CAUSATION AND THE ORIGIN OF LIFE. METABOLISM OR REPLICATION FIRST?

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Abstract. The conceptual gulf that separates the 'metabolism first' and 'replication first' mechanisms for the emergence of life continues to cloud the origin of life debate. In the present paper we analyze this aspect of the origin of life problem and offer arguments in favor of the 'replication first' school. Utilizing Wicken's two-tier approach to causation we argue that a causal connection between replication and metabolism can only be demonstrated if replication would have preceded metabolism. In conjunction with existing empirical evidence and theoretical reasoning, our analysis concludes that there is no substantive evidence for a 'metabolism first' mechanism for life's emergence, while a coherent case can be made for the 'replication first' group of mechanisms. The analysis reaffirms our conviction that life is an extreme expression of kinetic control, and that the emergence of metabolic pathways can be understood by considering life as a manifestation of 'replicative chemistry'.

Keywords: causation, chemical evolution, metabolism first, molecular replication, origin of life, replication first, teleology, teleonomy

1. Introduction

The resurgence of interest in the origin of life on earth that began early in the 20th century has been largely driven by the conviction that all living beings evolved from inanimate matter, and that life is no more than a complex set of physico-chemical processes (for recent reviews see: Fry, 2000; Lahav, 1999; Orgel, 1998, 1992; Lifson, 1997; Wächtershäuser, 1997; Miller and Lazcano, 1996; Maynard Smith and Szathmáry, 1995; Chyba and McDonald, 1995; Elitzur, 1994; Eigen, 1992). However, even a cursory look at existing theories reveals a major concern. Many of the evolutionary hypotheses are quite different to one another and often based on quite different premises. For example, where on the planet did life emerge – on the earth's surface in a prebiotic soup (Oparin, 1957), or in hydrothermal vents under the seas (Wächtershäuser, 1992)? Or did early life arrive here from some extraterrestrial source (Melosh, 1988)? What was the composition of the early atmosphere that led to life's emergence – a reducing atmosphere of methane, hydrogen, ammonia and water, or a neutral one containing mainly carbon dioxide, nitrogen and water (Kasting, 1993)? Did life initially emerge from a prebiotic aqueous environment, as was widely believed till quite recently, or did it derive from two-dimensional metabolic organization – possibly on iron sulfide (Wächtershäuser, 1997), or clay surfaces (Cairns-Smith, 1985)? And given that life systems

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are primarily characterized by a metabolism and the ability to reproduce, which came first – metabolism or replication? The issue of 'metabolism first' or 'replication first' is a particularly fundamental one since it bears on the very nature of biological complexification. The uncertainty surrounding this issue effectively declares that the physico-chemical principles that were responsible for the process of complexification remain unclear. So it is not just *historic* questions such as, *where* on earth did life originate, that await more definitive answers. Even the general principles by which animate matter emerged remain unresolved and in dispute. The purpose of this paper is therefore to address the issue of 'metabolism first' or 'replication first' in order to help clarify an *ahistoric* aspect of emergence – to better understand the physico-chemical principles that enabled matter to undergo a process of biological complexification, that eventually led to simple life forms. By applying Wicken's (1985) two-tier approach to causation, we believe a sound causal argument can be made that life began with replication, not metabolism.

2. Discussion

As noted above the current scientific confusion associated with the emergence of life debate appears to stem from both historic and ahistoric uncertainties. Consider historic uncertainty first. As the conditions that existed on the prebiotic earth are very uncertain, there are enormous practical difficulties in assessing life's mechanistic beginnings. The elucidation of a reaction mechanism is often problematical even when the reaction parameters and conditions (reactant concentrations, solvent, pH, temperature, pressure, catalysts, *etc.*) are all specified. Yet in addressing the question of life's emergence, we have to acknowledge the fact that there is almost *nothing* we know about that primordial process with any degree of certainty; we are unable to identify the initial reactants, nor the reaction conditions for the process that initiated that evolutionary transition from inanimate to animate. Clearly then, attempts to formulate a reaction mechanism for a process whose key reagents and reaction conditions are largely unknown, necessarily becomes a speculative endeavor.

But we would argue that in a fundamental sense the precise evolutionary pathway by which life emerged is actually a secondary one, and needs to be addressed within the context of a more basic *ahistoric* question: what is the nature of the physical and chemical laws that governed that evolutionary process of emergence? Wächtershäuser (1997) terms the science of chemistry 'an ahistoric science striving for universal laws, independent of space and time or of geography and the calendar'. Accordingly, in agreement with Wächtershäuser we believe the primary (and more realistic) challenge regarding the origin of life remains to reduce the historic process of evolution with all its inherent uncertainties, many of which are unlikely to be ever resolved, to a universal chemical law of evolution, whose validity would be independent of time and place. So, at least in the first instance, rather than ask:

what was the mechanistic path that led inanimate matter to the earliest life forms, we need to ask *what general features would characterize the transition from inanimate to animate.* What characteristics would define that *family* of mechanisms that could, in principle at least, lead to the emergence of life? Even though it is generally acknowledged that all biological systems derived from a process of complexification, the physico-chemical principles that would lead to the emergence of such highly complex far-from-equilibrium systems remain unclear. A clearer physico-chemical understanding of the principles underlying the emergence of life would also go some way toward resolving the long-standing (and fractious) debate regarding the *definition* of life. As recently discussed by Cleland and Chyba (2002), the possibility of defining life in an unambiguous manner rests on our ability to characterize life as a 'natural kind' (Putnam, 1973; Schwartz, 1977). However the ability to characterize life as a 'natural kind' in turn depends on a more fundamental understanding of the physico-chemical principles that would have governed life's emergence.

The above considerations lead us directly to the question of 'metabolism first' or 'replication first'. Two of life's most striking characteristics are: (a) its highly complex metabolic system, and, (b) its replicating capability. So can we, as a first step in describing the process of life's emergence, at least in general terms, determine which of these two characteristics emerged first? In contrast to many aspects of emergence this question is *unlikely* to be historical in character, as there may well be a *causal connection* between these two key life characteristics, one that is directly linked to the essence of life itself and indirectly to the nature of matter. In order therefore to address this question from a causal perspective we make some preliminary comments regarding causation.

2.1. Two-tier causation – driving force and mechanism

The question as to what causes change and motion in the universe has been the subject of scientific enquiry since the time of Aristotle and before. Though Aristotle outlined the framework for modern scientific thought, the teleological viewpoint that he helped establish proved unable to adequately explain the design and order so evident in the world, as manifested most strikingly in living systems. It was only during the seventeenth century, two thousand years after Aristotle, that the modern philosophical foundations of the natural sciences were laid down by Descartes, Bacon and others. The essence of that change was that the deeply entrenched teleological view of nature, in which purpose underlay natural phenomena (that is, processes occurred as means to achieve particular ends) was replaced by a mechanical-mechanistic world view, in which all of nature, including living systems, behaved according to well-defined laws of nature. The view attributed to van Helmont (1648): 'All life is chemistry', characterised this new way of thinking, and was reinforced 150 years later by Immanuel Kant (1952), though interestingly, Kant's view of living systems as a 'natural purpose' remained teleological, and led

to his famous comment that there could never be a Newton able to explain 'a single blade of grass.'

In line with modern scientific methodology, recent theories regarding the emergence of life tend to be mechanistic in their approach. Most address the mechanistic *how* question rather than the ostensibly inappropriate teleological *why* question. The *why* question seems to take us back to that discredited methodological approach in which purpose played such a dominant role. But the *why* question can be asked with a non-teleological intent. It can be asked in the sense of seeking out the *driving force* for some phenomenon. As Wicken (1985) has argued, asking the *why* question remains an essential component of scientific understanding; a two-tiered approach to causation is often crucial in obtaining a proper understanding of natural phenomena. Understanding *whys* is no less important to discovering *hows* and in fact in many cases may be an important preliminary step before the mechanistic *how* can be tackled. To make the point clear and to reaffirm the need for two-tier causation let us consider two examples – one physical in orientation: how and why does water flow on a given surface, and one chemical in orientation: how and why do chemical reactions occur?

Water flow may manifest itself in different ways: as a leaking roof, a small stream, a winding river, a waterfall, or there may be no flow at all, as in a desert, a pond, or a lake. Inspection of a physical surface, its slope and composition, and knowing the volume of water that is directed at that surface may well provide a reasonable answer to the question: how will water flow? But the basis of any attempt to answer the question of *how* water flows requires an understanding of *why* water flows. Newton's generalization regarding the existence of a universal gravitational force provides a powerful framework for answering the *why* question and this understanding then enables the *how* question to be usefully addressed. Mayr (1988) has termed such causal explanations (e.g., gravity as the explanation for water flow) as *teleomatic,* the term signifying that the *consequence* of a process (in the above case a lowering of potential energy) is offered as the *reason* for its occurrence.

Let us now move closer to home and consider the question of *how* and *why* chemical reactions occur. In the present context the example is particularly pertinent given the modern view that living beings are ultimately nothing more than complex chemical systems. In posing the above question the *how* enquires into the *mechanism* of a particular reaction – that is, the detailed description of the individual steps that lead from reactants to products. For example, does the reaction take place in a concerted one-step process, or are intermediates formed along the way? Is some form of energy input, such as irradiation, required for the reaction to occur? Is a catalyst involved? Does the reaction take place in solution or on some catalytic surface? Understanding *how* a reaction occurs - its mechanism, provides us with a measure of control over that reaction, suggesting ways to speed it up or slow it down, or possibly help eliminate unwanted side-reactions.

But, as in the case of water flow, understanding *why* the reaction occurs is a necessary preliminary step to understanding *how* it occurs, and it is the conceptual framework of thermodynamics that provides an answer to this question. The science of thermodynamics teaches us that energy flow has direction; closed macroscopic chemical systems react because there is a driving force that strives to lower the free energy of the reacting system till it reaches the point of minimum free energy – the so-called equilibrium state. Of course whether a particular reaction actually takes place also depends on the potential mechanism of the reaction. Thus for a macroscopic chemical system to react, both a thermodynamic driving force *and* a kinetically feasible mechanism are required. Here again we see that for a proper understanding of the factors controlling a chemical process, we need to answer both the mechanistic *how* and the teleomatic *why* questions. Thermodynamics is the science of the possible; kinetics and mechanism determine whether the possible will or will not occur. As we will subsequently see, this two-tier approach to causation may prove beneficial in our attempts to understand the process of life's emergence.

2.2. Metabolism first or replication first

The debate between proponents of 'metabolism first' and 'replication first' continues unabated with both approaches subject to criticism. The 'metabolism first' approach has been criticized by some of the leading workers in the field (Maynard Smith and Szathmáry, 1995; Orgel, 1992; Eigen, 1971; Lifson, 1997) based on the assessment that key steps in the building up of such a metabolic system are highly improbable. The 'replication first' approach is questioned based on the view that the *de novo* appearance of oligonucleotides is improbable, and that there is no clear path from an RNA world to the current dual world of proteins and nucleic acids (Shapiro, 1984, 2000). We wish to address this key issue and in particular to inquire how the ability of living things to both replicate and metabolize relate to one another. Within the context of life's emergence, could there be a causal relationship between these two life characteristics, and, if so, can that causal connection assist us to deduce which came first? A reasonably definitive answer to the above question would be a worthwhile step forward as it would significantly narrow the range of existing mechanistic possibilities for the emergence of life.

In considering the emergence of life problem in the context of replication and metabolism, one can in principle consider three alternative scenarios: (a) that metabolism preceded replication, (b) that replication preceded metabolism, and (c) that the process of emergence led to a primal system that was both metabolic *and* replicative. Categories (a) and (c) actually belong to the same conceptual class of 'metabolism first' mechanisms since it is the process by which a metabolic system can emerge (with or without a replicative capability), that characterises the 'metabolism first' grouping. In reality the more widely known 'metabolism first' mechanisms belong to the (c) category, i.e., they propose that the emerging

primal system was both metabolic *and* replicative, though the primal replicative capability is considered to have been compositional rather than genomic. Let us now consider the two views – 'metabolism first' and 'replication first' – from empirical, theoretical and causal standpoints.

2.2.1. *Metabolism First*

First, let us be clear as to what we mean by the term *metabolism*. Our usage conforms with conventional terminology and refers to that complex set of co-ordinated and regulated chemical reactions present in all living beings, both autotrophic and heterotrophic, whose primary role is to provide living entities with the necessary energy to fuel and maintain the organism's functions. The group of mechanisms for life's emergence that can be classified 'metabolism first', though differing greatly in their other features, contend that the emergence of metabolism emerged prior to (or simultaneously with) the emergence of a replicating capability. As a group this school proposes that metabolism emerged either spontaneously or by a process of random drift, and once established, may have also exhibited a crude, non-genomic replicating capability (Dyson, 1985; Kauffman, 2000, 1993; Wächtershäuser, 1997, Segre *et al.,* 2000, New and Pohorille, 2000). Only at some subsequent evolutionary phase was a genomic replicating capability (RNA or DNA based) incorporated into the existing system.

Let us begin by applying both a theoretical and an experimental test of this hypothesis. If the emergence of life was associated with the spontaneous formation of a metabolic system, two questions can be asked. Firstly, is there any experimental evidence that supports the proposal that a metabolic system can emerge spontaneously, and secondly, if we are unable to provide such experimental evidence, is there some physical or chemical principle that would support or predict the establishment of such a system?

At the current time there seems to be no experimental evidence to suggest that metabolic systems can spontaneously form, for example, through the mixing of their relevant components. The suggestion made by proponents of the 'metabolism first' school, such as Dyson and Kauffman, that disordered and inactive molecular systems can transform themselves, either by random drift or by sudden 'crystallisation', into actively metabolic ones (through what Kauffman terms *catalytic closure*) remains without experimental support. In this context it is important to note that the goal here would not be to generate the actual metabolic system that lead to life, but to *any* system that could be characterized as metabolic, as a demonstration that such systems can exist. Till now however such evidence is lacking. Indeed, precisely the reverse pattern is what we invariably see – metabolic systems are relatively fragile and easily destroyed, resulting in the death of the living entity. Though it is true that computer models have been developed that support the formation of non-genomic replicating systems (New and Pohorille, 2000; Segre *et al.,* 2000), such theoretical models have yet to be validated by experiment. Ultimately experiments must validate theoretical models, not the other way around.

Of course the fact that an experimental metabolic system has not been observed to date does not in itself preclude such a possibility; it may well be that the right 'formula' has not as yet been tried. However there does appear to be an inherent theoretical problem with the concept of a spontaneously emerging metabolic system. Orgel has recently analyzed two reaction schemes – the autocatalytic formose reaction in which formaldehyde is converted to glycoaldehyde, and the reductive (reverse) citric acid cycle on an FeS/FeS_2 surface and concluded that the likelihood that such cycles can self-organize, whether in solution or on a mineral surface, is remote (Orgel, 2000). If we apply Wicken's two-tier approach to causation, the question that needs to be asked is: *what would the driving force for the appearance of such a metabolic system be? Why* (in a driving force sense) would a disordered system spontaneously organise itself into an organized one displaying functional coherence and maintaining itself far from equilibrium? Spontaneous organization is, of course, a well-known phenomenon in chemistry. Micelle or vesicle formation and crystallization are just two obvious examples. But, in analogy to other physical and chemical processes, micelle formation and crystallization are driven by a thermodynamic force – the drive toward increased entropy. In contrast, the spontaneous emergence of a far-from-equilibrium metabolic system, as an isolated occurrence and unlinked to any other process, would be contrary to the directive of the Second Law. In this case the thermodynamic consequence would be the spontaneous conversion of a high entropy, disordered system into a far-from-equilibrium, low entropy, organized one, and this is not what normally takes place (we discuss the relevance of non-equilibrium 'dissipative structure' formation below). Note that the difficulty in explaining the spontaneous formation of a metabolic system arises regardless of whether that system would have some replicative capability or not.

Some comments regarding living systems as 'dissipative structures' now need to be made. It is true that the spontaneous generation of ordered, non-equilibrium, low entropy structures – termed 'dissipative structures', from an initially disordered state is now a well-established phenomenon, and this may well have some implications for the possible emergence of a metabolic system in particular, and life in general. However, the use of non-equilibrium 'dissipative structures' as a model for enhancing our understanding of living systems, though supported by many workers over recent years, has come under growing criticism (for recent reviews see: Pross, 2003; Corning and Kline, 1998). The problem may be summarized as follows: even if one dismisses the major objection that 'dissipative structures' do not constitute reasonable models for biological systems, the 'dissipative structure' paradigm fails to provide insights into the nature of biological function, or into the specific processes by which that function emerged. Accordingly, we are of the view, enunciated by Collier some years ago, that there is no evidence that the laws of non-equilibrium thermodynamics apply to biological systems in a *non-trivial* fashion (Collier, 1988). Once the 'dissipative structures' paradigm for living beings is put aside, we see no experimental or viable theoretical reason that sup-

ports the idea that a metabolic system, either replicative or non-replicative, can spontaneously emerge. Consequently, we believe there is no sound basis for the view that the emergence of life began with a chemical system that was: (i) initially both metabolic and replicative, or, (ii) initially metabolic, and subsequently became replicative. This analysis is in contrast to the corresponding analysis for a 'replication first' mechanism.

2.2.2. *Replication First*

Let us now apply the same experimental and theoretical tests and procedures we applied to the 'metabolism first' hypothesis to the 'replication first' hypothesis, and inquire if there is any basis for believing a system with a replicative capability can spontaneously emerge and subsequently become metabolic? Let us first consider step-one of the two-stage process: Is there any unambiguous experimental evidence for the existence of *non-metabolic, replicating systems*? The answer here is a definitive *yes.* In contrast to the *no* answer for *metabolic, non-replicating systems*, the existence of self-replicating molecular species is well established. Classical experiments carried out by Spiegelman (1967) and Eigen (1992) and more recently by Orgel (1992), Joyce, (1994), Sievers and von Kiedrowski (1994), Rebek (1994) and others, all make clear that molecular replication is a natural chemical phenomenon. One does not need to revert to theory to determine whether such processes occur – their occurrence is established empirical fact. It is true that many questions regarding the prebiotic conditions (we discuss this aspect subsequently) that would have enabled such a replication process to occur remain unanswered. It is also true that *non-enzymatic* replication is a rather fragile and unsustainable process, even in the hands of experienced chemists. But experiments beginning with those of Spiegelman (1967) and extending through to the recent demonstrations of *in vitro* evolution of polymerase ribozymes (Johnston *et al.*, 2001; Joyce, 2002) have clearly demonstrated the ability of nucleic acids to undergo cycles of replication, mutation and evolution. Thus the fundamental point – that molecular replicating entities exist, and under appropriate circumstances can undergo a process of replication, natural selection and Darwinian evolution, is beyond dispute.

Once the existence of evolving replicating entities is empirically established, can we provide an *in principle* explanation for the incorporation of a metabolic system into such a replicating system? We previously argued that the emergence of a *non-replicating* metabolic entity seems to be forbidden by existing physico-chemical principles. But would the emergence of a *metabolic* entity from a *non-metabolic* one be possible *within a replicating framework*? Would such a conversion be explicable in terms of established physico-chemical principles? In particular, could some causal connection between these two processes – replication and metabolism – *in that causal order*, be identified?

In a recent publication (Pross, 2003), we pointed out that life's processes, as a whole, are under *kinetic* rather than *thermodynamic* control. By this we mean that life's processes, when viewed in chemical terms at both a molecular and a

biological level, lead to the preferred formation of kinetic products that derive from replication and are *less* stable, rather than to non-replicative products that are thermodynamically *more* stable. The process of cell replication illustrates this point well. An *Escherichia Coli* sample when placed in a solution of glucose and essential mineral salts leads within hours to the production of *billions* of copies of the bacterium. In chemical terms, the reaction that has taken place is one in which 40% of the glucose has been converted to cellular material – the kinetic pathway, while just 60% has been oxidized to carbon dioxide and water – the thermodynamically preferred pathway (Monod, 1972, p. 19). But, significantly, the component that follows the thermodynamic pathway does not do so in *competition* with the kinetic pathway, but rather, as a necessary ancillary process that takes place in order to facilitate the primary kinetic pathway. The thermodynamic pathway to carbon dioxide and water only takes place so that the kinetic pathway to cellular material becomes energetically feasible; just enough glucose is oxidized to cover the energetic requirements of cell reproduction. Thus the *effective* driving force for life's processes is not the normal thermodynamic one that directs 'regular' chemical reactions, *but a kinetic one – the enormous kinetic power of replication,* and it is this 'force' that channels thermodynamic forces into a kinetically supporting role. Thus according to this view biological complexification generally, and the emergence of metabolic systems specifically, came about through a process of *kinetic selection.*

The pathway that would describe the conversion of simple non-equilibrium replicators to complex far-from-equilibrium metabolic replicators may be traced out, at least in outline. If we presume that life began with some simple self-replicating entity, initially non-metabolic, then kinetic selection would explore 'complexity space' for more effective replicators, and one result of this search would be the emergence of structurally more complex replicators (Pross, 2003). Simply put, complex replicators turn out to be more effective (kinetically stable) than simple ones (Pross and Khodorkovsky, 2004). However the trend toward greater complexity and effective replicating ability has negative thermodynamic consequences that have to be accommodated, and it is in this context that the driving force for the emergence of a metabolic capability within simple replicating systems becomes apparent. *We believe that the emergence of metabolism is merely the causal outcome of kinetic selection operating on an increasingly complex replicating entity.* The process of kinetic selection leads to the incorporation of *an energy gathering capability* that enables thermodynamic constraints associated with complexification to be overcome.

An example may help to illustrate the principle. Consider the possibility that a nucleic acid replicator undergoes self-assembly with a molecular photoreceptor that is either present naturally in the replicator's environment, or whose formation is catalytically induced by the replicator. This specific act of self-assembly, resulting in the formation of a replicating assembly capable of absorbing, for example, solar energy, would assist in enabling thermodynamic constraints associated with

ever-increasing complexification to be overcome. Photochemical activation of such a replicating assembly would increase the free energy of the system, thereby opening thermodynamic doors that would otherwise remain barred. Accordingly, this most rudimentary metabolic system illustrates the means by which a process that may appear to be locked into a *thermodynamically unfavorable* kinetic channel, might nevertheless proceed in a thermodynamically-allowed manner. Complexification, whatever its role (metabolic or non-metabolic), is thus a direct consequence of *kinetic* selection. Kinetic selection seeks out more effective replicators and since complex, far-from-equilibrium replicators are more effective than simple, non-equilibrium ones, that process of kinetic selection necessarily leads to a process of *metabolic complexification*. The point we are making is that the emergence of replication and metabolism can be causally related*, but this causal connection can only be understood if the emergence of replication preceded the emergence of metabolism.* The selection and incorporation of a thermodynamically-supportive energy gathering capability is only possible *within a replicative context*.

Note that by postulating that replication *preceded* metabolism, we are proposing a two-stage hypothesis for emergence, whose first step has experimental support, and whose second step can be seen to be causally connected to the first step, and is consistent with (or at least is not *inconsistent* with) established physico-chemical principles. Let us recall that in considering a process in *reverse* order (i.e., in which metabolism *preceded* replication) we need to postulate the emergence of a metabolic system from a random system for which there is no empirical support, and which, it has been argued (Lifson, 1997), may actually counter established physico-chemical principles. Alternatively, it requires the spontaneous emergence of a system with both metabolic and replicative capabilities, despite the fact that there is no obvious reason that systems possessing *both* of these highly unusual characteristics would spontaneously emerge. In comparing the two possible scenarios of emergence we believe the verdict is clear: the likelihood of the emergence of a replicating entity that subsequently becomes metabolic exceeds the likelihood of the spontaneous emergence of either a replicating metabolic system, or a non-replicating metabolic system that subsequently becomes replicative.

In the light of specific criticism that has been leveled at the ‘replication first’ approach, two questions should now be addressed. Firstly, how likely was it that a replicating molecule was formed *de novo* on the prebiotic earth? Clearly the ‘replication first’ scenario crucially depends on the prebiotic formation of such a molecule. Secondly, if such a molecule did in fact appear and resulted in the evolution of the extravagant life theater, can that molecule be identified? Much of the criticism of the ‘replication first’ school has been based on the idea that the likelihood of *de novo* synthesis is implausible (Shapiro, 2000).

In attempting to answer the first question one might facetiously rephrase the question as follows: given an effectively unknown reaction mixture, under effectively unknown reaction conditions, reacting to give unknown products by unknown mechanisms, could a particular product with a specific characteristic – namely,

the ability to self-replicate, have been included amongst the reaction products? The provocative manner the question has been phrased serves to indicate that it is difficult to make reliable statements of either a positive nature (what did happen) or a negative nature (what did not happen) regarding events we know little about, and all attempts to do so categorically seem to us unjustified. A priori, and given our current state of knowledge, the *possibility* of *de novo* synthesis of a molecular replicator cannot be summarily dismissed. But to the extent that there *is* some information regarding conditions on the prebiotic earth, it seems to us more supportive than dismissive of the thesis. In addition to the classic Urey-Miller experiments, that showed the relative ease with which a range of organic compounds could have been synthesized from a hypothesized (admittedly reducing) prebiotic atmosphere of ammonia, methane, and hydrogen, subsequent work has suggested that the synthesis of the four nitrogen bases (Oro, 1961; Sanchez *et al.,* 1967; Stoks and Schwartz, 1979; Robertson and Miller, 1995; Ferris *et al.,* 1968), the synthesis of sugars (Mizuno and Weiss, 1974) and sugar phosphates (Pitsch *et al.,* 1995) are also feasible under either abiotic or supposed prebiotic conditions. Thus current indications are that a wide range of biologically important molecules could well have been present on the prebiotic earth. On the other hand it is true that no synthesis of a replicating entity, such as an RNA oligomer, has been achieved to date under supposed prebiotic conditions. But that reservation must be treated with caution. Our inability to do something cannot be taken to mean that the particular thing cannot be done! Take flying for example - it took many centuries (and many unsuccessful attempts) before man finally succeeded in that particular endeavor. To summarise, given the enormous gaps in our knowledge of the prebiotic environment, the lack of information concerning *de novo* synthesis of some replicating entity certainly cannot be taken as definitive evidence that such a possibility could not have occurred.

Lastly, assuming there was a primal self-replicating molecule, what was its structure? The simple answer is that we currently do not know, and we may never know. As discussed previously, if it is assumed that life began with some replicating molecule, then inquiring into the identity of that molecule is a historical question that we can only answer by inspecting the historical record (for example, by examining fossil records and sequence analysis). Since there is no reason to believe that only one path from prebiotic to biotic could in principle have existed, and if the historical record is unable to supply us with the specific information needed to identify that molecule (as has recently been argued by Miller and Lazcano (1995)), we will have to satisfy ourselves with an *in principle* description of that early molecule. At the present time scenarios such the one provided by the 'RNA world' description, in which the first replicating molecule was either of an RNA-type, empowered with both replicative and catalytic capabilities, or some simpler precursor such as pRNA or PNA that evolved into an RNA type molecule, appear attractive (Orgel, 1992, 1998, 2000). However, our current understanding and the

state of the historical record are such that any detailed model should be considered indicative, rather than definitive.

3. Concluding Remarks

Enormous mechanistic confusion can derive from the fact that mechanisms alone do not define a process – understanding driving forces is equally important. In the absence of mechanistic information regarding a process, an understanding of the driving force can provide insight into the *kinds* of mechanistic pathways that are possible – mechanisms consistent with that driving force. If, as we believe, the driving force for the emergence of life is the enormous kinetic power of replication, then mechanisms for the emergence of life must reflect this kinetic imperative. Applying this rationale to the emergence of life problem, together with an examination of available empirical data, leads us to conclude that replication would most likely have preceded metabolism. We arrive at this conclusion based on the following arguments: (1) there is irrefutable empirical evidence for replicating-only molecular entities that undergo chemical evolution and selection. (2) A causal relationship between replication and metabolism can be demonstrated *if* replication would have preceded metabolism, but not if metabolism would have preceded replication. (3) The 'metabolism first' school of thought requires postulating the spontaneous emergence of a highly complex and coordinated chemical system, despite there being no empirical evidence that supports such an occurrence. Furthermore, such a process is theoretically problematical and appears to lack any identifiable driving force. (4) If, despite point 3, a metabolic system with a non-genomic replicative capability did manage to emerge, it is unclear how the subsequent transition to a *genomic* replicative system could take place; the transition would require a discontinuity in the very element that is central to life. A sudden change in the fundamental mechanism of storage and replication of biological information does not seem consistent with the principle of incremental change that seems to be central to the evolutionary process.

Finally, our arguments on the primacy of replication go to the very heart of the life debate. In recent years the view that life is an emergent property of complex systems has become more common. Our arguments, however, suggest that life's essence, rather than being a manifestation of complexity, is quintessentially simple. Life, first and foremost, derives from the fundamental process of replication. We argue that life's emergence must have begun with chemical replication, and indeed all of life chemistry should be classified as a distinct branch of chemistry that we would term *replicative chemistry* – a branch that deals with those molecular systems with the unusual capacity to self-replicate. Thus despite life's extraordinary complexity, this complexity is not inherent, but stems from an evolutionary process that involves continual complexification – a fundamental and ongoing process associated with replicative chemistry. The complexification process from single-

cell entities to multi-cell ones is now established evolutionary ideology, but we believe, in line with the 'replication first' school of thought, that the evolutionary process of complexification extends all the way down to a primal replicating entity. Complexity in its various facets – structural, informational, *and metabolic* – are all *adaptations* that kinetic selection (the equivalent of natural selection operating at the molecular level) introduced to further the replicating 'agenda'. Of course, metabolism, as an adaptation, is more fundamental than other evolutionary adaptations, such as the giraffe's long neck, but it is an adaptation nevertheless. Metabolism is the particular adaptation that was employed by kinetic selection to keep the thermodynamic tiger at bay, and as such must have been preceded by replication; kinetic selection can only operate once a replication-mutation cycle is underway. Thus we believe that life began with a process of molecular replication and that activity has remained central to all its subsequent evolutionary explorations through 'complexity space'. As we have noted previously, we believe life is a manifestation of replication, not the other way around. Going forward we believe the main challenges confronting the emergence of life field are in further clarifying the nature of the specific chemical processes associated with the incorporation of that structural, metabolic and informational capability into the primal replicating entity.

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