biochemical process by which the cell "computes and looks at DNA". Without providing this

biological description one is allowed to assume the computer analogy of instant computation, followed by consultation with DNA program for instructions, followed by change in state. However, for biochemists then (but not necessarily now) this is a flawed assumption. The correct algorithm for cellular decision making must include the vast operations of interconnected metabolic and other networks that are linked to one another and, through receptor states, to the outside world. This vast interconnected (epigenetic) network has its own logical forms that include regulation of DNA transcription. Therefore, while DNA programs constrain and specify a large part of the network components, there is also this parallel algorithm specification coming from epigenetic constraints. To leave out this parallel function is to leave out the cell and to replace its complex informational processing dynamics with a linear computer analogy where DNA is the misidentified sole source of instructions for complex behavior. This has been an omission with enormous negative consequences in biology to say nothing of the practical negative consequences we are now experiencing in medical and behavioral genetics.

Conclusions

Life sciences, including medicine, are now undergoing a profound change in theoretical and experimental outlook; the gene and molecule as *the* transcendent determinant of function is being questioned at all levels of biological organization. From single cells to the evolution of life, the theory of the gene is increasingly unable to provide explanations for the complexity of life now being revealed by molecular and organismal study. Why? The theory of the gene as initiated by Watson & Crick to illuminate the multilevel process of information storage... replication, transcription and translation ... has provided a research paradigm with universal application to all life forms. By any measure, the theory and paradigm of the gene stands as one of the great achievements in science. However, all major theories in science are susceptible to over extension[2] and in the past nearly half century biologists who have taken up the genetic paradigm have transformed it and have, illegitimately, expanded it from a theory of the gene to a theory of the cell and, indeed, to a theory of life. As such, the authority of the gene has been extended to a realm of complexity where it has little explanatory power and is showing all the signs of a paradigm in trouble[2]. The research community is increasingly aware of the limits of genetic determinism, and of the broader paradigm of Cartesian reductionism, to provide a basis for addressing the complex issues presented by

living systems. *Having no scientific overview with which to replace genetic determinism, that community now finds itself in crisis.*

Crisis: Where is the program?

The trouble with the extended theory of the gene is that genetic elements, while critical, are only one aspect of biological regulation. They cannot, in themselves, specify details of organismal phenotype, including complex diseases like sporadic cancer and cardiovascular diseases[10]. To be sure, there are cases in which genes may be said to "cause" attributes of an organism but these are rare; in the realm of human diseases they account for about 2% of our total disease load (see below). For the most part, complex attributes ... phenotypes of organisms... are not *caused* by genes even though genes are the ultimate agents used to create phenotypes[11]. But if genes don't determine us, if our disease causality cannot be located in genetic agents alone, if developmental processes characterized by high fidelity adherence to species form cannot be reduced to genetic programs, if the source of evolutionary change is not traced solely to random genetic mutation then what does determine us, where is disease causality located, where and what is the nature of programmed growth and development in living organisms, and what is the creative source of new morphology and function acting as substrates for natural selection? *In short, if the program for life is not in the genes ... and organisms are clearly programmed ..., then where is the program?*

The short answer is that the program is in no one place; it is *distributed* at many levels of the organism and all levels are open to environmental signals. Controls may be found distributed in gene circuits, in metabolic networks, in cytoskeletal structures, in membrane units, in extra cellular matrix elements, and finally in the cell as a whole and in networks of cells at the various levels of organization above the cell. These levels of control each have their own rules and all levels are interactive with one another and, in the case of cells and organisms, with the world around them. The major new idea here is that these levels of control are not reducibly connected; it is not possible, for example, to reduce common cancer to rules that govern DNA[4] just as it is not possible to reduce intelligence simply to the laws governing ion fluxes in brain neurons. DNA is involved in the phenotype "cancer" or "intelligence" but the cause of both lies elsewhere at higher levels of organization.

This short answer is already extremely complex compared to the idea of reducibility; that ultimate control is in the gene. Part of the current maturing of biology is the surrender of simple "storybook" explanations for how life works and the acceptance that life is beginning to appear more like a complex adaptive system than like a gene machine. This simple advance leads us (back) to a respect for complexity and even for mystery; a respect that is essential to the development of a true science of values that can relate to our deep spiritual needs and perhaps even lead to a method for their fulfillment. The quotation from Claude Bernard at the outset of this paper suggests one aspect of a science of values. For Bernard life is "powered" by a materialistic force vital only in the sense that it is unique to life. Today we identify a "vital force" with global regulatory processes and "physical agents" with genes. In modern terms the force may be thought of as one that provides, in the words of Walter Elsasser, *order above heterogenity,* and therefore provides a scientific basis for a future theory of design in living organisms.

References

1. This paper is based on a book chapter by R. Strohman to be published in 1998.

2. Strohman,RC. *The Coming Kuhnian Revolution in Biology* **Nature Biotechnology 15**:194-200 (1997)

3. Nordenskiold,E. The History of Biology **Tudor, N.Y.** (1928)

4. Goodwin, B. *How the Leopard Changed Its Spots* **Weidenfeld & Nicolson** London

5. Waddington,C. Toward a Theorteical Biology. **International Union of Biological Sciences and Edinburgh University Press** (1970)
For recent updates from Goodwin and Pattee see Webster,G. & Goodwin,B. *Form and Transformation: Generative and relational principles in biology.* **Cambridge University Press** (1996) and HH Pattee *The Limits of Formal Models of Measurement,Control, and Cognition.* **Applied Mathematics and Computation** 56:111-130 (1993)

6. Elsasser, W. Reflections on a Theory of Organisms.Editions **Orbis Publishing, Quebec Canada** (1987)

7 See article by P. Davies in Theoretical Biology, eds. B. Goodwin & P. Saunders. **Edinburgh University Press,** 1989

8 Polanyi, M. *Life's Irreducible Structure* **Science** 160:1308-1312 (1968)

9. These experiments by Waddington are given an up to date description in Jablonka,E. & Lamb, M.J. *Epigenetic Inheritance and Evolution.* **Oxford University Press** 1995.

10. Strohman, R.C.. *Ancient genomes, wise bodies, unhealthy people: Limits of a genetic paradigm in biology and medicine.* **Perspectives in Biol.& Med.** 37(1):112-145 (1993).

11. Strohman, R.C. Epigenetics: *The missing beat in biotechnology.* **Biotechnology.** 12:156-163 (1994)

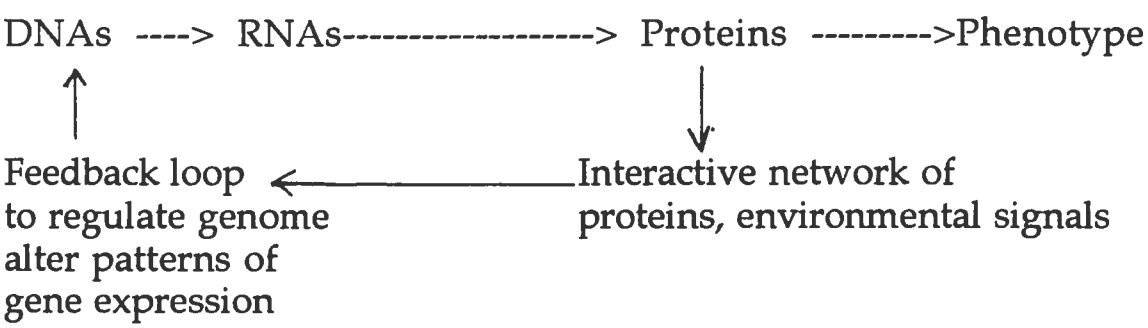
Figure 1. Two Informational Processing Systems

Genetic system:

DNAs ------> RNAs -------> Proteins ------> Phenotype

Phenotype reducible to "gene programs"
Governed by linear genetic rules
Genotype ---> Phenotype relation is largely independent of environment
Closed system, linear logic

Epigenetic system:



Proteins form complex interactive networks coextensive with the cell
Network of many proteins defines most phenotypes
Phenotype as emergent property of entire system
Network open to environmental signals
Network is governed by nonlinear dynamics
Network, through feedback to DNA, constrains and regulates patterns of gene expression

Life is non-linear, dynamic and open. Requires non-linear solutions.
Genetic mechanisms provide a necessary but insufficient basis for taking the next step.