States of Origin

Influences on Research into the Origins of Life.

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Declaration

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person, nor material which to a substantial extent has been accepted for the award of any other degree or diploma of a University or other institute of higher learning.

Idan Ben-Barak, 29 September 2014

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Introduction

"...from so simple an origin..." (Charles Darwin, 1842)

When, where and in what manner did life originate on Earth? This ancient question has long been discussed and debated (or, in many cases, etched in dogma) in the intellectual, religious and philosophical realms. The modern conception of the phenomena of life having a single origin, not caused by supernatural intervention, and therefore a question subject to scientific attempts to approach it, is a relatively recent arrival.

The question of the origin of life differs in several ways from most scientific questions. As a scientific problem, it lies within the realm of chemistry - roughly speaking, the field is concerned with tracing the original route whence biochemistry "arose" from inorganic chemistry via organic chemistry - but it is a very strange chemical question indeed, as it is in its essence historical. It refers to a presumed single incident that occurred in the distant past.

Hence, all the components of a standard chemical problem are unknown: even among the scientists who agree on the basic tenets of the modern mainstream of abiogenetic theory (i.e., that the first organism came to be by natural processes only, on planet Earth, sometime around 4 billion years ago) there is no agreement on what precisely the starting ingredients were, what the initial conditions for the "reaction" were like; how it progressed - at what speed, what intermediate steps were involved, whether any catalysts were present, etc.

There is no agreement even on the question of what the final products looked like; any details concerning the original living entity are contested. The first direct evidence we have for this reaction dates from several hundred million years after the event. We cannot even say with complete confidence at what point in time the event happened (current estimates put the origin of life at around 3.8 billion years ago - always noting that these estimates have a history of being modified every few decades).

Since Origin-of-Life research is an attempt to elucidate a historical occurrence, it is virtually unanimously agreed that it would be impossible to recreate faithfully the original event as it happened, or, should such a recreation be attempted, know whether it succeeded. Projects past and present all attempt to present ways (or, more commonly, stages thereof) in which life could have originated on the primitive Earth.

I.a. Motivation

Past scholarship of Origin-of Life research has provided good accounts of the field and its practitioners. To those accounts I wish to contribute my own interpretation of the influences and the motivations of Origin-of-Life research, and emphasise what I believe are important aspects of its history, up to the present day.

The initial motivation for this subject may be traced back to a simple, rather plaintive, complaint. When, as a youngster, I first became acquainted with the scientific research committed to answering the question "how did life on the ancient earth begin?", I was surprised to learn that the question was not already given a definitive answer. These were the 1980s and early 1990s, an age when biology

(and specifically molecular biology), seemed to be providing all the answers for the riddles of life. The open question of life's origins struck me as anomaly. What was holding them up?

This initial rather rudimentary viewpoint of science in general and of the Origin-of-Life question in particular has undergone significant modifications since those early days. The question, however, remains interesting, and in its more mature form it may be formulated as:

What are the elements responsible for shaping development and change in the field of research concerned with the Origin of Life question?

I.b. Aims

Due to the extensive and highly trans-disciplinary nature of the field, there are many issues relevant to the origin of life that I leave mostly or wholly untouched. Themes such as the optical chirality problem, endosymbiosis, the origins of the genetic code and the origin of translation (Yarus 2011), a treatment of the concept of information (Wilkins et al., 2011), the extensive debates regarding the different definition of life, and more. I have chosen to focus on the core themes in the Origin-of-Life field, the essential problems in the attempt to provide an explanation of the way life emerged on earth.

I will argue that Origin-of-Life[1] research is less a hypothesis-driven endeavour than it is discovery-driven and technology-driven; in addition, I will explore the influence that the Origin-of-Life research

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[1] Note on the text: throughout this work I have assigned the textual form "Origin-of-Life", which shall normally signify the scientific or intellectual treatment of the question, to distinguish it from "origin of life" which signifies the historical, physical event of the emergence of life.

field experiences from its prime financial backer - the United States government's National

Aeronautics and Space Administration (NASA). Lastly, I will present Origin-of-Life research as an

indicator of more general trends in the natural and life sciences.

I hasten to add that "development" in the context of my research question should not be equated

with "progress". Indeed, one of the fascinations that the Origin-of-Life question holds is precisely the

fact that no-one can definitively and comfortably pronounce any particular 'development', past or

present, as progress. This does not, of course, protect the commentator from falling prey to any

number of other sources of bias, but it does serve to provide some protection against the worst of so-

called Whiggish fallacies.

Although some minor theories of the Origin-of-Life (which will be examined throughout the

following chapters) have been shown to have no evidence supporting them, the main, often

competing lines of approach to the question have proven remarkably resilient; modern Origin-of-Life

research has been slow to approach any sort of generally accepted consensus beyond the basic

agreement on the need for an account of the event or process of abiogenesis.

The final resolution of the question, if it exists, is not known at present, and any commentary

regarding an Origin-of-Life theory, experiment, researcher or school of thought is therefore not

obfuscated by the commentator's prior knowledge on whether that particular endeavour was a "step

in the right direction" or heading towards an ultimate dead end. Indeed, the fiercer critics of

mainstream Origin-of-Life research claim that the entire field is precisely such a dead end, and that the

entire idea of Abiogenesis is fallacious.

I.b.1 Delegate theories

In addition to asserting the influence of technological development and discovery on theorising in the Origin-of-Life debate, I will point out a recurring dynamic in the field:

There is no necessary connection between a theory's explanatory power of current biological systems and its explanatory power regarding the origin of life. Nevertheless, they often go hand in hand. Researchers and thinkers – who are not dedicated Origin-of-Life workers – offer or espouse theories of abiogenesis that correspond very closely to their worldview and/or research interests. We find multiple instances of a scientist who develops a theory, or discovers a phenomenon, clarifying some aspect of how life works. Then, shortly afterwards, a corresponding (and usually far more speculative) Origin-of-Life theory is proposed (often by that scientist). For just about any school of thought in biochemistry, molecular biology or microbiology, there is a good chance that someone within it has formulated an Origin-of-Life scenario that gives primacy to its fundamental research subjects.

Since the question of the origin of life is still very much an open one, I suggest a view of it as a sort of arena, a microcosm of ideas which can be a battlefield, a negotiations table or a shared workspace, to which the different schools of thought in science send their 'delegates' – their theories of origin – to interact with each other. Thus, an examination of the small field of Origin-of-Life research, consisting of a few hundred workers at most, and significantly less in earlier times, can offer us an interesting assessment of trends in scientific thought.

I.b.2 Chance and necessity

As we shall see in chapter 3, Jacques Monod's *Chance and Necessity* (Monod, 1971) put forth the proposition that the appearance of life on earth was a chance event, with an *a priori* probability of "virtually zero".

The contingency question – what was the likelihood of life on the planet arising – is one of the most common ones in Origins-of-Life discussion. It is also of practical importance: its extension to worlds other than ours not only bears directly on humanity's view of the universe and our place within it, but also on the amount of effort we ought to put into space exploration in general, and life-finding attempts specifically.

In this 'chance and necessity', also known as the contingency problem in the origin of life debate, views range on a continuum. Monod lies at one end, and at the other end are scientists and thinkers who believe that the emergence of life is virtually certain given suitable starting conditions. The attitudes displayed towards the contingency problem of the Origin-of-Life question may be divided into five categories.

Faced with the need to explain how the complexity of life (even in the simplest form of it imaginable) has emerged via biogenesis, one can argue one of the following:

1) Life did not arise by an abiogenetic event at all. Proponents of this view will support either creationist theories, or other accounts of the genesis of life on earth, such as certain forms of Panspermia[2].

2) Life arose on earth by a freak occurrence. Proponents of this view accept that the chance for the formation of life on earth was indeed very small, but argue that, since even very unlikely events can happen, the fact that life appeared in a blaze of unlikelihood requires no further explanation. This view, unsurprisingly, is invariably the one invoked and attacked in creationist critiques of abiogenesis.

3) Life arose by chance, but the chance wasn't very small. Proponents of this view reject any law-like explanation of abiogenesis, and argue either: a) That abiogenesis was not a single "leap" from the chemical realm into the biological, but a stepwise process involving several intermediates; and/or, b) That the chance for the event of the formation of life on earth was very small, but the universe is very large and very old. There was enough time for the event to have taken place, and enough sites for it to happen (the "appeal to vastness"). "Nature did not have the opportunity to conduct carefully arranged

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[2] Panspermia adherents of the Hoyle-Wickramasinghe school of thought favour this approach, as we shall see. The similarity of views on this point (and few others) between creationists and Panspermia proponents can be demonstrated by the numerous occasions on which creationists use variations on Hoyle's famous "tornado in a junkyard" analogy to present their perceived view of abiogenesis. The final chapter of Hoyle and Wickramasinghe's 1981 Book *Evolution from Space* is titled *Convergence to God*, and delivers exactly that - though it should be said that the God being converged to is a largely abstract one, and the book pours derision over both established religions and Darwinism in equal measure. Hoyle's position was that it is statistically more reasonable to assume the existence of a cosmic intelligence than to accept the idea of random creation:

Rather than accept the fantastically small probability of life having arisen through the blind forces of nature, it seemed better to suppose that the origin of life was a deliberate intellectual act. By "better" I mean less likely to be wrong (Hoyle 1982; Morrell 1997).

evolution experiments using highly purified reagents, but did have the luxury of much greater reaction volumes and more time." (Joyce and Orgel, 2006)

4) That there is some law-like natural dynamic [one version of it is sometimes referred to as a "fourth law of thermodynamics" (Popa, 2004)] which governs non-living matter, and which, given appropriate (but not very narrow) starting conditions, will necessarily produce life. Life is thus seen as an "emergent property" of the laws of the universe.

Before moving on, we should acknowledge that there is a fifth option, and one that is popular among scientists: to refuse to be drawn on the question at all. A trivial reason for this position might be that the question is not interesting enough for the person asked, but a more considered position is that more information is required before giving a meaningful answer. Steven J. Gould embodies this position in his 2000 essay Will We Figure out How Life Began? (Gould, 2000), as does Francis Crick in his book Life Itself (Crick 1981).

Many scientists and thinkers, some highly notable, hold "chance"- inclined views and reject the idea of a law-like, deterministic emergence of life, but few seem to be as comfortable with the notion of a 'chance' formation of life as Monod was. Though Monod's book is well-known, I claim that Monod is not merely a prominent representative of the 'chance' camp in the scientific community, but its only unapologetic member[3]. In effect, the 'chance' narrative is no longer a working hypothesis in any

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[3] Harvard evolutionary biologist Ernest Mayr wrote in 1982 "a full realization of the near impossibility of an origin of life brings home the point how improbable this event was" (Mayr 1982, p.584, quoted in Fry 1995), but he appears to have reversed his opinion by 1995, writing (in an essay reaffirming the anti-SETI position he had taken up several times previously) "Yes, there is a high probability for the existence of other life, in the broadest sense, somewhere else in the universe" and "Biologists who are specialists in this field tend to think that the repeated origin of such life on planets throughout the universe is highly probable." (Mayr 1995). Monod, six years Mayr's junior, had little opportunity to reconsider his ideas in light of new findings, having died in 1976.

ongoing or recent Origin-of-Life research project. I will explore the views of Origin-of-Life researchers regarding the contingency question, and demonstrate that there is an emerging consensus among workers in the field. People do not actively work in the field, but observe Origin-of-Life research and comment on it hold a wide range of views. However, active researchers in the field have been converging onto the intermediate 'stepwise' view.

I.b.3 Definitions: life, abiogenesis, Origin-of-Life, exobiology and Astrobiology

I.b.3.1 Definition of life

A key point in discussing the origins of life is to define, or at least describe comprehensively, the concept of "life". The notion of 'vitalism' – the concept that there is a unique, fundamental property, a 'vital principle', shared by all living things – is nowadays rejected by mainstream Origin-of-Life researchers, who are committed to a mechanistic explanation of life. I explore the vitalist-mechanist debate in chapter 1.

Within the mechanistic framework, there is at present no consensual definition of life, nor is there likely to be one (Lahav 1999). There are no physical or organisational properties or processes that are shared by all entities that we intuitively consider 'living' and by no 'non-living' entities or processes. Requirements such as replication, self-organisation, or metabolism can each be shown to be shared by inanimate entities, including artificially-manufactured ones, while not being shared by entities we automatically ascribe to the 'living' realm.

In his discussion of the role of viruses in the Origin-of-Life debate, Scott Podolsky writes of the early 20th century: "Like Enlightenment philosophers nearly two centuries before them, scientists now firmly considered independence to be essential to 'life.'"(Podolsky, 1996). Over the course of the latter

half of the 20th century, the conception of life embodied by a single minimal unit - the organism, the cell, the gene - has been eroding in favour of conceptions of life as defined by other attributes such as variation and evolution (hence NASA's working definition of life, composed by Gerald Joyce, as "a self-sustaining system capable of Darwinian evolution"); organisation; and recently the perception of life as a property of systems.

The many attempts made to reduce the nature of living systems to a single living compound imply that life can be so well defined that the exact point at which it started can be established with the sudden appearance of the first replicating molecule. On the other hand, if the emergence of life is seen as the stepwise (but not necessarily slow) evolutionary transition between the non-living and the living, then it may be meaningless to draw a strict line between them. (Tirard et al., 2010)

It has been suggested that life should be defined as a scalar rather than as a discreet quality – the 'aliveness' of an entity could be described as a value on a scale of 0 to 1 rather than only as 'yes' or 'no' (Bruylans 2010).

The question of the definition of life is of interest in its own right, but in Origin-of-Life studies it carries a particularly strong weight. A definition of life is necessary in order to frame the entire field – to give theoreticians and experimentalists the explanandum, the end point of the process which they strive to discover.

A definition of life is particularly crucial to exobiologists who are concerned with searching for evidence of life outside planet earth. They need a definition of what it is they are searching for, in order to decide where to look, how to look, and how to know that they have found it. Here, reaching a definition of life cannot be attempted only by distilling the fundaments of life-as-we-know-it;

exobiologists must take into account that life elsewhere in the universe, if it exists, may well exist in an environment radically unlike the terrestrial one, and will thus exhibit radically different characteristics. Exobiology brings into sharp relief the question of what we can regard as living, and how different we should expect alien physical and chemical properties to be from ours. Indeed, it is precisely this prospect, of discovering radically different instances of life and comparing them to our own in order to arrive at a more accurate conception of what life is, that is often touted as a significant motivation for seeking extraterrestrial life in the first place.

For the purposes of exobiology, a definition of life often cited is Gerald Joyce's definition adopted as NASA's working definition: "a self-sustaining system capable of Darwinian evolution". It is also popular in Origin-of-Life circles (Luisi 1998). By avoiding all mention of specific physical and chemical properties, it opens the field for examining extra-terrestrial phenomena with relatively few pre-formed 'chauvinistic' concepts. In practice, however, the search for extraterrestrial life is constrained by technical and budgetary concerns. Therefore the forms of life that are searched for (and the extraterrestrial environments likely to harbour them), are not too different from life-as-we-know-it, because these are the easiest forms to look for. In addition, the discussion is informed by discoveries concerning the abundance of water and of basic organic molecules in the universe: if the basic building blocks of life on earth are found in many extraterrestrial environments, it makes more sense to look for life resembling our own rather than search for exotic forms. We will see how these concerns play out during NASA's Viking missions and elsewhere.

'Pure' Origin-of-Life research can inform these practical considerations, as it seeks to provide models of the possible ways in which life can develop from inanimate matter. However, Origin-of-Life researchers differ in their conception of what the "first living entity" on earth was.

Historically, the scientific understanding of living systems has developed enormously throughout the last centuries, and particularly throughout the 20th century. This posed a problem for Origin-of-Life studies: developments in the life sciences meant that there was more to explain. Whereas prior to the 20th century scientists and thinkers could still discuss more-or-less homogenous cellular 'protoplasm' as the stuff of life, the late 19th century and 20th century discoveries of the ever-increasing intricacies of the basics of the living cell made it necessary for theories of the origin of life to become correspondingly more intricate. If there are multiple sorts of materials and processes needed to perform even the most rudimentary cellular functions, then an Origin-of-Life explanation must address these. These challenges have tested the mettle of abiogenesis theories, and at times have lessened their attraction. For instance, the early 20th century saw the rise of both 'neo-vitalist' and Panspermia theories, since abiogenesis did not have the required explanatory clout in the face of discoveries in cell biology (Fry 2006). We will see this pattern – of technological and scientific advance leading to change in the definitions of life, and subsequently to the reformulation of Origin-of-Life theories – play out several times, up to the present day.

The schools of thought throughout the history of the field are defined by their commitment to their different definitions of life: the 'metabolism-first' and 'genes-first' branches are the two main players in this field. I describe these branchings, and argue that in recent years they are beginning to draw closer together.

I.b.3.2 Abiogenesis

'Abiogenesis' is the process of life arising from non-life. As we shall see in chapter 1, many people throughout history accepted as a fact that life repeatedly arises from non-life. This is known as 'Spontaneous Generation', whereas the term 'abiogenesis' is nowadays used specifically to denote the

(presumed) historical event that occurred billions of years ago and from which all existing life has subsequently evolved.

The entire field of modern Origin-of-Life research is based on the theory that spontaneous generation does not occur, and that abiogenesis happened only once – or rather, that it may have happened several times, but only the products of one such event have survived in earth and in the fossil record.

There is some speculation of a 'shadow biosphere' – an entire domain of microbial life on earth that started from a radically different source and does not share the attributes common to all known life (Cleland 2004). This so-called 'weird life' has not been detected yet, the theory argues, because all of our detection methods are geared towards detecting known life. This is an intriguing theory, but is yet to produce any convincing evidence.

I.b.3.3 Origin-of-Life, exobiology and Astrobiology

Origin-of-Life studies are concerned with the origins of life on earth, while 'Exobiology' was the term coined for the scientific search for and study of life elsewhere in the universe. As we shall see, the two fields are closely related, to the point where NASA's exobiology program became one part of a larger Astrobiology program. This program combines exobiology, Origin-of-Life studies and related research: Astrobiology is defined on NASA's Astrobiology website as "the study of the origin, evolution, distribution, and future of life in the universe" (NASA 2014).

I.b.4 The role of biological discovery in the Origin-of-Life questions

The notion of 'fieldwork' in the Origin-of-Life question seems curious at first. It is accepted as a

given that there is no chance of finding direct historical evidence of abiogenesis.

When discussing the "origin of life question", a distinction must be made between two closely related questions: the first, how life in general can in principle develop from inanimate matter; the second, how life on earth historically developed from inanimate matter. The first question lends itself to 'bottom-up' investigative efforts that start from basic chemistry and end at abiogenesis, while the second question guides 'top-down' investigation that begins with the commonalities of known life and seeks to discover the simplest possible entity (such as the 'minimal cell' or 'first replicator') that could have been at the root of life.(Lahav 2001)

'Top-down' researchers attempt to extrapolate back from what we know to be common to all existing life today, and thus attempt to puzzle out the features of the Last Universal Common Ancestor (LUCA). However, the original living cell (or entity) preceded LUCA by hundreds of millions of years and was undoubtedly quite different and much simpler. Any clues to its character have been eradicated.

Given this, one may assume that Origin-of-Life researchers would be free to work 'bottom-up', from first principles. Since the Origin-of-Life question is one of the most purely theoretical questions in the natural sciences, it is a good candidate for pure theorising. In order to construct a working hypothesis for an origin of life scenario, all that scientists should require from the natural world are:

a) The general principles of life as we know it today;

b) The set of physico-chemical laws that govern what can and cannot happen in the transition between a pre-biotic environment and the first living entity; and finally

c) The best estimates of the possible conditions of the different environments on planet earth

in the period before life appeared.

Given these three parameters, researchers would then 'build up' a testable theory of abiogenesis, and then perform laboratory experiments to test it. In practice, this idealised notion is not followed. I argue that, despite Origin-of-Life researchers being, as a rule, creative and imaginative with their theories, they nevertheless benefit remarkably from surprising 'field' discoveries of organisms in the natural world outside the laboratory. Time and time again, organisms are found that surpass the boundaries of what was hitherto considered possible. These findings serve to stretch and re-define the limits of the forms that life can assume, both in terms of theory – the 'minimal cells' are found that are even more minimal than previously thought possible, organisms are found in environmental conditions that are more extreme than was deemed fit for life, and so on – as well as in terms of practical capabilities – the newly-discovered organisms become models, subjects of experimentation, and platforms for the creation of artificial designs.

I.b.5. The utility of in silico modelling in Abiogenesis studies

A number of theorists have proposed computer models of Abiogenesis. These models are normally concerned with information and its behaviour in an abstract information phase space. I will argue in section 4.6 that these models, ingenious and elegant though they may be, do not translate into chemical experiments. There is a divide between the computer lab and the chemical lab. In short, what happens in silico stays in silico.

I.b.6. The Origin-of-Life research community

The modern manifestation of the Origins-of-Life field started out as a small, loose collection of individual researchers, but has, as we will relate, expanded considerably since. Today there are dozens

of labs performing research directly relevant to the question, not counting the many projects with a peripheral relevancy to this interdisciplinary question. Research publications on the subject number in their thousands, with more findings coming out on a daily basis.

Up until the mid-20th century, there was no real community of Origin-of-life research, no financial support for such research, and no academic or organisational body. Rather, there were a few individuals interested in the question. Word of Oparin's work from the 1930s and beyond, and the Miller-Urey experiments of 1953, led to interest in the subject[4]. In 1957, the first International Conference of the Origin of Life (ICOL) was held in Moscow, and brought together a small community of Origin-of-Life researchers (Strick and Dick 2004), leading to the formation of the International Society for the study of the Origin of Life (ISSOL), with conferences held have been held once every three years[5]. The society's official journal, Origins of Life and Evolution of Biospheres, has been appearing since 1968.

Today the Origin-of-Life research community includes several hundred people and several dozen labs. It is still a relatively loose aggregation: researchers belong to their respective departments. There are no academic departments specialising in the field; NASA has been, since the 1950s, the central hub around which most of the activity in Origin-of-Life realm takes place. It provides most of the funding, organisation and facilities for dedicated Origin-of-Life research, and has done so throughout virtually the entire term of the Origin-of-Life field's existence (Strick 2004). Such a close,

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[4] A classic demonstration of the paucity of interest and funding comes from Stanley miller's oft-told story of his performing his seminal experiments as a side-project during his doctoral studies, using equipment scrounged from other experiments (Strick and Dick 2004).

[5] The society has since changed its name, and is now the International Astrobiological Society.

long-lasting association between an institute and a field of study is quite rare. It also requires

explanation: the core missions of NASA are not directly related to the Origin-of-Life question. I will

sketch out the influence of NASA's involvement with the Origin-of-life field, and argue that NASA has a

vested interest in keeping it active and productive.

I.c. Scope

As related above, Origin-of-Life research today involves dozens of labs performing research directly relevant to the question, not counting the many projects with a peripheral relevancy to this interdisciplinary question. Research publications on the subject number in their thousands, with more findings coming out on a daily basis. Thus, it would be foolish to try and review, let alone analyse, the entire field.

Apart from the many Origin-of-Life researchers who publish reviews and opinions of their field and their work (de Duve, 2005, Gánti, 2003, Hazen, 2005, Kauffman, 1995, Keosian, 1964, Lahav, 1999, Luisi, 2006, Miller, 1974, Oparin, 1968, Orgel, 1973, Popa, 2004, Shapiro, 1986), scholars have been studying Origin-of-Life research either in itself or as a part of science, its history and the philosophical issues relevant to it (Crowe, 1986, Dick, 1996, Farley, 1974, Fruton, 1972, Fry, 2000, Morange, 2008, Popa, 2004, Strick, 2000, Strick, 2004b).

Of the latter category, two works, both fairly recent, focus exclusively on the history of Origin-of-Life research ,and are thus particularly relevant to my work; the first is The Emergence of Life on Earth by historian and philosopher of science Iris Fry (Fry, 2000); the second is The living universe: NASA and the development of astrobiology by historians of science Steven Dick and James E. Strick(Strick, 2004b). Fry's book is an excellent review and analysis of the main developments in the Origin-of-Life from the historical and philosophical angles; Dick and Strick's book likewise gives a thorough historical coverage of the involvement of NASA in the Origin-of-Life field. Between these

two books little ground is left uncovered in terms of the history of the field. Therefore, I retread this

path - the scientific literature of the Origin-of-Life field - but with an eye toward providing a narrative

of the interactions between theory, discovery and experiment in Origin-of-Life research, and the

influence of external factors - funding, motivation, and the social and cultural landscape within which

the scientists operated. To that end I critically analyse scientific texts (papers and books), as well as

historical and biographical material, and engage with texts dealing with the more philosophical issues

inherent in the Origins question.

I.d. Form

The first chapter of this thesis consists of a review of the 'pre-history' of the Origin-of-Life field, up until the year 1959.It is meant as mostly an introductory overview and contains little original thought and analysis.

Chapters 2, 3 and 4 each review a defined period of time, and present analyses of themes that were central to understanding the processes in that period[6]. The final chapter provides an overall summation and analysis of the field.

The second chapter reviews the 1960s. This was, as is often noted, a period of vigorous activity in Origin-of- Life research. Much of it revolved around the NASA Exobiology program, beginning in 1959, and its offshoots. NASA's involvement in Origin-of-Life research will be examined, including the convictions and motivations of the agency and some of the central figures within it, and the significant effects the program had on Origin-of-Life research from that point on.

This period was, however, remarkably thin on theoretical progress and model formation. I will suggest that Origin-of-Life research was focussed towards a certain direction by the American space program, while at the same time the new techniques and ideas arriving from the advances in molecular biology had still not matured enough for meaningful use in the Origin-of- Life question -

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[6] Because of the numerous events and processes occurring concurrently, and the wish to present a coherent and convincing narrative for each section, there will be some overlap between sections in different chapters.

these new conceptions of the physico-chemical basis of life, not yet well formulated enough themselves, did not enable the Origin-of-Life question to be formulated in molecular terms, and therefore the new molecular tools being developed constantly throughout this period could not yet be used. I will also examine the first steps taken in the 'minimal cell' concept.

The third chapter examines some of the many theoretical prebiotic 'worlds' that were proposed starting in the late 1960s. "RNA World"-type theories were suggested in 1968 by several researchers - almost immediately after Sol Spiegelman's work enabling efficient manipulation of RNA, and especially his revolutionary "evolution in a test tube" experiments. It was one of several theories emerging during a remarkably short period. We will explain what the reasons for this theoretical bloom were, and follow the second chapter of the RNA World saga, which waited until the 1982 (non-Origin-of-Life related) discovery of ribozymes, whereupon the theory began to take serious hold in professional circles. In much the same vein, we will show how the discovery of extremophilic organisms had the effect of broadening researchers' and theoreticians' conceptions on the possible "limits of life".

The project around which NASA's Life Sciences efforts between 1968 and 1976 were concentrated was the Viking Mars mission, which influenced NASA's involvement with Origin-of-Life research for at least the two following decades. We will see what the preconceptions of the Viking scientists and decision-makers were, how they affected the preparations for this ambitious project, and what its results meant for the future of NASA's Origin-of-Life interests.

The fourth chapter examines the last major shift in Origin-of-Life thinking, which took place in the late 1970s and early 1980s. This chapter discusses the factors that influenced this shift, and how they came about. I will deal with the influential ideas of Carl Woese and his 'top-down' molecular phylogeny, advances in lipid research and the 'metabolic' tradition, and devote attention to the

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increasingly collaborative endeavours and models that have been surfacing for the last decade or so,

discussing their scientific justifications as well as other motivations (such as the current shift towards

increasingly collaborative, interdisciplinary, multi-member efforts in modern science). Finally, we shall

discuss NASA's role in Origin-of Life research under its new heading as 'Astrobiology'.

Chapter 1 : Origin-of-Life views from antiquity to 1959

1.1. The Origin of the Origin: Origin-of-Life "Prehistory"

The historical introduction to modern Origin-of-Life research and philosophy must include several heavily intertwining themes: the Vitalist-Mechanist debate; the Spontaneous Generation debate; the rise of biochemistry; evolution; and finally perceptions of Divinity. All these subjects have, of course, been extensively studied; this section makes no claim of originality, and relies heavily on existing histories of biology, chemistry and biochemistry (Strick, 2000, Kamminga, 1988, Fry, 2006, Fry, 2000, Farley, 1974, Fruton, 1972, Hein, 1969, Sapp, 2003). I will try to outline the history of Origin-of-Life succinctly and note the influence of these themes on each other and on Origin-of-Life studies.

Three main ideas of the origin of life can be seen as dominant in Western thought: the first, that all life was created in the manner described in the book of Genesis: a single event of divine creation of multiple kinds of creatures, which henceforth procreate sexually (this is emphasised both in the original creation story - the biblical text stresses the creation of both male and female of each species - and in the description of the Flood). The divine origin narrative also strongly implies that species are fixed, discrete categories.

The second origin story, known by the general name of Spontaneous Generation (SG) postulated that 'lower' (as normally determined by morphological complexity) creatures – flies, maggots, intestinal worms, etc.[7], and, at a later stage, microorganisms – can originate from matter (either decaying organic matter or inanimate matter) (Farley 1974).

This view was widespread throughout many cultures, ages and social classes. In Christian Europe this process of emergence of life was considered separate from and/or complementary to divine creation as recounted in the bible (Farley 1974). The relationship of SG to the biblical creation story is not a simple one; throughout history religious forces can at times be seen trying to disprove or eradicate belief in SG, while other religious thinkers have tried to reconcile the two.

The third theory of Origin-of-Life, commonly known today as abiogenesis, can also be found in ancient thought, but it enjoyed little popularity until the mid-19th century when a combination of developments made it come to the forefront of learned thought. In our time, popular conception has it that abiogenesis has in effect displaced or disproved SG and divine creation theories, but that is not exactly the case: looking at the history of the Origin-of-Life debate, abiogenesis has from its inception often been seen (favourably or not) as a "special case" of SG and, to some extent, its rightful heir; this inheritance includes a host of problems.

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[7] Mice were famously included in one description, produced from wheat in the presence of a soiled shirt in a seventeenth-century van Helmont experiment; geese were reported to arise from pine resin under the influence of sea salt by Alexander Neckham in the 12th century (Fry, 2001, p.21).

1.1.a. The Vitalism vs. Mechanism Debate

"Vitalism" and "Mechanism" are two opposing approaches to the "problem of life"– the perceived need to explain the phenomena of living matter and its dissimilarities from nonliving matter. Vitalism is the notion that there is a distinction between living and nonliving matter, that there is a force of nature (commonly referred to as a "vital principle") that is not subject to physico-chemical laws, or not only to them. Mechanism, in the context of this debate, consists of the denial of this distinction; for a mechanist, all natural phenomena can be explained by natural physical laws only. The argument dates back to ancient times (Farley 1974).

A major challenge to vitalism was issued by Descartes (1596-1650), who in his philosophical system rejected vitalism. Descartes espoused a Mind-Body Dualism, a separation between soul and body but not between 'living' and 'nonliving', as living things are nothing but machines. This contradicted animist beliefs (following Aristotle) – for an animist, 'life' and 'soul' are inseparable; all living things possess a soul, no nonliving thing does. The Cartesian view at that point in history was difficult for most people to accept - the properties of living creatures appeared to be too complex for a purely mechanical explanation.

During the years following Descartes and leading up to the 19th century, vitalism formed a legitimate part of theoretical thought in natural philosophy. In the 18th century, for instance, naturalists Buffon and Maupertuis, under the influence of Newtonianism, extended the Newtonian description of the natural world to the living world to create "Newtonian vitalism"; for them, an attractive force analogous to gravitation works to create the organism from more basic components (organic particles). These particles retain a 'memory' of their origin, thus explaining the similarities of

offspring to parents. This then-influential view has had the historical effect of helping to establish biology as a science in its own right: by postulating a fundamental natural force operating specifically on living matter, vitalism provided justification to research in biology that could be unconnected to the rest of the natural world (Farley 1974).

As mechanistic explanations for biological processes accrued throughout the centuries, especially with the rapid advances in chemistry, biochemistry and physiology in the 18th and 19th centuries, the vitalist position in regards to the life sciences - which was originally taken to be quite sound, even commonsensical - became less defensible. The distinction between 'organic' and 'inorganic' matter gradually crumbled[8]. One can see throughout these centuries a recurring case of a thinker arguing from a vitalist position who would put forth a more elaborate and less "strong" version of vitalism, while referring to preceding vitalist theories as "naïve". The final blows to vitalism as such landed during the late 19th century. Thinkers who might be considered vitalists from this era include philosopher Henri Bergson and embryologist Hans Driesch[9] (see also below). Today outright vitalist notions are virtually nonexistent in scientific and philosophical discussion, and remain largely of historical interest[10], though organicism and the concept of 'emergence' could be viewed as a contemporary descendant of vitalism, challenging the currently dominant mechanistic outlook in scientific culture (Fry 2000).

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[8] The watershed event commonly pointed at is Wöhler's synthesis of urea from inorganic compounds in 1828. The unfolding of the events at the time was less clear cut.

[9] Bergson's élan vital was probably not meant by him as a straightforward vitalist concept, more likely a type of metaphor used for a teleological explanation of life. Driesch's theories, too, were more concerned with teleology than with a positive theory of a vital principle as traditionally understood.

[10] With the exception of homeopathy, a therapeutical system founded on vitalist notions, which has remained a going concern until the present day.

The origin of life in its modern form of abiogenesis is a mechanistic concept, with the research efforts seeking to provide a physico-chemical explanation for the creation of life. A traditionally vitalist conception of the origin of life would necessitate an explanation of whence the "vital principle" arrived from (Hein, 1969).

Modern Origin-of-Life research is essentially a reductionist endeavour. Despite the current prominence of the reductionist outlook in science and its practitioners, the task of producing a detailed, scientifically plausible description of abiogenesis on the primitive Earth is nevertheless an important one for scientists. Such a description – provided, of course, that it would turn out to be along the lines of the ones currently under consideration – would provide a demonstration of the 'self-organising' properties inherent in matter and the natural laws describing it, and deny the action of any overarching, super-natural 'organising principle' at this critical point in the history of life. Such a description would likewise be a substantiating achievement for evolutionary theory (see below).

1.1.b. Spontaneous Generation - Introduction

The concept of Spontaneous Generation, the debates surrounding it and the experiments performed as part of these debates are probably the most direct precursors to modern Origin-of-Life research. As had been noted above, abiogenesis is an extension of the theory of Spontaneous Generation in some respects; to a committed biblical creationist, for example, it comes naturally to view the history of Origin-of-Life debate as a struggle between the biblical account of creation and SG theories, with SG sympathisers steadily conceding ground as empirical evidence gathers throughout the centuries, until they are left clinging to the last bastion of abiogenesis: a special, single, irreproducible event of SG buried deep in time – and thus irrefutable (Fry 2000).

In other important respects, abiogenesis is diametrically opposed to "traditional" SG, but many of the problems plaguing Origin-of-Life research today can be seen to have been encountered first within the spontaneous generation debates; these debates have a long history that is not, as is frequently assumed, a simple victory of evidence over prejudice. The story of spontaneous generation is a long and complicated one and is the subject of several book-length studies (Farley, 1974, Strick, 2000). Here we will only sketch out the main points and historical stages.

1.1.c. Spontaneous Generation: Early History

The Aristotelian views on generation dominated Western culture throughout the Middle Ages. Put simply, for Aristotle the organic forms of life were eternal and unchanging. Any individual organism is an embodiment or iteration of a particular ideal form or essence of the species to which it belongs. Generation is viewed as a teleological process. This is supposed to be the case both in sexual reproduction and SG, but here a problem arises, as SG seems to contain arbitrary elements. Aristotle recognises SG as a fact of nature, but its induction into his philosophical system was not clear, which generated differing interpretations in subsequent debate.

St. Augustine (354-430), a primary authority in Christian theology until well into the Middle Ages, maintained that God formed the "seed-principles" (rationes seminales), of all the species at the moment of creation, the potentials of all future living creatures. SG and sexual reproduction are the two methods of the realisation of the pre-ordained divine plan. This realisation can, according to Augustine, take the form of gradual development.

The influential theologian Thomas Aquinas (1225-1274) set out to combine Christian and Aristotelian systems and resolve the conflict between the Aristotelian conception of species as fixed

and Augustinian acceptance of gradual development. The resulting theory held that each species was created at a certain moment (not necessarily at biblical Genesis), and remained, unchanging, from that point onwards. Emphasis is placed on God's direct intervention in this process of creation. SG was still, at this point, unanimously acknowledged as a reality. Nor was this situation to change much. Descartes accepted SG - although his position was that it occurs as a result of natural law, not through divine intervention. Likewise, Francis Bacon accepted SG as evidence of continuity of organic and inorganic matter.

1.1.d. Spontaneous Generation: Preformation, Pre-existence, Problems and Epigenesis

Preformation and pre-existence theories arose in the 17th century as an answer to a problem: an accumulation of microscopic findings of the time revealed complexity in creatures and processes previously considered simple (insects, sex cells, etc.). Simple Cartesian mechanistic explanations of life as a consequence of mechanical law could no longer be entertained seriously. In addition, matter appeared to be passive, not active as Descartes posited it to be. Evidence of widespread phenomena of metamorphosis of insects was discovered (Farley 1974).

A new notion called preformation or pre-existence of the germ was advanced that was to be a mechanistic alternative to SG compatible with divine creation: In the moment of divine creation, each "germ" created had within itself all future generations encased within each other in miniature form (like Russian Matryoshka dolls), and each generation 'unrolls' in a purely mechanical fashion when its

time comes[11]. This idea seemed quite reasonable at a time when the age of the Universe was considered to be several thousand years, and no minimal limit was assumed for living matter or matter generally.

Modern popular histories of the SG debates normally begin with Francisco Redi (1627-1698), who performed experiments to see whether maggots do indeed arise spontaneously from rotting organic matter. His observations are seen as the first major step in the rejection of the SG theory, and to a large extent this is true. It should be noted, however, that Redi was operating within two nontrivial contexts: the first, that he was performing a controlled experiment under, to some extent, artificial conditions (spreading a fine cloth or muslin over the decomposing matter). This acceptance of experiment as a valid way of arriving at truth is something that had only begun to emerge in this period – and that, only gradually. Redi's wrapping up of meat or fish in cloth, incidentally, was not his own invention but a version of common practice of tradesmen of his times - butchers, hunters, and so on (Farley, 1974).

The second context we should pay attention to is that, as we have noted above, up until this period SG was not contested or seen as problematic by the church. The new mechanistic ideas, however, challenged accepted Christian concepts, and SG was now becoming something of a nuisance to the church. Redi was a firm preformationist, and worked within that context.

It is worthwhile to note, however, that Redi did not reject all possibility of SG occurring in nature – for him, the "peculiar potency of that soul or principle" that creates plants, may also give rise

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[11] In the original Latin this unrolling was évolvere – "Evolution" was originally used as a term describing embryonic development (Bowler 1975).

to the worms and insects that are found within it (Farley 1974 p.15). Redi, Swammerdam and other naturalists working within that framework were above all opposed to the random element in SG theory. For them, the fact that certain insects and worms are found regularly on certain plants, and other regular features of that sort, served to provide a sense of order in nature - and therefore, a sense of purpose and teleological cause. Perhaps, for instance, a plant exists so that it would be used by the insect species that use it.

Redi's experiment had mostly satisfied his contemporaries of the non-occurrence of SG in animals, but the newly-discovered class of microscopic creatures could still be reasonably assumed to arise by SG. In 1590 the optical microscope was invented, and improved versions would appear from that point on. By the second half of the 17th century, the magnification capabilities of microscopes had increased to the point where cells and microorganisms could be identified (van Leeuwenhoek used one with a magnification power of 275).

The discovery of 'animacules' by microscopists did not, at first, have a profound effect on the SG debate[12]. Preformation and pre-existence theories suffered more serious blows by studies of heredity that showed that the contribution of the father to the offspring's traits is significant. This clashed with the preformation theory, whose explanation of the differences in traits between mother and offspring relied on environmental effects.

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[12] According to preformation theory, semen was not supposed to contribute much at all to the development and final characteristics of offspring, but the 'animacules' observed in semen were not taken to have a role in reproduction. Sperm cells were initially seen as possible parasites. Animaculism, the idea that these animacules are in fact "seeds" of the future offspring that are "sown" into the ovum, was advanced by van Leeuwenhoek and some others, but did not garner too much support despite its evident appeal to the male psyche, because it could not fit well into the preexistence framework, and because contemporary conception held that nature could not be regarded as so abundantly wasteful as to produce such a mass of seeds for the production of one progeny.

In addition, the discovery of regeneration phenomena – organisms able to regrow limbs – was incompatible with the 'unfolding' narrative of preexistence. But the biggest thorn in the preformation-preexistence (P-P) consensus' side, one which was to plague opponents of SG until the mid-nineteenth century, was the continued mystery of the appearance of parasitic worms in human and animal bodies.

P-P theory was losing its hold, and a new philosophy, epigenesis, was gaining credence in mid-eighteenth-century France (though its origins can be found in Aristotle and, later, in the work of Harvey). Influenced by Newtonianism, epigenesis held that an organism developed from a homogenous initial mass into its final form by a dynamic process of growth and differentiation directed by an attractive force (the "moulé interieur", as Buffon called it) specific to living matter. This view of growth and differentiation naturally extends itself beyond sexual reproduction into the firm possibility of the spontaneous generation of organisms from decomposing, previously-existing organic matter. Note that this is thus strictly a view of SG as heterogenesis. Buffon also provided a mathematical treatment of preexistence theory that gave a reductio ad absurdum result: after only a few generations of germs 'contained' within each other we arrive at staggeringly small 'germ' sizes, unless one accepted matter as truly infinitely divisible (which Buffon rejected on philosophical grounds). Buffon was a strident supporter of SG, and declared "There are perhaps as many beings produced by the fortuitous mingling of organic molecules as there are [those] which can produce by a constant succession of generation" (Farley 1974 p.24).

1.1.e. Spontaneous Generation Contested

The P-P vs. epigenesis conflict led to an oft-referenced series of experimentation and debate focusing on the experiments of two natural philosophers: John Needham (1713-1781), an Englishman, and Lazzaro Spallanzani (1729-1799), an Italian (both men, incidentally, were ordained catholic priests)[13]. The initial step was work of Louis Joblot (1645-1723), whose experiments on hay infusions sought to disprove SG:

...this presumption which is so dangerous to religion by attributing to chance, that is to say to a cause which is neither apparent nor necessary, that which is assuredly the most perfect work of an infinite power. (Joblot, 1718, quoted in Lechevalier 1976)[14].

Needham, supported by Buffon, performed experiments which consisted of heating organic solutions in sealed flasks and observing whether signs of life appeared. The results (published in 1748) led him to conclude that SG does indeed occur in the microscopic realm; Spallanzani's experiments were modelled after Needham's, and their results, published in 1767, agreed with Needham's insofar as the appearance of microscopic life in boiled infusions was concerned.

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[13] Spallanzani was a productive naturalist: he pioneered echolocation studies in bats, studied circulatory systems and contributed heavily to the study of human reproduction. He was also a major contributor to the discovery of regeneration phenomena as discussed above, which is interesting in light of the SG debate.

[14] In this excerpt from Joblot's writings we may find not only the prevailing public attitude to SG, but also, perhaps, some hint of the worldview that made the separation between spontaneously-generated creatures from those that are not:

... One usually despises insects and other small animals which men believe owe their birth to decaying matter; but it is easy to show that this scorn is unfair and that it is based only on ignorance....The smallest gnats are as perfect as the largest animals: the proportions of their members are as good asthose of others...(Joblot, 1718, quoted in Lechevalier 1976).

Spallanzani's added step of heating the air inside the flasks as well as the meat broth itself

permitted him to come to different conclusions than Needham's and Buffon's. He postulated that

animacules are able to travel through the air. When Needham objected that the reason why no life

appeared is that heating the bottle had caused the air itself to lose its life-supporting qualities,

Spallanzani broke the necks of the 'clean' bottles to show that the broth could be contaminated, but

this was still proof of Spallanzani's conclusion only if one accepted Spallanzani's hypothesis that

animacules travel through the air contaminating the broth, rather than that some quality of the air

itself (which is lost by heating) is unfavourable to SG in the broth.

SG had lost some more ground, but was yet undefeated; further experiments throughout the

19th century failed to yield conclusive results, and SG - now in a more restricted form than in ages past

- was considered a viable hypothesis even by eminent thinkers, among them leading naturalists such

as Lamarck and Erasmus Darwin (see the "evolution" section below for details). The final blow – at

least in popular opinion, both then and now – was landed by Louis Pasteur in his famous experimental

refutation of SG. Pasteur's experiments once more involved the boiling of broths under various

conditions. Pasteur conducted his experiments as a response to the results of Félix Archimède Pouchet

(1800-1872), a naturalist who wished to reclaim SG (specifically heterogenesis) from its irreligious ties

and bring it back into the realm of divine creation, arguing from a vitalist stance. His experiments with

infusions of boiled hay, conducted from 1855 onwards, showed the presence – and, he argued, the

possible generation – of microorganisms. Pasteur set to prove Pouchet's experimental method wrong,

and, more generally, to disprove SG.

It should be noted that Pasteur, justifiably admired as a scientist, was not without his

underlying biases. A religious Catholic, he saw Pouchet's attempt to re-legitimise SG as an attack on

religious teachings. This can be added to a pre-existing (though to some extent justifiable, if one allows the scientist to form a consistent worldview) scientific bias: Pasteur became interested in the question as a result of his studies in fermentation; his theory of fermentation would be lent strength if the microorganisms responsible for fermentation were shown to reproduce from one another (and thus, presumably, retain their specificity) rather than being generated spontaneously (Farley 1974). In addition, Pasteur's discovery and study of the phenomenon of chirality in bio-molecules would make him intellectually deeply suspicious of any claim hinting at "chance" in the formation of living organisms.

The Pasteur experiments and their results, published in 1861, attracted much attention both at the time and in subsequent periods, and are commonly brought forth as exemplifying the experimental method in general. Historical research in recent times has revealed a more nuanced picture, casting doubt on Pasteur's scientific integrity (his research notebooks, published in the 1970s, show him ignoring results that did not suit his hypothesis) and on his experimental results. Pasteur could not have "disproven" SG, first because showing that a certain effect does not occur in a certain setting cannot be taken as proof that this effect never occurs (a fact Pasteur himself stated early on, in 1860 (Farley 1974 p.116)); secondly because, as was established several short years after Pasteur's experiments, certain microorganisms can indeed survive, in the form of heat-resistant spores, under such conditions as Pouchet produced, and therefore Pouchet's experimental results are valid – though his conclusions were not.

Nevertheless, Pasteur's opinion prevailed, aided by his scientific clout and by the prevailing political climate in France at the time. The image of "the death of SG" by the hand of Pasteur is an enduring one[15].

1.1.f. Spontaneous Generation after Pasteur

Despite the triumph of Pasteur, Spontaneous Generation was still a going concern in Europe's scientific community after 1860 (though in France we find much less support of it than in England or Germany). Taking their cue from Pasteur, opponents of SG would normally focus on looking for experimental errors in SG experiments.

In England, Henry Charlton Bastian's arguments against Pasteur, Huxley and Tyndall were taken seriously in the 1870s (especially by the medical community). Although this stance suffered a major blow upon Cohn's 1875 discovery of heat-resistant bacterial spores[16], this did not mark the end of the spontaneous generation school.

However, by the end of the 1870s, SG, though not completely dead as a concept, had taken enough damage from various fronts, and was no longer considered a viable hypothesis. Darwinism was at that point supplanting any alternative generation theory and dominating to no small measure the Origin-of-Life debate. The emergence, reproduction and transmission of parasitic life-forms within and between their hosts' bodies, for many years a stronghold of SG theories and a mystery to natural

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[15] Pasteur's own statements regarding SG grew more cautious in his later years. In a well-known comments from 1878 he says "I have looked for [spontaneous generation] for over 20 years without discovering it. No, I do not judge it impossible." (Farley 1974, p.118).

[16] A discovery which, it should be noted, gave credence to Bastian's experimental claims and refuted his opponents' earlier claims of his inadequate experimental procedures.

historians, was also being explained and elucidated by researchers discovering the complex life-cycles these organisms undergo.

While the experimental results of Pasteur and his camp had their influence in themselves, one must also not forget the immense practical uses to which the techniques these experimenters developed were put in the years following the Pasteur demonstrations. Fermentation and sterilisation methods were quickly developed. Although practice could not prove the theory right, the increasing number and success of the applications in the fields of industry and medicine lent the 'Germ Theory camp's arguments much strength.

Spontaneous Generation theories were also losing explanatory ground due to the consequences of cell theory with its findings of complexity within the cells casting doubt on the possibility of such a structure arising spontaneously from non-living compounds. In addition, studies of heredity (initially focusing on plants) were showing in detail how traits are passed.

1.1.g. Spontaneous Generation in the 20th century

After Oparin's work (see below) became known (Oparin 1957) the term "Spontaneous Generation" was considered outdated and had fallen out of favour. A few thinkers and scientists continued to use it until well into the 20th century (notably George Wald and Sidney Fox) but the majority of thinkers on the subject deemed SG to connote (or, at any rate, hint at) a simple, single-step, and still-occurring event, and therefore unsuitable for any modern conception of the origin of life.

1.1.h. Evolution

Pre-Darwinian theories of evolution do not take up too much space in the history of the Origin-of-Life debate: although they did reject the non-changeability of species, they could not contribute a convincing narrative of Origin-of-Life beyond what we have seen thus far.

Darwinian evolutionary theory emerged into the public consciousness at nearly the same time as Pasteur's popular refutation of SG. Its implications on Origin-of-Life concepts were huge: although it was not Charles Darwin who first put forth the idea that species change, it was Darwinism that consolidated the concept of the "Tree of Life" and the viable explanation of the mechanism leading from one ("or a few") original organism to the current diversity of species. Thus it is to Darwinism that we can point to for the idea that there was in fact a single origin to all life. It is at this point that the need for an abiogenetic explanation becomes real.

Darwinian theory is important to the Origin-of-Life debate in another, more subtle, manner as well: it presents us with the latter half of an explanation to the creation of life as we know it today; it provides the outline of the narrative from the point whence the first organism is able to reproduce and respond to natural selection pressures, but does not (Darwin's now-famous "warm little pond" passage, originally appearing in private correspondence in 1871, notwithstanding) attempt to describe how that first organism came to be. Although this "partial explanation" is a step toward a full explanation of the phenomenon of life on earth, it creates a tension that calls to be resolved, both to the scientist who accepts Darwinism (since the 'solution' of part of the problem would add a sense of urgency to the internal motivation of the individual and the community to resolve the other part) and

in the face of external criticism. An acceptable demonstration of abiogenesis would be a major triumph for supporters of Darwinism, both scientifically and politically.

It should be noted, however, that this type of motivation is not a necessary outcome of Darwinian views; as Farley notes (Farley 1974 p.81), in the empirical traditions of science, prevalent in mid-nineteenth century Britain, the role of the scientist was to explain a phenomenon in terms of preceding events that caused it, and indeed Darwin writes (see Fry 2000, p.56) that his theory may be compared to Newton's laws of attraction, in that Newton did not attempt to explain the origin of the force of gravity, only to describe it. The origin of life was considered by the first generation of Darwinists to be an event with no preceding causes that could be discerned scientifically and therefore was destined to remain outside the domain of scientific enquiry. Both Darwin (in all editions of The Origin of Species) and T.H. Huxley publicly proclaimed that an acceptance of Darwinism does not preclude a divine origin of life. That they both did not believe this was the case is also well-documented, but nevertheless, Darwinism does not necessarily imply abiogenesis, and in the early days of Darwinism Origin-of-Life was not a particularly relevant part of that debate (Fry 2000, Lahav 1999).

This conceptual separation of Origin-of-Life and Darwinism became progressively more artificial and disturbing as scientific inquiry began to map more and more hitherto-uncharted waters in various fields, and questions that were previously judged to be obviously unscientific began to be seriously considered by men of science. This could be well illustrated by considering Darwin's comment about the origins of life "One might as well speculate about the origins of matter". At an age when questions about the origins of matter and the universe were the subject of serious scientific research, the origin of life was bound to be seen as a legitimate question.

1.1.i. Darwinism and Spontaneous Generation

As noted, Darwinian theory posited a tree of life originating from one or a few origins. Perhaps surprisingly for some modern readers, this does not, and did not for Darwin and his contemporaries, preclude the possibility of ongoing Spontaneous Generation, especially in the form of heterogenesis. Nevertheless, Darwinian theory had little use for SG explanations, and SG theories, as discussed above, were on their way out at that time anyway, propelled by trends that were largely independent of Darwinism. SG theories were therefore not popular among Darwinists; an alternative sort of explanation was necessary, and for the latter decades of the 19th century "protoplasm" was a popular answer.

1.1.j. Thomas Henry Huxley, Protoplasm and Bathybius

Protoplasm, the 'stuff of life', is a homogenous matter that was thought (most notably by T.H. Huxley) to be common to all living creatures. Protoplasm was described as a gelatinous fluid containing protein and other small organic molecules. The term originated in the mid-19th century. Physiologist Jan Purkinje was apparently the first to use the word - in 1840, in reference to the 'formative material' of animal embryos. Botanist Hugo van Mohl used it to describe the content of plant cells. Ferdinand Cohn suggested in 1850 that protoplasm could be described both for animal and plant cells, and that it was protoplasm, rather than the cell structure itself, that was the more fundamental feature of living organisms. (Welch, 1995)

Cell theory was gaining ground and respectability, and its findings and description of the complexity of the living cell was problematic for supporters of Darwinism, an issue that persists to

some extent to this day. Protoplasmic theory provided a convenient materialistic and mechanistic way out of the difficulty.

In 1868 Huxley announced his observation of such a primitive cell in samples of ocean-bottom mud. *Bathybius haeckelii*, named by him in honour of Ernest Häeckel, was suggested to be an example of the *Urschliem*. *Urschliem*, the primordial slime, was nothing more than a lump of spontaneously-generated protoplasm that Häeckel suggested was the most primitive class of organisms, which he called *Monera*. Häeckel speculated that *Monera* had formed early in the history of the earth, covering the ocean depth and giving rise eventually to more sophisticated forms. Huxley's 1869 lecture *On the Physical Basis of Life* (Huxley, 1869) aroused much public and scientific interest and popularised the notion of protoplasm as the basis of life. In 1870 Huxley coined the term *abiogenesis* to signify the process of a stepwise process leading from nonliving to living matter, a process in which protoplasm was a key concept.

Huxley's *Bathybius* was found to be an artefact a few years after its discovery; protoplasmic theory did not disappear as a result, but in the following two decades it gradually faded into disuse. The term and the theory surrounding it were never very well-defined, and various interpretations of it conflicted with each other. As time went on and more biochemical findings of the cellular composition became known, the view of protoplasm as a homogenous essence of life was replaced with views giving it an increasingly complex makeup, and breaking it down into various types of components. After the resurfacing of Mendel's work near the turn of the 20th century, the concept of a single 'stuff of life' was replaced by the 'genotype-phenotype' distinction.

The term 'protoplasm' itself, having been used by Huxley and his contemporaries primarily as a reductionist concept, had become more or less obsolete, as the physical reality it had been

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attempting to define had been reduced further as time went on, and thus the term became associated (once again) with vitalist connotations. Talk of protoplasm did not die out until well into the 20th century, but the mainstream of biological thought and practice had turned to the emerging disciplines of cellular biology, enzymology and biochemistry for describing the mechanisms of life, and to genetics for descriptions of heredity. The two streams would not combine until the establishment of molecular biology in the second half of the century.

1.1.k. Chemical Evolution

Historical accounts of Origin-of-Life in scientific and popular literature tend to start with Oparin. Discussion of pre-Oparin events will focus briefly on the SG debates, ending with Pasteur's triumph. Until recently, the accepted conception was that there were several decades of virtual inactivity in Origin-of-Life, and very little was accomplished between 1860 and the arrival of Oparin and Haldane on the scene, with biochemistry's principles being well established. This, as some historians have now shown, is not quite the case, although one cannot deny the immense effect of the Oparin-Haldane model that eclipsed much that came before it.

A number of interesting projects were carried out within that period, and while a large number of them led to no clear successes, many of them produced valuable results and ideas. Others are of mostly historical and sociological interest. Taken together, this 'barren' period provides not only the foundations for the Oparin-Haldane model, but also precursors and forerunners to most of the modern approaches - and debates - that are still ongoing today in Origin-of-Life and Synthetic Biology.

Whether it was gathered under the banner of Protoplasmic theory or not, the mainstream of Origin-of-Life thought became focussed on what was to be known as chemical evolution theories - the

term itself dates from the early 20th century (Kamminga, 1988). Taking into account both Pasteur's work and Darwinism, attempting to reconcile the postulated root of the Darwinian 'tree of life' with Pasteur's demonstration of the impossibility of modern bacterial life arising spontaneously from nonliving material, these theories postulated a natural series of chemical reactions leading to a single, specialised event of biogenesis. Inorganic chemicals would form organic molecules, which would then form protein molecules, and the first living entity would arise. The earlier of these theories employed protoplasm as a necessary component of this progression; but, as mentioned above, this fell out of use later on. This event was taken to be restricted to conditions on primitive Earth (conditions that were far from being universally agreed upon at the time - a recurring theme in the Origin-of-Life debate, as we shall see) and was not replicable naturally in the modern period.

It is also worth noting here that the estimates given for the age of the Earth (and thus the timeframes allowed for the development of life) were changing during this period (Lahav 1999). Buffon's 1779 estimate of 75,000 years did not last long; 19th century scientists calculated the Earth's age using then-available physical, geological and astronomical knowledge. The influential William Thomson (later Lord Kelvin) estimated the figure in 1896 to be 20-400 million years, and most authoritative estimates of that period revolved around 20 million years. Becquerel's 1896 discovery of radioactivity revolutionised the calculations age of the Earth, as it disrupted the old estimates. The new method of radiometric dating, however, was yet to be developed, and it would take some time for it to become a trusted scientific tool. Radioactive dating gained prominence and reliability slowly, and it was only in 1931 that this method - and the estimates it produced - was pronounced reliable. Thus, for the decades under discussion, the timeframe allowed for the process of abiogenesis was a rather vague one.

Some of the early abiogenetic theorists include:

- Physician Henry Charlton Bastian who, as noted above, continued to deny Pasteur's conclusions and to fight for a version of Spontaneous Generation until well into the 20th century - his definitive book on the subject was published in 1911 (Bastian 1911). He was a respected physician, and an able debater and experimenter, and formed the last bastion of SG theory in late 19th and early 20th century Britain (Strick, 2000).

- Physicist John Tyndall, vocal Darwin supporter and equally vocal opponent of Bastian, described the search for the origin of life as an effort to "Trace the line of life backwards, and see it approaching more and more to what we call the purely physical condition."(Lahav, 1999, Bernal, 1967)

- Chemical Physiologist Eduard Pflüger put forth in 1875 what is probably the first chemically defined abiogenetic theory. The details, relying on protoplasmic theory, suggested the formation of the first living cell via cyanogen compounds (Fry 2000, p.58, Lahav 1999, p.35).

- One of the lesser-known and earliest researchers in 'modern' Origin-of-Life was John Butler Burke, who around the turn of the 20th century conducted and published a series of experiments testing the possibility of a radioactive origin of life (Burke, 1906, 1905). Burke infused radium salts with sterilised organic medium and claimed to observe the subsequent formation of dividing, multiplying organic bodies, which he called radiobes. He suggested that a similar sort of entity may have been produced by similar forces in the original creation of life on Earth, and may have been the transitive form between the merely organic and the living bacterial cell as we know it.

Burke's experiments were wildly off-track and are now almost entirely forgotten, but should be noted for the amount of public interest they aroused (most likely because radioactivity was at that

period an extremely exciting phenomenon both in scientific circles and in public perception), and for the fact that this is possibly the first-ever straightforwardly scientific claim to the creation of "artificial life" in the laboratory[17].

- Konstantin Merezhkowsky, a prominent Russian biologist focusing on lichen, merits a brief mention here for being the first to suggest Symbiogenesis – the idea that complex cells evolve from symbiotic relationships between simpler cells. This was an important precursor to modern endosymbiotic theory (Sapp 2002).

- Alfonso L. Herrera started out his extensive experimental program during the late 19th century by attempting to elucidate experimentally the origin of protoplasm – a mechanistically-geared field he called plasmogeny. His experiments involved mixing various organic and inorganic substances in presumed "primitive earth" conditions, to create what he suggested were protocells (Fox 1988). In 1912 Herrera produced many varieties of sulphobes – microstructures resembling cells in gross structure (Rasmussen, 2009). Though subsequently determined not to be living entities, they did demonstrate a 'proof of concept' of sorts. In 1942, near the end of his career and a decade before the Miller-Urey experiments, he reported the formation of two types of amino acids from simulated 'primitive-earth' chemical reactions (Negrón-Mendoza, 1995). Much like Burke (who was aware of Herrera's work) his work was a dead end, but can be viewed as a pioneer of experimentation in Origin-of-Life and the 'synthetic life' field[18].

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[17] It should be noted, however, that Burke's metaphysics are a far cry away from the reductionist-mechanist school that would go on to propose - and, in recent times, attempt - the creation of artificial life in the laboratory.

[18] Herrera worked in Mexico in a difficult academic and political climate, far removed from the centres of scientific community.

1.1.m. Genetics in the origin of life

Another important factor of Origin-of-Life research was also gaining substance and attention between 1860 and 1930. This was the burgeoning field of genetics, and early practitioners had things to say about the origin of life:

In 1914 American biochemist, physicist and psychophysiologist Leonard Troland, building on Morgan's recent work on the physical characteristics of the unit of heredity - the gene - and on E.A. Minchin's assertion in 1912 that the primordial formation of chromatin was the first step towards life (Podolsky, 1996), hypothesised that the origin of life could be traced back to the appearance of a molecule in the primordial earth that was endowed with autocatalytic abilities (the capacity to copy itself), which could explain not only how multiplication was first achieved, but also the mechanisms of mutation – as changes in the structure and function of the molecule. Troland also endowed his molecule with heterocatalytic capabilities - the ability to catalyse other chemical reactions, and thus the primitive protoplasm structure was synthesised. He equated this enzymatic molecule with the (then theoretical) gene, and, with remarkable prescience, suggested it was composed of nucleic acid. (Lazcano, 2008, Fry, 2006). This theory is the first modern form of what are now known as 'genes-first' theories of Origin-of-Life, which we shall discuss at length in later chapters.

Troland's theory was not popularly accepted, but it did influence eminent geneticist Herman J. Muller, best known for his work on mutation, who in 1926 proposed the gene as the unit of life (Farley, 1974). Troland and Muller's models were the original manifestations of the 'genes first' approach, and opposed to the 'metabolic' approach demonstrated by the aforementioned organicists, and later by Oparin. Muller's theory also advocated a more or less sudden appearance of the gene, not

a long evolutionary development. The rationale he gave for this argument was an early form of the 'appeal to vastness' - the statistical truism that even such an unlikely event will happen, given a long enough period of time for it to happen in.

As Podolsky(Podolsky, 1996) notes, viruses formed an important part of Muller's (among others) 'genes-first' theoretical approach in its early days, serving as contemporary representations of a basic independent life-form, one with no cytoplasm or metabolism, and thus a life-form closely related to the concept of the 'free' primordial gene in its environment.

There were, of course, other types of theories expounded at that time: Panspermia had its first modern manifestations in this period (see chapter 3). A final surge of vitalism appeared as a response to the mechanistic approach that had gained much popularity in late 19th century biology (Fry 2006). Hans Driesch, perhaps the most prominent among the 'neo-vitalists', re-proposed the (originally Aristotelian) concept of entelechy, a teleological view of a purpose-driven 'life force' permeating living matter (Strick 2000).

Another approach, more nuanced than what its proponents saw as the two extremes of reductionist mechanism and neo-vitalism, was organicism, or the "organismic movement" (Strick 2000). This school of thought rejected the metaphysical concept of 'life-forces' but argued that physico-chemical forces could not provide an adequate description of the organism, and that a more holistic approach, focusing on systemic self-regulation and dynamic equilibrium in cells and organisms, was necessary. This approach was a natural extension of advances exposing the importance of self-regulation in physiological systems and biochemical cycles; it could not, however, adequately explain the initial formation of these cycles, and thus the question of the origin of life could not be even tentatively answered by Organicists of that period. Indeed, a workable, scientific, generally accepted

theory of Origin-of-Life was not offered by any one of the abovementioned until Oparin's 1924

publication.

1.2. Colloidal chemistry and Oparin

1.2.a. Colloidal chemistry

Today the term colloid (from the Greek kolla, for "glue") is used by chemists, physicists and chemical engineers for a specific type of mixture, but starting in the second half of the 19th century, and gaining prominence in the first decades of the 20th century, 'colloid chemistry' was a general and influential approach that covered many types of molecules in both organic and inorganic chemistry, and was used as a theoretical framework for understanding the processes of life.

The term was originally coined by Thomas Graham in 1861 and was used to distinguish colloids from crystalloids such as sugar and salt (Davies, 2002, Lahav, 1999). Graham suggested that colloids are a unique, dynamic state of matter, capable of change and possessing "energia", and pointed out similarities between colloids and life processes. Subsequent colloid chemists diverged in their opinion of whether colloid properties were only analogous to living systems, or whether they were one and the same (Ede, 2007)

Colloids were thus considered to be a unique state of matter, and for Graham as well as other colloid scientists they represented the basis of a primarily vitalist theory of life. Colloids were present in every living cell, and their properties were what made the living cell different from nonliving material. The colloid protein micelle was taken to be the smallest manifestation of the phenomenon of life; its relationship with its environment was comparable to an organism's. Non-colloidal organic substances, such as urea, were not 'stuff of life' and could be studied and synthesised in agreement with known physico-chemical laws, but colloids were a different sort of matter, obeying a special set of

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laws (and therefore requiring a special kind of science to study them). This view was also quite tempting from an empirical point of view: since inorganic colloids are, according to colloid science, simpler counterparts of organic colloids, research on the complex, difficult biological molecules could advance by studying these simple colloids.

Colloid chemistry also presented biochemists of the early 20th century with a way to maintain the protoplasmic view of cellular function, while incorporating the new research regarding enzyme functions into a theoretical view of the living cell. Enzymes were seen to perform specific, different chemical reactions; the simplistic protoplasmic approach which stressed the homogeneity of cellular matter, could not reconcile itself with these findings. Colloidal science could thus present a more nuanced form of protoplasmic theory.

Having reached its peak popularity during the 1920s, By the 1930s colloidal chemistry as a separate science was facing a crisis from which it would not recover. Internally it was troubled, as there was no generally agreed-upon theory or functional definition of colloids among the colloidal research community. Research was not producing the desired results; the sought-after simple building blocks of colloidal matter were not being found[19].

From the outside, research in physical chemistry was unravelling the fundamental properties of colloidal solutions, showing them to be 'ordinary' matter after all, and not a special category of matter. On the biological front, the structures and functions of proteins, especially enzymes, and other biomolecules were also being explained by biochemists (Jacques Loeb prominent among them) who

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[19] As frequently occurs, colloid research did produce some good, significant and useful results. These results, however, ultimately did little to support the theory that drove the research in the first place.

saw no need to resort to colloid theory. Colloid research diminished to its current dimensions as an ordinary subdivision of chemistry.

It should also be noted that the colloidal notions of cellular composition and function were naturally in relation to the techniques available to study the cell. The study of cellular components invariably involved some physical and/or chemical agitation of the cell, and this produced small molecules. The study of 'macromolecules' – long strings of amino acids (or any other type of bio-molecule) in fixed, static order – was not technically feasible up until the 1930s. Biochemists tended to think of cellular processes as a dynamic movement of much smaller molecules – ones the technology at their disposal could detect and study (Judson, 1979).

1.2.b. Oparin

Russian botanist and biochemist Alexandr Ivanovich Oparin first came into attention when colloidal chemistry was in its heyday, and the first iterations of his theory of the origin of life – a theory which is probably the most influential one in the modern history of the field – lie firmly within the realm of colloidal science.

Oparin's first thoughts on the origin of life took the form of a manuscript submitted in 1918. It was rejected for publication, probably since the Darwinian views therein were at that point, before the new communist ideas had taken over intellectual life, anathema in Russian academia (Graham, 1987). The rejection gave Oparin time and motivation to revise his ideas, and in 1922 he presented them in a lecture, which was printed as a booklet in 1924. An expanded and further revised version appeared in 1936, whose widely-read 1938 English translation was the first to bring Oparin's ideas to the

consciousness of the scientific community outside his homeland (Schopf, 1999, Miller, 1997). Further books followed.

Oparin's scenario was initially founded upon colloid chemistry; he described an earth environment with a reducing atmosphere, which enabled vigorous chemical activity. The aqueous environment in the earth's seas abounded with molecules such as hydrogen ammonia and water vapour, which grew more complex, and formed organic molecules and finally colloid aggregates, which he called coacervates. These had the property of being able to absorb and assimilate other organic molecules in a proto-metabolic manner, until the first replicating proto-cell (or eubiont, as Oparin called it) appeared. It was a heterotroph, feeding on the abundant organic substances surrounding it; the more complex biochemical pathways of chemoautotrophy and photoautotrophy appeared later on, as an evolutionary adaptation to the dwindling supply of organic material.

The novelty of Oparin's ideas emerged from his consideration of several issues: As an admirer of Darwinism (no trivial matter in the Czarist Russia of his education) he was intellectually disposed towards an explanation of the origin of life by a historic progression from simple to complex. Oparin extended Darwin's model of descent with modification 'backwards' into the realm of chemistry, suggesting that not only organisms but also molecules can also undergo natural selection and modification in a manner resembling Darwinian evolutionary mechanisms[20].

This was the first sound proposal of what continues to be a key (though not undisputed) concept in Origin-of-Life – that of chemical evolution. This view – and theoretical demonstration of

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[20] Oparin is sometimes called the "Darwin of the 20th century", for expanding Darwinian evolution back into the chemical realm.

possibility – of the stepwise appearance of life on earth, rather than in one decisive and definite step, has found much favour in scientific thought. It is perhaps the most significant step of Origin-of-Life research out of the spontaneous generation concept that the field was to a large extent based on. It could now be convincingly argued that primordial life did not require one sudden, highly unlikely formation of a viable cell (including all of the complex cellular components it was now known to consist of) from inorganic precursors, but instead emerged gradually over time.

Also informing Oparin's ideas was his background as a botanist, which most likely made him appreciate the complexity of cellular organisation in photoautotrophic organisms (plants) – which was being uncovered in this period, as mentioned above – as compared to the relatively simple mechanisms of heterotrophy. The intermingling of this with the Darwinian 'simple to complex progression made him consider the notion that heterotrophy preceded autotrophy (Schopf, 1999), a reversal of the popular notion established by Häeckel seven decades before.

Another important influence on Oparin's thought were the ideas advanced by the great Russian chemist Dmitri I. Mendeleev, who in 1877 devised a theory of the abiotic origin of petroleum (Mendeleev, 1877). Hydrocarbons, Mendeleev argued, were formed chemically from inorganic molecules. Although this theory was incorrect, it did influence Oparin's thoughts on chemical evolution.

A crucial consideration in Oparin's scheme was Verdansky's concept of the biogenic origin of oxygen, and the general composition of the ancient earth's atmosphere. (Verdansky, 1986 [1926]). If plants are responsible for the prevalence of oxygen, then prebiotic earth would have been nearly devoid of oxygen. Astronomical discoveries of methane-containing atmospheres on Jupiter and elsewhere suggested the possibility of a reducing atmosphere on the primitive earth (Oparin, 1957,

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Oparin, 1968). In a more general perspective, it is important to note that these theories of primordial

earth that emerged at the beginning of the 20th century postulated the novel notion that the

conditions in the primordial earth were radically different to what we see around us; this opened up

new chemical possibilities for consideration, and Oparin's scenario for the formation of life is the first

to take advantage of this idea. The chemical processes he suggested would not readily occur under

present atmospheric conditions. Thus, the concept of spontaneous generation, which up until now had

been considered by both supporters and detractors alike to occur under existing conditions, could be

replaced with the concept of an historical event that, in happening, would change the conditions so

that it could not happen again.

It has frequently been noted that between the appearance of the original 1924 booklet and

the publication of the 1936 work, Oparin's ideas underwent a significant transformation (Graham,

1987): his early ideas tended more towards a reductionist stance, and considered the origin of life in a

'spontaneous' manner favoured at the time; by 1936 he argues for a more emergentist view, claiming

that at some point during the process of nonlife becoming life, the conditions enabling Darwinian

dynamics to start operating had been achieved. This conceptual shift is attributed both to his

evaluation of his ideas in view of new empirical data, and to the socio-political environment he was

working within:

Scientifically, the advances in technology which were quickly eroding colloid science's

arguments were influencing Oparin. The invention of the ultracentrifuge and advances in microscope

technology enabled for the first time the detailed study of small subcellular components, and the

biochemical findings were pointing away from colloid-based theory and towards a more complex view

of the workings of the cell, weakening the contemporary reductionist-mechanist position. Also

important to the development of Oparin's theory was de Jong's 1932 work on hydrophilic colloids, especially the droplets formed in the fluid phase of hydrophilic colloids, which de Jong called coacervates. These were seen by Oparin to have a particular importance in the formation of eubionts due to their chemical properties and to their exhibiting, in his mind, a primitive sort of natural selection. Coacervates were to feature prominently in his writings on the subject from then on.

Politically and philosophically, the Marxist philosophy of dialectical materialism, as applied to the natural sciences by Engels in his 1877 Anti-Dühring and later in Dialectics of Nature, was an attractive framework for Oparin, due both to its intellectually stimulating viewpoint and to the obvious benefits of following a strict Marxist philosophy in communist Russia.

In dialectical materialism, nature is viewed as being in a constant process of change and development. Opposing forces meet, and their struggle gives birth to something new. This dynamic is repeated on all levels of being, from the purely physical forces all the way to human behaviour and politics (Graham, 1987).For a dialectical materialist, the emergence of life from a non-living environment is an inevitable part of a fundamental dynamic of the universe. As Leon Trotsky wrote: "Consciousness grew out of the unconscious, psychology out of physiology, the organic world out of the inorganic, the solar system out of the nebulae." (Pomper 1998)

How much had Oparin's commitment to dialectical materialism been informed by a genuine belief in its truth, and how much by the added 'side effects'? The question is of course unanswerable. Critics of Oparin point out the benefits and the professional and political clout Oparin gained by adhering firmly to the communist party line, and to his close ties with the notorious Lysenko. Conversely, Loren Graham, in his wide-ranging study of science in the USSR (which devotes an entire chapter to Oparin) demonstrates that dialectical materialism's tenets were not only genuinely held,

but also quite useful for Oparin, as they were for other prominent Russian scientists (Graham 1987). It is also frequently remarked on that two of the other most prominent early theoreticians of modern Origin-of-Life – Haldane and Bernal, both British – were also committed Marxists.

Oparin's views of the origin of life conflicted strongly with those of Muller, the early champion of the 'genes-first' approach, who saw Oparin's views as inextricably tainted in political ideology – which is pretty fair, since Oparin himself consistently reiterated his ideas' commitment to a Marxist worldview. Oparin was critical of the privileged status of nucleic acids in Origin-of-Life that was becoming increasingly evident throughout the 1940s and especially 1950s; his opposition to the genes-first concept and his view of the beginning of life as a process rather than an event (or a DNA molecule) was coupled with his position in the Soviet scientific establishment. Under Stalin and the influence of Lysenkoism, the winds were blowing away from DNA, and Oparin was not particularly inclined at first to go against them[21].

1.2.c. Oparin's legacy

All of the above formed the starting point for Oparin's model of the origin of life; its strength as we assess it today lies not in the accuracy of its details – the large part of Oparin's assumptions and hypothesised processes are today considered false – but in its consideration of chemical evolution, and mostly in the fact that the details were provided at all. It was the first modern theory of Origin-of-Life that was not too vague or theoretical. It could in principle be empirically tested from the bottom up,

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[21] By 1959, however, we see that Oparin's view had reconciled itself to the new ideas regarding nucleic acids, and his later writings suggest models of Origin-of-Life that include nucleic acid metabolism in "his" prebiotic systems (Sanger 1957).

i.e. not by observing living creatures (or entities that were thought to be alive), but by starting with chemical reactions.

Oparin's ideas are often stated to be a turning point in Origin-of-Life studies. They are said to have revived and revitalised the field, giving it a new framework in which there now were new avenues to explore and, no less importantly, new questions to be answered (Keosian, 1964, Bernal, 1967). That said, actual experiments concerning Oparin's ideas were not readily forthcoming. Oparin's theory was fairly well disseminated throughout the scientific community by 1938, but the first notable experiments to take Oparin's scenario into account were the landmark Miller-Urey experiment in 1953, which sparked off a flurry of related experiments, and, independently, Sidney W. Fox's work on peptides, which also began in the mid-1950s[22].

That lag of about 15 years between theory and lab-work is an intriguing one; given the numerous plaudits attached to the hypothesis as the harbinger of a new and thrilling phase in Origin-of-Life research, one wonders why there should have been a lag at all. A number of reasons might be suggested for it, among them the eruption of the Second World War shortly after Oparin's publication, which was bound to divert attention and resources from 'origin' questions into more practical avenues.

Another explanation is technological in nature: any experiment attempting to show the formation of bio-molecules such a nucleic acids or amino acids would need to rely on analytical

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[22]Oparin himself, and his associates, conducted a number of experiments in coacervate formation related to his primitive-earth scenario, but nothing much came out of these. Oparin, by most accounts including his own, was not a very enthusiastic researcher, preferring theoretical work (Graham 1987). Furthermore, Oparin was trained as a botanist, not a chemist.

chemistry methods which were not well developed until the 1950s (Miller, 1997). We shall examine this idea in the next section.

1.3. 1953-1959: Prebiotic Chemistry

1953 was a momentous year in Origin-of-Life research, for two reasons: The Miller-Urey experiment had enormous repercussions in scientific and popular thought about the origin of life, and the elucidation of the structure of DNA marked a crucial event in the emergence of molecular biology as a leading research discipline, which was highly significant to Origin-of-Life research. It also had the effect of posing the difficult, and at present unanswered, chicken and egg' problem in the conception of the origin of life.

We will now examine the six-year period between these two landmark discoveries and up until the inception of NASA's Exobiology program, the first major research program in Origin-of-Life, in 1959. Did the landmark discoveries immediately trigger a host of experiments and theories, or was there something missing, and if so, was it a lack of institutional organisation? Funding? Techniques and equipment? A lack of interest – there being better things to be studied in this heady period of molecular biology? Or was there yet no theoretical model to be "justified by origin", no stable model of life to understand and explain the origins of?

As mentioned at the end of the previous section, the common science narrative for Origin-of-Life nearly invariably moves directly from Oparin in 1938 to the Miller-Urey experiment in 1953, which is portrayed as the first significant experimental step in modern Origin-of-Life[23].

It is less often mentioned that Miller was not the only one trying at the time to simulate the origin of life. The Miller-Urey experiments were highly influenced by the 1950 experiments of biochemist Melvin Calvin, who performed essentially similar experiments – but with oxygen-rich atmospheric conditions, which Urey suggested replacing with reducing conditions (Dick, 1996, Fry, 2000)

Several other groups were working on roughly similar approaches, and indeed, as Bada and Lazcano note, when Miller's paper was delayed in publication, he grew concerned that his work might be pre-empted (Bada and Lazcano, 2003). It should be noted, however, that none of the other labs (Bada and Lazcano mention three of them) that were performing similar experiments at the time achieved positive results.

Melvin Calvin tried to simulate the synthesis of organic compounds under primitive Earth conditions with high-energy radiation sources. He and his group had limited success: the irradiation of CO_2 solutions with the Crocker Laboratory's 60-inch cyclotron led only to formic acid, albeit in fairly high yields.(Bada and Lazcano, 2003)

Very few experiments directly concerned with the origin of life were being preformed. Herrera was doing his solitary work over in Mexico, while the much more prominent Sidney Fox, directly and

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[23] An influential theoretical 1945 paper by Norman Horowitz elaborated on Oparin's ideas. (Horowitz 1945; Miller 1959).

profoundly influenced by Oparin's ideas, was experimenting with protein structures, an endeavour he was to carry on for the next decades, and about which more later. That, however, was just about all that was happening at the time.

We can point to several historical reasons for this 15-year 'gap', but the fact nevertheless remains that the Miller-Urey setup is very simple – Scientific American at one later point published instructions for a Do-it-Yourself Miller-Urey apparatus for its readers to set up in their garage or basement. Apparently no-one thought it would be that simple (it is an oft-repeated story that Urey at first objected to Miller's proposal, saying it would be a waste of time), and Miller himself was surprised by the quick results. So why hadn't it been done before?

1.3.a. The Miller-Urey experiments

1.3.a.1. Precursors to the Miller-Urey experiments

An interesting answer is that a version of the Miller-Urey experiment was in fact performed before 1953 – indeed before Oparin even formed his theories, let alone published them. German chemist Walther Löb (no connection to Jacques Löb) had a similar set of experiments published in 1913. Miller acknowledged this in a follow-up paper to his original 1953 article (italics mine):

While there have been many studies with ultraviolet light and electric discharges on various combinations of compounds, there have been none with methane, ammonia, water and hydrogen taken together. The only work that would have any bearing on the reducing

atmosphere would be the experiments of Loeb, who obtained glycine by the action of a silent

discharge on a mixture of carbon monoxide, ammonia and water. (Miller, 1955)

Löb, however, performed his experiment, not with carbon monoxide, but with carbon dioxide.

In his historical analysis of the Löb-Miller episode, Hubert Yockey finds that this was a problem of

mistranslation:

The mistranslation of Kohlensaure appears in Glockler and Lind's monograph on the electrochemistry

of gases, which gives a discussion of the techniques used in glow discharge, silent electrical discharges,

sparks, other forms of electrical discharges, and a fairly complete list of references up to about 1938.

Anyone who wished to work in this field would have consulted that book. Lob is cited frequently. One

finds on pages 190-191 the sentence referring to Lob's 1913 paper: 'Tests for amino acids were also

obtained from moist carbon monoxide and ammonia, which was the first time this synthesis was ever

accomplished.' Lob used carbon dioxide (Kohlensaure) not carbon monoxide (Kohlenoxyd). The

mistranslation of (Kohlensaure) is repeated in Akerlof and Wills' 1951 reference book of abstracts, in an

abstract of Lob's 1913 paper on page 125. Miller cited these two references and accepted the

mistranslation of (Kohlensaure), perhaps because Lind was a well-known authority in this field.

(Yockey, 1997)

The Miller-Urey experiment, or rather series of experiments, had been performed before; it had,

in fact, been a part of serious research effort by (mainly German) chemists. Dozens and dozens of

experiments are described in Rabinowich (Morowitz, 1962); "Artificial photosynthesis" was an active

research endeavour from the 1890s onwards.

So the question might shift from "why was the Miller-Urey experiment not performed?" to

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"why wasn't it noticed?"

As noted in the previous chapter, in the late 19th century and up until Oparin's theories, the first living organism was assumed to have been photoautotrophic. It was this avenue of inquiry into the mechanism of photosynthesis, which Löb was a part of, that demonstrated the complexity of the reactions involved, and therefore made the notion of the appearance of a photosynthesising primordial organism appear highly unlikely.

Schopf, in his book Cradle of Life (Schopf, 1999), claims that the difficulty lay not in the experimental setup itself but in the analysis of the products of the experiment. Miller analysed his results by paper chromatography, developed in 1944. Löb used the ninhydrin reaction, significantly more cumbersome to perform and providing inferior results. It took him a lot of time to ascertain that the product of the reaction was indeed glycine. Until paper chromatography was a well-established analytical method, potential experimenters would most probably have shied away from such an involved analysis of results, no matter how simple the experiment that produced them.

It is an illuminating fact to note that when original samples from the Miller-Urey 1953 experiments, which were left in their original sealed flasks for decades, were analysed using advanced gas and liquid chromatography techniques, the results showed that in some cases significantly more types of amino acids were produced than Miller's original analysis had picked up (Johnson et al., 2008).

The correct elution time on the amino-acid analyzer is obviously insufficient by itself to identify an amino acid. Many nonprotein amino acids have peaks that coincide with the protein amino acids...The same limitation is true for paper chromatography or electrophoresis, even with several different solvents. Coincidence of the radioactivity of an unknown with the color of a known sample on

paper chromatography has led to several errors. The only methods that seem reliable for amino acids are identification by the melting point and mixed melting point of a suitable derivative, or analysis by gas chromatography - mass spectrometry. (Ring, 1972)

1.3.a.2. The Miller-Urey experiments' effect

Once it had emerged into scientific and public consciousness, the Miller-Urey experiment provided (and, to some extent, still provides) a glittering beacon of possibility for scientific research. In an era when science was providing emphatic demonstrations of its power both in the practical and the theoretical realms, the Miller-Urey experiment was held up by many as a sign that this problem, hitherto considered nearly intractable, might have a solution – indeed, even a relatively simple one awaiting in the near future.

The Miller-Urey experiment results were remarkable also in that, instead of the gloopy hodgepodge of resins and tar that chemists find so familiar and which might contain (among much else) some minute concentrations of amino acids, the analysis showed that biochemically interesting materials were present in far larger amounts than anyone would have expected (although there was no shortage of side-reaction products in Miller's flasks).

1.3.a.3. After the Miller-Urey experiments

As in the case of Oparin, one might have expected to see a flurry of activity, eager researchers building on the Miller-Urey results and pushing further. Origin-of-Life texts sometimes give that impression. Indeed, repeats of, and elaborations on, the Miller-Urey experiment by Miller himself as well as other scientists followed over the next few years (Woese, 1967), and the initial experimental parameters were tinkered with: energy sources were varied to include ultraviolet light, sunlight and

high-energy radiation that could conceivably have originated from cosmic or radioactive sources. The chemical composition of the initial mixture was likewise altered (Miller, 1959). The results of these subsequent experiments were in agreement with the original experiments. However, they were not particularly significant, and it is difficult to find any mention or details of them in later reviews of the field, whether scientific or popular. The next development that is almost universally mentioned and acknowledged as a milestone is Juan Oró's 1960 synthesis of the nucleobase Adenine (Oró and Kimball, 1961).

The Miller-Urey experiment was, as we have seen, not the only one of its kind in the field. It was, however, the first one of its contemporaries to achieve success, and to prove that complex prebiotic molecules can indeed be produced from abiotic molecules without the assistance of existing biochemical machinery. It was an experimental demonstration that bears, in its effect, some resemblance to Wöhler's synthesis of urea over a century before, in that it enabled the research community to glimpse the hitherto largely speculative 'bridge' between the nonliving and living realms.

Furthermore, given the Miller-Urey experiment's characteristics – the unexpected ease and rapidity by which the results were arrived at, the variety of the reaction products and their close agreement with existing amino acids, and not least the dramatic aspects of the experimental setup – one could hardly refrain from associating the electric discharges used in the experiment with other manifestations of electricity. The 'spark of life' is a powerful cultural symbol in science, fiction and myth, from the Gods in Greek mythology to Galvani and that potent icon of science, Mary Shelly's Frankenstein. As it happens, experiments in the following years clearly indicated that the electric spark, or indeed any sort of intense application of energy, is by no means necessary for facilitating the

prebiotic chemical reactions, but by that point the image had been firmly set in the public mind.

Robert Shapiro argues that the results of the Miller-Urey experiment and its successors suffer from what he terms a 'predestinist' fallacy (Shapiro, 1986). It is, he argues, one thing to detect minute quantities of simple amino acids or nucleotides in a prebiotic mixture; it is another thing entirely to infer from this result that the more complex molecules are somehow bound to appear after the necessary adjustments and improvements to the experimental setup will be made. Such dubious inferences are indeed perhaps not very good in the long term, but the history of science is rife with unsubstantiated intuitions and hopes of this sort; scientists, especially when faced with an exciting new result, are prone to some daring presumptions; some of these turn out, after the dust had settled, to have some measure of truth behind them.

In the case of Origin-of-Life research, the hopes for a quick advance in understanding were not realised in the years immediately following the Miller-Urey experiment; the experiments following it and informed by it failed to yield dramatic results, providing only variations on the Miller-Urey 'theme'. Not only that, but the timing was unfortunate: a new understanding of life's processes had arrived on the scene. And the Miller-Urey results had to be considered in its light:

1.3.a.4. The Chicken-and-egg problem

The Miller-Urey paper appeared in the 15th May 1953 issue of Science[24]. Three weeks earlier, Watson and Crick's seminal paper on the structure of DNA was published in Nature, ushering in the so-called "Molecular era" in the biosciences. Oswald Avery's 1944 paper (Avery et al., 1944) had already

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[24] Miller had actually submitted his paper in mid-December 1952, but the publication was delayed by a sceptical reviewer.

given a strong indication of the role of DNA in heredity, but there was still much resistance to the idea[25]. The Watson and Crick paper powerfully dispelled these notions.

The 1953 Watson and Crick paper can rightly be considered to be a major milestone in the emergence of the 'golden age' of molecular biology, one that continues to be a significant influence up to the present day. The emerging discipline had its roots some years before that (Kay, 1993, Kay, 1996, de Chadarevian and Rheinberger, 2009, Morange and Cobb, 2000, Judson, 1979). Of particular interest to Origin-of-Life ideas is Erwin Schrödinger's What is Life? which appeared in 1944 and is cited by many prominent molecular biologists as an early influence (Schrödinger, 1944) and set out his physicist's theoretical conception of the problem of life. It was only after 1953, however, that molecular biology presented its first true influence on Origin-of-Life studies.

We have seen that the debate between the 'nucleocentric' and 'cytoplasmic' approaches to the origin of life dates back to the 19th century (Sapp, 1987). But even within the nucleocentric approach, the nucleic constituent responsible for heredity – and, by extension, reasoned to have been the first self-propagating element – was universally considered to be a "nucleoprotein". Since proteins were known to have both structural and functional roles, it was natural to picture a protein-centred Origin-of-Life scenario (cf. Horowitz 1945). Thus, pre-1953 Origin-of-Life research was concerned with the

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[25] The most prominent criticism was that that the DNA samples that Avery and his colleagues used in their experiments were not pure, and were still contaminated by trace amounts of some other biomolecule - protein was the obvious candidate - which may have been responsible for the observed effects. The paper details the various chemical, enzymatic, immunological, serological and physicochemical tests, some of them only newly available, that were performed in order to ascertain that the "transforming principle" is indeed DNA rather than protein (or RNA). Avery et al did however find it necessary to qualify their assertions, stating

It is, of course, possible that the biological activity of the substances described is not an inherentproperty of the nucleic acid but is due to minute amounts of some other substance adsorbed to it or so intimately associated with it as to escape detection.

study of proteins and the possible ways by which they might have been created, their characteristics, etc. The Miller-Urey experiment was supposed to be a substantial leap forward for Origin-of-Life, but, just when protein-centred Origin-of-Life research was finally getting some results, the focus was dramatically shifted to nucleic acids[26].

A nucleic acid gene provided an added complication, one that plagues Origin-of-Life research to this day. The model of heredity based on nucleic acids provided Origin-of-Life with a significant new puzzle to address, known as the chicken and egg problem. Briefly: had genes proven to be composed of proteins or protein-like molecules, it would be fairly straightforward to construct some theories of a protein 'evolutionary tree' stemming from one (or a few) original amino acid polymers formed by chance in the prebiotic soup and endowed with a modest reproductive and catalytic capability, and branching out to the form the entire range of proteins and genes in the modern biosphere. The question of membrane formation would of course still remain, but the basic idea of genetics and metabolism would be on its way to solution. Since, however, genes are not proteinaceous, and since existing mechanisms of gene replication are heavily reliant on the activity of enzymes composed entirely or mostly of amino acids, then any model of the origin of life which maintains that the original replicating entity was a type of nucleic acid (DNA, RNA or any other type) now has to explain how these nucleic acids originally came to replicate themselves in a more or less faithful manner without using these enzymes. The converse is of course also true: a protein-centred model of the origin of life must contend with the fact that genes are made of nucleic acids, and explain not only how proteins

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[26] Protein sequencing was also just beginning to be available; it was only in 1951 that Sanger had shown that a protein molecule could be sequenced - indeed, that protein molecules had a regular amino acid sequence that could be discerned experimentally, a unique structure that is common to all units of that particular protein and to no other.

can self-replicate without them, but also how it came to pass that protein replication shifted so decisively to nucleic acids. Hybrid models, positing a co-reliant stepwise development of the two molecule types, are also possible, but they too require a detailed working out.

In short, the finding that proteins are not genes confounded the hope that the origin of life may be found to have been a relatively straightforward process – and this happened about three weeks before this hope was to be given its most significant boost.

Even the most decisive scientific discoveries need a little time before they can 'sink in' and be accepted by all scientists, and the idea of DNA as genetic material was no exception. We have noted the formidable resistance with which the idea was received following Avery's results[27]; even the Watson and Crick paper did not win everyone over immediately, and many biochemists tenaciously held on to their conception of the dominance of the protein in the scheme of life.

Even if the role of DNA as the agent of heredity is accepted, it does not mean that it was always thus, and, indeed, as we shall see, 'DNA World' theories of Origin-of-Life were short-lived, since DNA quickly proved to be a very poor candidate for an autonomously self-replicating molecule. The earliest constituents of prebiotic chemistry were therefore to be sought elsewhere – and at that point proteins seemed to be the obvious candidates.

Protein chemist Sidney W. Fox, an early, prominent Origin-of-Life researcher whose commitment to a 'proteins-first' approach was a direct continuation of Oparin's theories, claimed that it was proteins who were formed first and were the basis of the first proto-living metabolic cycle, while

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[27] Avery himself came only reluctantly to the conclusion that DNA was his "transforming principle" rather than a "monotonous molecule". (Judson 1878, p.36).

genetic material as we know it was a later development. Although it can be plausibly denied in every instance, we can nevertheless suspect that scientists who are committed to an idea, a method or even a class of molecules they work with, would find it appealing to picture 'their' area of experience and expertise as forming a crucial part of the basic premises of their general field. To a protein scientist raised in the biochemical tradition and trained to think of proteins as the primary, perhaps sole, movers and shakers of the living world, the conception of inert nucleic acids coming first would meet with some resistance.

Fox himself spent many years testing and advocating his theories, but as we shall see, their power to convince diminished over the years, and in later decades the influence he retained in the field was due more to his political and organisational standing than to the results coming forth from his laboratory (Strick, 2004b).

We see that between 1953 and 1958, Origin-of-Life studies were in a curious position: on one hand the burgeoning field had just received the most influential experimental boost to its goals and aspirations; on the other hand, some of the core assumptions on which further research was to be held were being quickly eroded, with no new ones available. Molecular biology (as it came to be named) was an exciting young field, attracting the best minds and a large bulk of funding, but it had a long way to go before it could present anything resembling a plausible theoretical explanation of life – one whose origins could be tested and justified or rejected. Nor had novel experimental techniques with which to examine the implications been put forth (aside from Sanger's 1951 protein sequencing method – but RNA and DNA sequencing was still decades away).

Molecular biology received strong foundational support from the Rockefeller Trust (Kay, 1993). Conversely, Origin-of-Life research (though obviously a much smaller endeavour), had no such

support, and its lack of practical goals meant that it was confined to whatever isolated laboratories could scrape together the interest, manpower and funding to conduct experiments. This, however, was about to change, as NASA entered the picture.

1.3.b. NASA

1.3.b.1. Funding of Origin-of-Life research

Science became a matter for professionals starting with the efforts of the "X Club" in England, and by the turn of the 20th century the fact of the scientific profession was accepted on both sides of the Atlantic. One of the obvious consequences of the shift from the pursuit of science as a gentlemanly hobby to its execution by professional practitioners, and of the growing awareness of the relevance of science to the development of technology and the well-being of society, was the growing need for a model (or models) of funding for scientific research. In France and Germany, for example, research institutes were traditionally primarily funded by the national government, and the British government followed suit in the late 19th century (Jonas 1989, p.38) providing research funds to the Royal Society.

In the United States, which in the early 20th century was deep within an even more than usually capitalist phase, government funding was not forthcoming – but on the other hand, it did produce some highly successful capitalists. A substantial portion of scientific research was being paid for by private means.

Enabled by hitherto unheard of wealth and power, and driven by a variety of personal, cultural and sometimes religious motivations, many of the most prominent capitalists of the late 19th and early 20th century established philanthropic foundations that exceeded, in magnitude of aims and resources, just about any previous charity in history. In addition, these modern philanthropists were not content

to merely feed the hungry or clothe the poor, but wished to improve the lot of their fellow humans by contributing to their education and by enlarging the scope of human knowledge (Jonas, 1989).

Some of these enlightened philanthropists founded universities; the Carnegie foundation built libraries. The Rockefeller foundation concentrated its efforts on biomedical research, and became a major source of funding for projects concerned with molecular biology in its halcyon days.

It has been argued (Kay 1993) that the Rockefeller foundation had a major influence on the direction of biological research in the mid-20th century: the Rockefeller "philanthropoids" (the administrators who were in charge of the allocation of charitable funds) had a social and ideological agenda, and funded projects in light of that agenda.

Large-scale government funding of scientific research projects could be said to have begun in earnest during World War II, with the Manhattan project forming a highly conspicuous example of the success that could be achieved when science – even highly theoretical science – met the capabilities of the industrial and technological behemoth that the US could conjure. 'Big Science' was the new way to go, and private philanthropy, although it did not disappear, now took on a more subdued role in funding scientific research.

Origin-of-Life research did not originally attract much interest from either public or private sectors; the combination of feasibility, interest (scientific or otherwise) and discernible applicability of results which normally makes a scientific program attractive for funding agencies was severely lacking on all three counts until well into the 1950s. It was only then that an interested party came on the scene: the newly founded NASA.

1.3.b.2 NASA's origin and its uptake of Origin-of-Life research

NASA was created in July 1958, a reaction to the Soviet Union's successful launch of the Sputnik

satellite in October 1957. Its involvement with research on the possibility of life outside planet Earth

was remarkably swift, and owes much to the efforts of Joshua Lederberg. One of the most prominent

scientists of the period, and winner of the 1958 Nobel prize for his work in bacterial genetics, in late

1957 he voiced his concerns regarding the possibility of both contamination of Earth by lunar

microorganisms via spaceship, as well as contamination of the lunar environment by terrestrial

organisms, in a letter to the National Academy of Sciences (NAS), and a short while later in an article

published in Science (Lederberg and Cowie, 1958). The NAS had by August 1958 also established its

Space Science Board (SSB), one of whose 11 committees, the Committee on Psychological and

Biological Research, was concerned with the life sciences. Initially this committee focussed on the

effects of space travel on human physiology rather than issues of extra-terrestrial life, but a few years

later a Committee on Exobiology was established, from which the Exobiology lab developed[28].

Some American scientists of the period viewed with concern the nationalistic attitudes that

were prevalent in their society and government, and saw an exobiology program as a way to make

space science a more global, a-political concern (Wolfe, 2002)[29]. As the story goes, Lederberg first

conceived of the 'contamination' problem while dining with J.B.S. Haldane and speculating on the

possibility of the Soviets exploding a bomb on the moon; he saw the problem (and its solution, via

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[28] The term exobiology was coined by Lederberg in 1960.

[29] To briefly illustrate the mood, as well as the significance of the space program in the scientific community at the time, see the attached recruiting advertisement for scientific personnel taken from a 1962 issue of Scientific American (see appendix 1 below). Note the repeated references to "security" and "freedom".

international agreements and coordination) as a way to foster international cooperation rather than competition in the exploration of outer space.

Any such attempt to work within a system while answering a different agenda to the system is invariably a tricky task to pull off, but both the exobiologists and NASA administration found it worth their while to carry on this relationship. The generous funding awarded to NASA in its first years undoubtedly drew the attention of life scientists, as did the potential to explore new realms of the universe.

NASA, on the other hand, could use "The Search for Life" as an additional (and rather inexpensive) justification for its space program. Moreover, the American space program was at that point seen as technologically backward; the Soviets had started earlier, had achieved better results and were advancing at a quick pace. Exobiology was one field where the USA could (and should) keep up with the Soviets[30].

The relationship between NASA and its exobiology program was, however, strained. NASA's primary mission was the achievement of man-in-space goals; the exobiologists could contribute nothing toward the engineering tasks involved (indeed, if the problem of contamination was to be taken seriously, it would add a new complication).

Moreover, if what NASA was trying to achieve in its 'regular' space program was imaginative and daring, exobiology was dangerously close to the realms of science fiction. Even the fact that some of

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[30] The first international conference on the origin of life was held in August 1957 in Moscow; many prominent Origin-of-Life researchers from the West attended – not a trivial matter at the height of the Cold War. American attendees were contacted by their government and asked to report what they could on the state of Soviet Origin-of-Life research (Strick 2004).

the world's most respected life scientists were involved did not lessen the suspicion that the entire concept was vague, far-fetched and highly theoretical - in stark contrast to NASA's engineering culture. No matter how carefully Lederberg and his colleagues were (and how their successors are) to distinguish the search for life outside planet Earth from the search for intelligent life outside planet Earth, the echoes of the 'little green men' myth never fail to reverberate in the public sphere, causing both contempt and excitement.

This contentious position of the exobiology lab (and its current descendant, the Astrobiology program) within NASA has remained as a permanent feature, though its intensity has declined over the years. The issues of funding distribution, public relations and operational constraints have remained to the present day – and they sometimes afford the participants positive results.

NASA had a political motivation to further develop Origin-of-Life research, and especially advance that part of Origin-of-Life which would be sympathetic to the view that extra-terrestrial life may well be abundant. As Cyril Ponnamperuma, head of the Chemical Evolution Division within NASA's Exobiology Division, said in 1982:

In the early days, there was no question about it, NASA felt that if it wanted to search for life beyond the earth....you want to establish the processes, the fact that life appears to be an inevitable result of evolution in the universe. You can't go and look for life elsewhere unless you know it will originate somewhere.(Strick, 2004b)

It is this motivation, I believe, which has allowed the search for extra-terrestrial life to remain within the framework of NASA for the past 50 years, with some perhaps surprising results relevant also – I would argue, primarily – to terrestrial life as well. The effects of its slant towards theories and

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projects tending towards the 'necessity' end of the contingency problem will become more relevant as we progress towards the 1960s and 1970s.

In the meantime, one might also note that there is some irony inherent in the fact that the political climate in the USSR at that time was also highly favourable to the 'necessity' view – but for very different reasons. The basis for this attitude was inherent in the philosophical roots of Marxism – as we have discussed, the principles of dialectical materialism as put forth by Engels more or less decree it. In addition to his huge scientific influence of Western Origin-of-Life, Oparin was a politically dominant force in Soviet science, and his approach to the question of Origin-of-Life fit very neatly within Party dogma[31]. The "inevitable" view of chemical evolution was therefore taken up by the two bitterly opposed sides in the Cold War; this originally Marxist conception found a warm welcome inside the most non-Marxist framework of NASA.

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[31] The relations between Oparin, Origin-of-Life and Marxism have already been touched upon in the previous section.

ASW...

A NAVY PROGRAM DEDICATED TO THE FREEDOM OF "INNER SPACE"

A high-priority national program involving the exploration and security of outer space is currently the rightful concern of dedicated, select men of science. Simultaneously, equally dedicated and select men are engaged in the exploration and security of *"inner space"* . . . the vast mantle of water that covers 70 per cent of the earth's surface.

Here, in the great oceans of the world, the crucial campaign which may turn the tide toward freedom or totalitarianism may well take place. It is to the security and freedom of this *"inner space"* that the *ASW* program of the Naval Laboratories of California is dedicated. Here, men as well as machines serve to create the artifacts of underwater defense against enemy submarines . . . employing the latest scientific and technological advances in underwater detection, discrimination and effective weaponry. Here, men working with established research equipment like the deep-sea Bathyscaph *Trieste* (NEL), weaponry like the ship-launched ASROC (NOTS) and recent developments such as the miniature submarine, *Moray*, combine to form the vital, ever expanding Anti-Submarine Warfare program of research, development, test and evaluation. *ASW* is only *one* of the many programs currently in progress at the Naval Laboratories of California in the fields of underwater ordnance, missiles and space, and nuclear science.

Qualified scientists and engineers are invited to explore employment opportunities at U.S. Naval Laboratories of California by contacting the Personnel Coordinator, Dept. A, at the laboratory of their choice.

U.S. Navy Electronics Laboratory (NEL), San Diego
U.S. Naval Ordnance Test Station (NOTS), China Lake and Pasadena
U.S. Naval Ordnance Laboratory (NOLC), Corona
Pacific Missile Range (PMR) and U.S. Naval Missile Center, Point Mugu
U.S. Naval Radiological Defense Laboratory (NRDL), San Francisco
U.S. Naval Civil Engineering Laboratory (NCEL), Port Hueneme
U.S. Naval Personnel Research Activity (NPRA), San Diego

All qualified applicants will receive consideration for employment without regard to race, creed or color, or national origin.

U.S. Naval Laboratories of California

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500 building blocks, the cell would have a complement of 150 large molecules. This purely theoretical cell would be delicate in the extreme, its ability to reproduce successfully always threatened by the random thermal motion of its constituents.

The smallest living organism actually observed—the .1-micron, or 1,000-angstrom, elementary body of *M. laidlawii*—is only twice this diameter. Its mass, of course, is eight times larger, and calculation from its observed density shows that it may contain 1,200 large molecules. This is a quite finite number, and since the organism grows to considerably larger size in the course of its reproductive cycle it cannot be said that 1,200 large molecules constitute its complete biochemical equipment. In the case of *M. gallisepticum*, however, we know that a diameter of .25 micron—only five times the theoretical lower limit—does encompass an autonomous metabolic and reproductive system. Our chemical analysis shows that the entire system is embodied in something less than 20,000 large molecules [*see chart on page 123*].

This is still an exceedingly small amount of material to sustain the complexity of biochemical function necessary to life. In fact, the portion of it allotted to the genetic function seems inadequate to the task. The 4 per cent of its dry substance that is DNA has a total molecular weight of 45 million. Since, according to current views of genetic coding, it takes an amount of DNA with a molecular weight of one million to encode the information for the synthesis of one enzyme molecule, *M. gallisepticum* would seem to contain enough genetic material to encode only a few enzymes beyond the 40 we have identified so far. That is far short of the 100 enzymes thought to be the minimum for cellular functions. It may be that the enzymes of very small cells are less specific and hence more versatile in their action than the enzymes of larger ones. On the other hand, it may prove necessary to re-examine prevailing ideas about the way information is encoded in the genetic material.

Questions of this kind suggest the principal challenge of very small cells. If they are indeed simpler than other cells, they can tell much about the basic mechanisms of cell function. If, on the other hand, they are functionally as complicated as other cells, they pose the fundamental question of how such functional complexity can be carried in such tiny pieces of genetic material.

American:

Chapter2: 1959-1968: Meteors, Minimal cells and outer worlds

2.1. The NASA Agenda

As related in the previous chapter, and explicated in the Ponnamperuma quote given therein, NASA can be seen to hold a vested interest in supporting the view that life exists outside planet earth, and that in the "chance vs. necessity" question, the formation of life would thus tend to be viewed as geared more towards the "necessity" pole.

Before we go into the details of NASA-supported research, it should be noted that justification can be seen to apply in the opposite direction as well: With the advent of space programs and the real possibility of the exploration of extra-terrestrial environments, Origin-of-Life research was transformed from a theoretical problem with no real-world application[32] to a pursuit with possible practical importance. The philosophical and theoretical questions concerning issues such as the definition of life, the possibility of other forms of living systems and the range of variability from terrestrial life it could exhibit, the range of conditions under which life could emerge – all of these could now form and inform scientific experiments and policy decisions.

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[32] The prospect of synthetic life could perhaps be considered an exception to this statement, as it does constitute the creation of an interesting and useful product, but it, too, was at that point not much more than a far-fetched notion. In recent years, of course, synthetic life is a thriving research field with strong industrial and commercial implications, which we will be revisiting in chapter 4.

The symbiosis of interests is clear: Origins-of-Life research was providing NASA with theoretical justification for carrying out its space program, while the technological advances that made space missions possible gave Origins-of-Life research justification for existence and experimentation. In a recent paper, Strick argues persuasively that this factor, combined with the funding opportunities offered by NASA, was a major one in turning Origin-of-Life research from disparate research projects carried out by relatively isolated workers in different fields and traditions, into a much more cohesive community (Strick, 2004a). This is another demonstration of the theme of the interplay of technology and research in origin of life studies.

It is no accident that the first scientific journal dedicated to Origin-of-Life studies – first known as Space Life Sciences, now retitled Origins of Life and the Evolution of the Biospheres - was established by NASA in the year 1968.

NASA's public profile is a high one for a government agency. Its institutional goals and its various projects and programs have, throughout the decades of its existence, received substantial public attention, and often been praised for its successes and bold vision, but a high profile has its disadvantages; there has always been a measure of scepticism from critics both within and outside the scientific community who were prone to label particular aspects of NASA's operation as overly ambitious, overly costly, too vaguely defined or of little immediate importance. In addition to coping with such ever-present criticisms and justifying its existence and funding to the taxpayers and legislators, something any government agency must constantly do, NASA must address unique public

reservations: some of its projects are often perceived to be speculative, and too "science fiction-y"[33].

The arguments relating to cost-effectiveness tend to dominate in recent years, but in its early days, and especially before it had any major successful achievements in could present, NASA funding was less restricted, while detractors from within scientific circles were more pronounced. Here, for example, is a quote from Wolf Vishniac, NASA scientist in the 1950s and 1960s: "I was told unofficially that [the grant application made to the NIH] received a low priority because I was 'NASAing around'" (Strick 2004, p.52)

A look at the projects funded by the NASA Life Sciences Office since its inception in 1960 and throughout the following decade, which was characterised by a relatively generous allocation of government funds to the agency, shows (Strick, 2004b) the projects divided into three broad categories: the first, "life detector" projects, developed for the purpose of being put on spacecraft in order to analyse extra-terrestrial environments. To this we can add sterilisation projects, aimed at ensuring that contamination and back-contamination in extra-terrestrial environments would not occur. The second category comprised a modest number of studies of (terrestrial) microbial life in extreme conditions and environments. Lastly, a surprisingly large amount of money was granted to ambitious theoretical projects (Strick and Dick 2004). Some were almost esoteric (notably a small grant to dolphin researcher John Lilly for the study of "feasibility of communications between man and other species"); others were more mainstream and encouraged established Origins-of-Life researchers (such

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[33] This criticism applies with even more force to SETI, the discipline devoted to the detection of extra-terrestrial intelligence. The relationships between NASA and SETI research efforts are an interesting topic in itself; they will not be discussed here. Nowadays, when NASA announces new research findings in its quest for life (even if not related to SETI), it is very likely that at least some media outlets will report the news with a tongue-in-cheek mention of "little green men", with or without the appropriate images, regardless of whether or not the research had anything to do with extra-terrestrial intelligence.

as Joan Oró, who will be discussed below) in their studies. A large portion of the funding, both in this category and overall, was given to Sidney Fox, a notable figure in Origins-of-Life research.

2.2. Sidney Fox – a commitment to a 'proteins-first' origin of life

Sidney W. Fox was a protein chemist who developed an early interest in the origin of life question, and became a fixture of the field and, for a long period, one of its most active and prominent practitioners. He is credited with popularising the concept of molecular evolution – the idea that evolution did not start at the point when the first reproducing cell was formed at the prior stage of interactions between prebiotic molecules[34]. His actual research, however, went on a different tangent to the mainstream, and his work gradually became marginalised: his focus on protein structures as an early step in Origin-of-Life fitted in neatly with research trends and findings in the late 1940s and early 1950s, but started to run contrary to the theories prevailing from the mid-1950s onwards. His story provides a prime example of an Origin-of-Life researcher's commitment to a particular viewpoint of what life is. Its later chapters also serve to exemplify how being in line with institutional thinking (in this case, NASA's) could help with research funding.

Fox's experiments relating directly to Origin-of-Life began after 1953; he was aware, from the outset, of the role of nucleic acids in heredity. His experimental results were initially promising: he observed the spontaneous polymerisation of amino acids, which he named proteinoids, under dry, heated conditions.

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[34] Molecular evolution was by no means a new idea; as we have seen, Oparin, of whom Fox was an admirer and whose work Fox saw himself as continuing, had advanced the notion long before. However, Fox was relentless in its advocacy, and was selected in 1997 to speak before the pope on the subject of evolution and the origin of life.

Fox's work in the 1940s (Fox et al., 1995) focussed on the development of amino acid sequencing analytical methods (until the superior Sanger method was developed in 1951). Through analysing the amino acid polymers that they had fortuitously developed and spotted in early experiments, Fox and his colleagues came to realise that the sequences were non-random – the amino acid composition of these polymers was not divided equally among all amino acid types. A further experimental result, announced in 1959, was the spontaneous formation, under hot, aqueous conditions[35], of amino acid polymers into globular bodies (which Fox referred to as microspheres). Much like Oparin's coacervate droplets and Herrera's sulphobes, microspheres looked strikingly life-like, and exhibited strikingly life-like properties, including division[36] (Fox, 1965).

These findings (as well as his 1969 analysis of moon rocks brought back from Apollo missions that found evidence for amino acids[37]) formed the foundation of Fox's scientific and philosophical

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[35] The differences between the conditions that enable one step in a proposed spontaneous synthetic chemical reaction and the conditions that enable the next step of that reaction (in this case, the difference between the dry conditions required for proteinoid formation and the aqueous conditions required for microsphere assembly) have been a major source of criticism for many Origin-of-Life theories. Various explanations and workarounds have been suggested for these problems, but the issue remains one of the weak points of most if not all proposed Origin-of-Life scenarios.

[36] In a biographical article, Sidney Fox's son, now a retired physicist interested in Origin-of-Life research, writes:

Unless one has looked at microspheres under the microscope there is no other way to convey in mere words some of the attractiveness of this model...It is possible to watch Brownian motion vigorously animate the spheres in a way not easily distinguished from looking at some types of live bacteria...Using a thermally controlled microscope stage, it is possible to observe microsphere formation as the boiled aqueous solution cools. Once a sphere has nucleated, subsequent sphere formations can be buds or even divisions. De novo generation of spheres also continues.... The division was assisted by the Brownian motion, at the end of which two daughter spheres would go off at random from each other. It is unexplained why the population of spheres is so uniform in diameter, in contrast to preparations of lipid bilayer membranes. (Fox, 2008)

[37] Fox's group's findings were contested by other groups within NASA, who identified the results as contamination from terrestrial sources. This criticism was dominant in the communications to the 'outside' - the scientific community external to the NASA groups set to work on the analysis, and the general public (Strick 2004).

conviction[38]: for him, life was an emergent property of the physical world, and was concentrated on proteins, their properties and functions. The physico-chemical laws of the universe dictate the formation of molecules from atoms, and also the formation of increasingly complex chemical entities up to the formation of living cells – and the first cells were protein structures. The external membranes were proteinaceous, and were later gradually replaced by phospholipid moieties. Fox pointed out that protein molecules are still the ones regulating the transfer of matter in and out of "modern" cells, an ability that lipids lack. In the same vein, the first cells were "non-templated" (Fox, 1988), and nucleic acid templates were likewise a late development on the protocellular scene.

This approach sharply contrasted with the work and views of prominent researchers from the 1960s onwards; for Fox, he was an upholder of a tradition of thought and theory running from Darwin to Oparin– and including Einstein (Fox, 1988).

The root of the problem, for Fox, was the introduction of the conception of randomness to natural law with the advent of Quantum physics in the early decades of the 20th century. The influx of physicists into the biological sciences introduced these ideas into the field – and, as an offshoot, theories of the origin of life advancing the element of randomness and the chance appearance of the first replicating entities. Fox, a chemist dedicated to the chemical (and biochemical) tradition, was vocally opposed to the physics-influenced 'molecular' tradition that was rapidly developing around him throughout his career.

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[38] Fox himself would most likely not agree with having any philosophical conceptions influencing his views. He insisted from the outset that his thinking was based solely on the empirical results – for instance, when describing his rationale for the protein-first scenario, he insists that "this reasoning occurred after the creative act in the laboratory, not before it." (Fox, 1988, p.33, italics in the original).

This view, and the strength with which he asserted it, made him unpopular amongst his fellow researchers[39]. Furthermore, his experimental results were difficult to replicate, and did not yield results that his most of his contemporaries found interesting enough to follow up on. Nevertheless, his personality and organisational skills kept him a force to be reckoned with in the Origins-of-Life community, and from the 1960s onwards he founded and ran a large and active research group, first as the director of the Oceanographic Institute at Florida State University, then at the University of Miami, Illinois University, and finally, in the concluding chapter of a research career spanning six decades, at the University of South Alabama.

Compensating somewhat for his relative lack of popularity amongst his peers was Fox's competence at representing his research to administrators. This ability stood him in good stead at NASA, from which he would receive substantial amounts throughout the years. This was especially apparent in the first years of the institute of life sciences within NASA, beginning in 1960; when the grants awarded to different Fox projects amounted to a large proportion of the total (at the time, rather generous) allocation of funds to scientific projects.

This is not to imply that there is anything untoward about the interaction of Fox and NASA bureaucracy; his ideas and results were not only promising, but they also were very attractive to NASA's institutional thinking. A deterministic view of the development of life would have given NASA a strong philosophical basis for its efforts to locate extra-terrestrial life or evidence thereof, and Fox's research program provided an initially clear path for NASA extra-terrestrial life-identification efforts to

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[39] For instance, several prominent Origin-of-Life scientists, including Stanley Miller and Norman Horowitz, were conspicuously absent from the second international conference on the Origin of Life, which he organised, held in 1963 at the University of Florida.

follow – a proteins-first model of Origin-of-Life points immediately to further experiments that could be attempted. Moreover, among the different classes of biomolecules, amino acids are technically relatively easy to identify and analyse.

In his later years, Fox went so far as to claim that the problem of the Origins-of-Life was not only solvable, but was now in essence already solved (with his work a significant element in that solution); the crucial steps leading from inanimate matter to living cells had been empirically demonstrated, leaving only the secondary details to be elucidated, and the evolutionary pathway from the original, proteinaceous, cell to current cells, encased in lipid and replicating using nucleic acids. In the final chapter of his review of his view of the origin of life, The Emergence of Life, (Fox, 1988), Fox went on to present his own 'grand theory', by comparing his microspheres to neuron cells (Fox et al., 1995), and attempting to make a (tenuously argued) case for the microspheres exhibiting consciousness, making life synonymous with mind (see also Shapiro 1982 p.203).

These later efforts and attitudes could be dismissively viewed as indicative of Fox's capacity for forming grand theories of everything, a not unheard-of affliction in scientists of his advanced age at the time[40]. This, however, does not do justice to the life-work of a scientist, who, whatever the worth of his specific research program turned out to be (or will turn out to be in the future), was prominent as an early and vocal proponent of the Origin-of-Life as an empirical question; as a mentor under

[40] Fox's son writes:

When Sid had the bypass surgery [in 1989] he did not awaken from the anesthesia after the operation. For 13 weeks he remained in a coma ...Sid woke up and, to everyone's surprise, seemed mentally unimpaired. However, there were initially unappreciated subtle side effects, including increased irascibility and bouts of irrationality. These effects were manifested at scientific meetings, so I am told by friends who were attendees. I experienced it first hand on several occasions and toward the end of his life, Sid openly expressed the desire to disown me because I would not accept that he had already solved the problem of the origins of life." (Fox, 2008).

whose tutelage passed many young researchers, some of whom would later be prominent in Origins-of-Life research – at least one of whom went on to criticise Fox's approach quite harshly (Day, 1979) – and as a crucial persona in the 'synthetic' (as contrasted with reductionist) tradition in Origins-of-Life research. In 1988, repeating much earlier sentiments, Fox wrote of:

...the dominant tendency of scientists to be reductionistic even when it is clearly shown that evolution itself moves in a constructionistic direction – that is, involves synthesis plus assembly. (Fox, 1988)

This aspect of Fox's contention with the physico-stochastic-reductionistic-molecular school of thought has now found its place within the mainstream of Origin of Life research programs. In his day, he was essentially alone in his view that the retracing of the evolutionary pathway – the synthesis of a cell from the 'bottom up', from inorganic molecules to living entities – was a viable goal of contemporary science. In that respect also his work might be viewed as a continuation of Oparin's: their specific theories regarding the Origins of Life were apparently off-track, but their vocal enthusiasm, staying power and political influence did contribute to thought and experimentation in the field.

2.3. Oró and Kimball – nucleic acid synthesis

It would have been a perfect triumph for science had the 1953 Miller-Urey experiment been synchronised with the Watson-Crick findings not only in its publication time, but also in terms of the results obtained – had Miller and Urey announced that an abundance of nucleic acid been found in the prebiotic sludge. Alas, no nucleic acids appeared in Miller's apparatus.

As the 1950s progressed, and the genetic role of DNA became increasingly more substantiated and reliable, its effect on the question of the origin of life became more pressing. If nucleic acids could be shown to have formed spontaneously under prebiotic conditions, and to organise into gene-like compositions, then the 'genes-first' theory of the origin of life would be all but proven.

In 1960, Joan Oró of the University of Huston showed that the oligomerisation of the simple gas hydrogencyanate (HCN) can produce the nucleic acid purine base Adenine. Oró had used, unchanged, a Miller-type experimental setup that he previously put together to study the synthesis of amino acids "under suggested primitive earth conditions" (that is, a reducing environment), (Michael, 1960)[41]. This result was followed by further experiments explicating the chemical steps involved in

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[41] In a 1976 paper, Oró describes the experiment by which he originally detected adenine in a prebiotic-type reaction: HCN was bubbled through an aqueous solution of NH_4OH, refluxed, and the supernatant spotted on filter paper for chromatography. Treatment with a specific reagent for adenine (a Gerlach-Döring test) gave a faint result which he did not pay attention to and considered an artefact, especially since finding evidence of amino acid formation (by spraying the chromatogram with ninhydrin solution) excited him and diverted him from pursuing the adenine result. After the amino acid work was completed he resumed his search for adenine, performed the same experiment with a more concentrated solution, and analysed the chromatogram by UV light (as well as by spraying

adenine synthesis, and synthesis of other purines (Oró and Kimball, 1962, Oró and Kimball, 1961, Basile et al., 1984)[42].

Since adenine is an essential building block of nucleic acids and of the most important coenzymes, and since hydrogen cyanide, ammonia and water are common natural constituents of the solar system, these experiments are considered of significance in relation to the problem of the origin of life. In particular, the experiments provide the first demonstration of the spontaneous synthesis of adenine from simple compounds of carbon and nitrogen under conditions presumed to have existed on the primitive earth.(Oró and Kimball, 1961)

The synthesis, under roughly similar prebiotic conditions and following similar experimental techniques, of the more chemically complex bases known as pyrimidines (cytosine and guanine) was also demonstrated by Leslie Orgel and co-workers (Sanchez et al., 1966, Ferris et al., 1968).

These results gave Origin-of-Life researchers and theorists the great hope that the elucidation of the secret of life, unfolding as it was within laboratories around the world, would be coupled with the elucidation of the secret of life's origin. For example: in their 1968 paper, Orgel et al. referred to the similarities in the conditions and chemical precursors required for purine, pyrimidine and amino acid formation:

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with a specific reagent for amino imidazoles), and got very positive results, suggesting the synthesis of adenine, as well as the necessary intermediates for purines, in the reaction products. (Oró 1976).

[42]Oró and Kimball's 1961-2 experiments were funded by the NSF; later in the 1960s he joined NASA to work on the Viking missions, designing experiments that could be performed for the analysis of soil specimens collected by the Viking vehicle, and on analysis of moon rocks.

We believe it to be highly suggestive that such a wide variety of prebiotic syntheses can be brought about with a small family of molecules related both in their structure and their modes of prebiotic synthesis. (Ferris et al., 1968)

Indeed, for anyone experiencing the rapid progress made in the new 'molecular' sciences, the leaps in knowledge and understanding made in such a short time, such a hope was reasonable. DNA was established as the stuff of genes – and as we have seen, the idea that the formation of genes was the first step in the formation of life had already been formulated decades ago, in the days of Troland and, later, Muller. If only some more elaborate Miller-Urey/Oró-Kimball-type experiments could show the formation of a rudimentary form of gene, then the most extreme version of the 'replicator-first' approach, the one now known as the 'naked gene' hypothesis, could be seriously considered.

The idea of an independent nucleic acid polymer being serendipitously created from free nucleic acids (or their chemical precursors) in a prebiotic environment, then going forth to create more of its kind – this elegant picture of the beginning of life is to a large extent still present, even predominant, in many scientific and popular accounts of Origin-of-Life. In the early 1960s it fitted in very well with the excitement enveloping the molecular advances in biology.

Alas, again, the promise of the initial Oró-Kimball experiments failed to provide quick results. Whereas the study of nucleic acid function in the living cell was advancing increasingly more quickly in the early 1960s, the study of the prebiotic origin of nucleic acids, nucleotides and their polymeric structures at that period had mostly bogged down. Purines and pyrimidines may have been shown to appear in inorganic mixtures, but the prebiotic conditions necessary for the creation of full nucleotide

polymers, composed of the base and sugar-phosphate chains, in sufficient quantity and with sufficient

stability for any meaningful biological-like function , were found to be highly restricted (Orgel, 2000).

If Fox had argued with limited success for the idea of amino acids forming spontaneously and

self-organising into proto-biological bodies, the evidence available from the empirical studies made it

far harder to argue for a similar scenario for nucleic acids – that of nucleic acids forming spontaneously

into rudimentary genes.

It should also be noted here that Oró was also the first to hypothesise that comets could carry

organic molecules to earth (Oró 1961), an idea I will discuss in more detail in section 4.6.

2.4. Molecular Biology: Knowledge, Tools and Techniques

As we have seen in earlier stages of the Origin-of-Life question, and applicable to much of

science, an advance in technique, knowledge and understanding of the system under examination

necessarily brings with it the accompanying problem of explaining the phenomena and mechanisms

that have been unearthed.

A few short centuries prior, the idea that entire organisms could spontaneously form was

taken as reasonable; in the late 19th century, the organism was seen as obviously too complex to form

just like that, but the living cell was proposed to be composed of more or less homogenous

protoplasm. Later on, that too proved simplistic, and the biochemists had the job of explaining the

function of the cell as relates to its component molecules. The molecular revolution was in the process

of resolving many of the mysteries enveloping cellular and genetic mechanisms, but the levels of

complexity that were exposed piled numerous additional explanatory problems on Origin-of-Life

research.

There was no a priori reason to expect that the basic processes of the transfer of genetic

information and regulation of cellular activity must necessarily be so intricate, and that they should

involve several disparate classes of biomolecules. However, this was found to be so; furthermore it

was found to hold true for all classes of living organisms[43].

There is no existing 'Ur-example' of a simpler mechanism operating in a living thing, and any

Origin-of-Life theory, in order to be considered comprehensive, was now required to explain the

development of the entire natural contrivance – DNA replication, messenger RNA, transfer RNA, the

ribosome, etc.

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[43] The very simplest of living or quasi-living systems are viruses and prions. The role of viruses in Origin-of-Life theory and experiment has been well reviewed by Podolsky (Podolsky 1996). Prions, whose existence was hypothesised in the 1960s, but actually discovered only in 1982, are small protein molecules that constitute a misfolded form of a specific protein inside a living tissue. A prion molecule has the ability to attach to an existing, properly folded protein molecule, and convert it into a copy of itself, using itself as a template, and thus achieving a form of self-replication with no use of any DNA, RNA or other genetic, "informational" molecule. Prions are, as far as we presently know, strictly parasitical forms, and no "free-living" forms have been detected outside host organisms. The existence of prions constitutes a partial proof-of-principle for the "protein-first" approach to Origin-of-Life, and thus generates some attention from supporters of this approach, but as prions are found only in environments that already contain large concentrations of their templates, there has been little consideration of the prion as a candidate for Origin-of-Life research - I have been able to find only a single, highly speculative, article on the subject (Lupi, 2006)

2.5. RNA, the first 'RNA World' hypotheses, and 'evolution in a test tube'

The existence of RNA had been known for several decades prior to the 1950s, and indications of its connection to the cell's growth process had been noted in the 1930s, but little was understood of the processes involved, and the role of RNA was especially unclear (Judson 1979). In contrast with DNA, the (then unknown) multiple roles and types of RNA in the living cell meant that quantitative analyses of cellular RNA produced confusing results. Complicating matters was the fact that due to their generally shorter and normally single-stranded structure, RNA molecules are notoriously prone to damage in experimental conditions, especially degradation through accidental contamination with RNAses (RNA-degrading enzymes) which are ubiquitous in the environment, and special procedures are required to work with RNA, making any research involving RNA a difficult task to this day (Nielsen, 2011).

In the mid-1950s, following the unmasking of DNA's role in the living cell, the obvious next puzzle was how genes facilitate and control the production of proteins. RNA was one of the prime contenders, and much effort was made to try and work out its role (Judson, 1979). Sol Spiegelman, who had been interested in protein synthesis and regulation since pre-Beadle and Tatum days, focussed his efforts on studying nucleic acid synthesis in bacterial and yeast cells and later, viruses.

By 1958 Arthur Kornberg had isolated DNA Polymerase, the enzyme facilitating DNA replication, and Spiegelman, following Kornberg's lead, succeeded in finding a DNA-dependent RNA Polymerase (Spiegelman, 1958). In 1965, Spiegelman's lab produced a DNA:RNA hybridisation technique (Gillespie and Spiegelman, 1965); Fred Sanger introduced his gene sequencing method,

utilising radioisotope radiolabelling and separation polyacrylamide gel electrophoresis, that year (Sanger, 1965). All these interrelated developments gave researchers the ability to address the fine structure and composition (and, consequently, sequence) of RNA molecules, rather than merely identifying RNA in a chemical solution.

The discovery of the role of DNA in heredity immediately gave rise to thoughts about a possible 'DNA World', giving substance to the 'naked gene' theories of Troland and Muller. In this scenario, DNA was the original replicating molecule formed from prebiotic molecules. However, as the modus operandi of DNA was being elucidated in the 1950s-1960s, the notion of an active DNA molecule operating alone in a pre-biological setting was widely discredited, and no serious DNA World hypothesis has been advanced since.

With the understanding of RNA's multiple forms, cellular roles and abilities, and with its position as an intermediate link between the core genetic material in DNA and its expression in the functional cellular machinery of proteins, it became more readily apparent that RNA might prove a likely candidate for the job of the original 'naked gene'. 1967-8 saw the first theoretical formulations of pre-DNA worlds.

The idea of an "RNA World" (the phrase was first used by Gilbert, in 1986) was first suggested by Rich in 1962 (Rich, 1962) but a serious proposal was first provided in those years by Carl Woese (Woese, 1967) and independently, in two back-to-back papers, by Crick (Crick, 1968) and Orgel (Orgel, 1968) (see chapter3 for an extension of the RNA World discussion). The suggestions postulated, as an all-important component, a catalytic role for RNA: in order for the 'RNA World' to be feasible, RNA molecules must have the potential capability to cleave organic molecules (including RNA itself). Such a

role was not known at the time (Miller, 1974); the discovery that RNA molecules can indeed manifest that capability lay more than a decade in the future.

These suggestions, made by prominent figures in the field, present two intriguing questions: why did they appear when they did (the appearance of three almost simultaneous theories strongly suggests that this can hardly be attributed to chance alone)? And why were they not followed up?

To answer the first question, we turn to the state of the knowledge and technique that was newly available: as we have seen in the previous section, it was only at that point in the mid-1960s that effective tools for studying specific RNA composition were available.

In a striking demonstration of the possibilities of the new power of nucleic acid analysis tools, and of importance not only to evolutionary studies but also to Origin-of-Life research in general and the role of nucleic acids in particular, in 1967 Spiegelman and colleagues produced the well-known series of experiments where Qβ viruses were subjected to "evolution in a test tube" (Mills, 1967). The RNA viruses were placed in a test tube containing no cells, but only a rich environment containing raw materials necessary for replication, as well as RNA Polymerase, and allowed (by a succession of transfers to new test tube 'environments') to multiply without restriction of any sort excepting the inherent rate of the transcription process. As a result, the Qβ RNA was shown, by an analysis of the resulting sequences, to shrink progressively in length, until it had been reduced to a fraction of its original length.

Although it was not by any means intended as a demonstration of a possible Origin-of-Life scenario (the presence of the polymerase and the precursor-rich environment ruled that out), the

Spiegelman experiments gave Origin-of-Life research a strong, if somewhat tantalising, demonstration of what a 'replicator-first' scenario might look like.

In a further development, Orgel's group demonstrated the possibility of non-enzymatic polymerisation of nucleotides on the surface of minerals (Sulston, 1968). Although extremely inefficient relative to enzymatic replication, this result made speculations about a nucleic-acid world a little more plausible – and paved the way for Woese's, Crick's and Orgel's suggestions.

Now to the second question – why were the theoretical suggestions not followed up? In retrospect, it is not too difficult to conceive of a Spiegelman-type experiment selecting for catalytic abilities of an RNA molecule[44]. The excellent experimental competencies of all three researchers cannot be disputed; we also cannot, due to their respective high profiles in the field and the prominent publications their suggestions appeared in, claim that these suggestions could have 'flown under the radar' of the scientific community at large.

Since lack of competence or lack of awareness are therefore ruled out, we might therefore attribute the lack of results to either lack of will, lack of success, or lack of possibility. I suggest that the third option is the correct one: at the time, there was no real way to perform those kinds of experiments. For a reasonably robust RNA Life theory to be presented, it had to be shown that RNA can take the role of protein enzymes and exhibit catalytic abilities. In order to do that, catalytic RNA molecules had to either be synthesised artificially, or to be discovered already in operation in nature. RNA technology of the late 1960s allowed for laborious analysis and basic manipulation of the

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[44] Indeed, many such experiments have since been performed (cf. Bartel and Szostak, 1993).

molecules, but the idea of a purposefully-designed RNA molecule was beyond the contemporary state of the field.

Here is Francis Crick remarking on nucleic acid synthesis in a series of lectures delivered in 1966 and subsequently collected in a book:

At the moment it is not very easy, for technical chemical reasons, to synthesize a piece of nucleic acid with a defined sequence of bases... it appears only a matter of time before we can synthesize sequences of reasonable length...whereas in principle we can conceive synthesizing a defined sequence of, say, six thousand nucleotides to make up a piece of virus nucleic acid, in practice the yields are likely to be rather low. Even if we get a 99-per-cent yield at every step, by the time we have   carried out six thousand successive steps the amount of finished material will be very small indeed compared with our starting material. We shall often find for biological objects that it is theoretically possible to synthesize a particular molecule, but because of its very large size it may be almost impossible to do this in practice without taking an enormous amount of time and huge quantities of raw material.(Crick, 1966)

In addition to the technical difficulty, I suspect that the formidable challenge posed by an experiment requiring artificial nucleic acid synthesis was exacerbated by the fact that until the 1982 discovery of ribozymes, there was no 'proof of concept' to draw on, no natural model to guide the researchers.

2.6. Mycoplasma and the first steps in the 'minimal cell' concept.

During the 1960s, Harold J. Morowitz, a Yale researcher, was studying a family of microorganisms named PPLOs (for "pleuropneumonia-like organisms"), later to be renamed Mycoplasma. The genus Mycoplasma, belonging to the class Mollicutes, are parasitic bacteria found in a large number of host species, including humans (Razin, 1998). Apart from interest in them as pathogens and as pervasive contaminants of cell cultures, Mycoplasma are known to be the smallest (both in cell size and genome size) self-replicating organisms; the cell size of the smallest ones may be one-tenth the size of an E.coli cell. Indeed, their ability to pass through bacterial filters caused some initial confusion as to whether they were viruses, bacteria, or an intermediate type of organism (Morowitz, 1962).

Mycoplasma were initially thought of as a possible type of microbial 'living fossil' – contemporary organisms with a simple, primitive, genetic complement, that could perhaps be indicative of the genetic (and possibly biochemical) makeup of bacterial precursors. Today this is considered wrong; comparative genomic studies clarify that the ancestors of Mycoplasma were larger, 'regular'-sized bacteria, and that Mycoplasma had devolved from those; 'unnecessary' genes were gradually deleted as these microorganisms became increasingly less independent and more reliant on their hosts' metabolism for some key biochemical functions.

Morowitz was interested in Mycoplasma's ability to live and reproduce at such a small scale, and was studying them in an attempt to find the simplest, most fundamental requirements for life – the minimal cell concept, as it became known. From 1961 to 1992 he would receive funding from the NASA exobiology program for his project (Strick, 2004b).

In a 1998 review article of Mycoplasma biology, Shmuel Razin recalled:

[I]n 1962 Morowitz and Tourtellotte published an article in Scientific American on mycoplasmas as the smallest living cells [Morowitz 1962] and organized, with the support of the National Aeronautics and Space Administration, the first meeting on the molecular biology of mycoplasmas. We were then enchanted by the 'crazy' idea of assembling a living cell from its components. It should be recalled that these were the 1960s, a period of revolutionary ideas including the trip to the Moon. (Razin, 1998)

This preliminary idea was not taken further at the time, but research on Mycoplasma as the closest natural entities to the ideal of the minimal cell (though no longer to the 'primordial cell' or the Last Universal Common Ancestor) continues to this day, and has since seen some interesting developments, which we will discuss in a later chapter. In addition, Morowitz made a significant contribution to the development of the 'metabolism-first' approach in Origin-of-Life studies; coming as he did from the field of biophysics, he was primarily concerned with the functioning cell and its metabolic activities[45], and has attempted to theoretically reconstruct the metabolic pathways of the

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[45] Morowitz's maxim "metabolism recapitulates biogenesis" is intentionally reminiscent of Häeckel's famous phrase. It signifies Morowitz's 'membranes first' notion– that virtually all processes of metabolism, interactions between nucleic acids and proteins etc. - developed only after their inclusion within membranes (Margulis and Sagan 1995, p.66).

universal last common ancestor by comparing the biochemical processes of extant living things from

diverse branches of the tree of life. He argues for the primacy of a membrane-enclosed vesicle over

the 'genes-first' theories, and his ideas have had a significant influence on later thinkers such as Stuart

Kauffman. I will discuss these ideas further in section 4.5.a.

2.7. Meteorites

Origin-of-Life research has always had a particular interest in the contents of meteorites landing on earth. Meteorites are samples of extraterrestrial matter, and thus provide hints to the composition of the universe outside the earth. These hints have, several times, led researchers to arrive at conclusions regarding the origin of life on earth and the possibility of extraterrestrial life. It is instructive to compare how meteorites that landed at different points in recent history were studied. We will see how technology enables and directs the research.

2.7.a. The Murchison meteorite

In September 1969, a meteorite was spotted landing near the rural town of Murchison, in Victoria, Australia. It garners a mention in a majority of accounts of Origin-of-Life research, due to the fact that, on analysis of its composition, it was found to contain over 100 amino acids[46] (Kvenvolden et al., 1970). The timing was on one hand (as is often pointed out) fortuitous for Origins-of-Life research in general and NASA in particular: just as humanity was on the verge of its first serious attempt to search for signs of extra-terrestrial life, it received for the first time a strong indication that at least some elementary biomolecules were indeed to be found outside the earth.

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[46] Recent analysis has also found the Murchison meteorite to contain nucleobases of "confirmed extra-terrestrial origin", as determined by carbon isotope measurements (Martins 2008), as well as amphiphilic molecules, discussed in chapter 4.

I maintain that, although the landing of the meteorite was indeed nicely timed, the fact that it provided the evidence that it did was less surprising: for the first time in history, the requisite technology and technical proficiency were in place. First, the detection of amino acids was possible; in addition, the scientific workers who made the initial discovery and handling of the Murchison meteorite were aware of the possibility of something organically interesting to be found within the meteorite, and were thus careful with it.

Most importantly, the first 'meteorite clean lab' dedicated to analysing moon rocks brought back from space, was available at NASA's Johnston Space Center in Houston, Texas (Strick and Dick 2004). Before this lab existed, any claim of detection of unusual material in a meteorite sample could be (and indeed was) countered by accusations of terrestrial contamination. For a strong claim of extra-terrestrial origin to be put forth, such a specialised facility had to be built first, and the reason for building it was that NASA was preparing to search for just such artefacts – on space missions.

2.7.b. Earlier meteorites

It is instructive to compare the Murchison event to earlier episodes: scientists had been searching for organic molecules and other evidence of life in meteorites for many decades, even before the question of the origin of the meteorites themselves had been settled. The earliest instance of this was no less than the eminent chemist Jöns Jakob Berzelius, who examined samples of the Alais meteorite, and reported in 1833 to have found indications of organic matter (though the report was rather equivocal about this) (Burke 1986).

Berzelius was followed by quite a few others in the 1860s and 1870s (cf. Wöhler, 1859) who found strong evidence for the presence of hydrocarbons in meteor samples. The question of whether

the origin of this organic matter was biological could not be answered with any degree of confidence, and scientific heavyweights Sir William Thompson and Hermann von Helmholtz, who were both in favour of the "biogenic" interpretation, advanced hypotheses of meteor-borne germ life, which sparked a lively debate involving the origin of meteorites, comparisons of meteorites with coal and petroleum, intellectual convictions regarding the origin of life, Darwinism and germ theory (Burke 1986). A German lawyer named Otto Hahn even claimed in the late 1870s to have discovered fossils of organisms in meteorite samples. He was given short shrift by experts, but received a kinder treatment from the popular press.

Some decades later, in the early 1930s, respected bacteriologist Charles Lipman of UC Berkeley claimed to have isolated living bacteria from meteorite samples, setting off another round of popular speculation (the New York Times proclaiming "life in meteors") and a brief and inconclusive professional debate (Burke, 1986, Oparin, 1957)[47].

But perhaps the most telling case was the debate arising from the Orgueil meteorite. It landed (in several separate fragments) in 1864 in western France, but the debate arose nearly a century later, just a few years before the landing of the Murchison meteorite: although the, after its initial examination the meteorite fragments were consigned to museums, and:

…study of the organic matter in the extraterrestrial rocks was largely forgotten by the scientific community until the middle of the twentieth century when the question was reopened by Mueller (1953) in connection with his interests in primordial carbon on the surface of the Earth. This revival of

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[47] Oparin relates that in a letter Lipman sent him, he "did not insist that his results were completely unequivocal" (Oparin 1957, p.56).

interest in a long forgotten carbonaceous meteorite came at a time when analytical methods were reaching a new level of sophistication with greatly increased ability to resolve mixtures and with greatly increased levels of sensitivity. The principal new analytical approaches had been developed in the petroleum industry and depended heavily upon chromatographic procedures (largely gas chromatography) and mass spectrometry. The analysts involved in the work were acutely aware of the role played by organisms in the genesis of petroleum and were very sensitive to the fossil biochemical compounds(Baker, 1971)

The 1953 Mueller article referenced in this passage argued that the organic matter found in the meteorite were not of biological origin:

It is often implied in popular works that the presence of organic substances in meteorites would indicate the existence of life on the celestial body of their origin. However, the extracts from the Cold Bokevelt meteorite proved to have no measurable optical rotation, and this fact must be held to indicate a non-biological origin. The earth's biologically formed carbonaceous minerals, such as oils, or retorting products of coals, etc., invariably show optical rotation. In the light of modern organic chemical experience, there seems to be no great difficulty in accounting for a non-biological origin of the organic substances.(Mueller, 1953)

However, in 1961 Nagy and co-workers reported evidence – obtained by mass spectrometry, a technique whose application to organic molecules was developed in 1956 (Beynon, 1956) and was therefore not available to Mueller in 1953 – of biogenic hydrocarbons in samples taken from the meteor. Furthermore, they claimed they found what they called 'organized elements': microscopic

particles whose formation was suggestive of the presence of organic molecules, and also permitted some speculation about their constituting evidence of compartmentalised life forms (Nagy, 1961).

In a repetition of previous cycles of interest in the 'meteors and life' connection, this finding sparked some interest in the matter: a 1962 issue of Nature included another Nagy article on the subject (Nagy, 1962), and a critical assessment of the Nagy results (Fitch, 1962). As well, other, similar, findings in samples taken from other meteorites were reported (Briggs, 1962), and contributions from Harold Urey and J.D. Bernal argued that these structures may lend weight to a panspermic origin of life (Urey, 1962, Bernal, 1962). Mueller weighted in later that year to reiterate his original opinion that the molecules were not of biogenic origin (Mueller, 1962). Sidney Fox, unsurprisingly, saw these elements as naturally-produced formations resembling (and thus lending validity to) his laboratory-produced proteinoid microsphere structures we discussed above (Fox, 1964).

The nature of the early-1960s debate, in short, was not very different from the ones that took place fifty or a hundred years previously. And yet, the Murchison analyses coming less than a decade later encountered virtually no such challenges; the force of the new analytical tools that were developed in the interim was such that there was very little that could be contested. The Murchison meteorite was newly landed and carefully collected, so contamination issues (both at the landing site and at storage sites) were reduced to a minimum; the analytical methods that were available were providing much more conclusive results; and most significantly, there was a specialised facility, built

for this exact purpose, at hand, by an institution whose dedicated purpose was this avenue of research[48].

2.7.c. The ALH84001 meteorite and 'nanobacteria'

This section would not be complete without a discussion of the ALH84001 meteorite, and the linked topic of nanobacteria. These episodes provide us with a further instance of the role of analytical methods in the Origin-of-Life debate.

The ALH84001 meteorite was found in the Alan Hills region of Antarctica in 1984. Before delving into the specifics of this case, we should remember that NASA's overall position was at that time a far cry from its 1950s-1960s heydays. The cold war had lost much of its early edge, and the space race was no longer seen as a top national priority; the excitement of the first missions and landings was over, and since the financial crisis of 1973, the agency's budget was severely restricted.

The ALH84001 meteorite was recognised as a Martian rock based on a comparison to Martian rocks obtained from Viking expeditions in 1976. It was estimated to be billions of years old, and to have landed in Antarctica about 16 million years ago, the region's climate and environmental conditions having preserved it from degradation.

The meteor did not attract too much attention until 1996, when it was examined by a team of NASA researchers led by David McKay, who claimed to have found 'microfossils' in the inner volume of

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[48] A final note on the Orgueil meteorite would have to be the intriguing suggestion made (though without overmuch conviction) a couple of years later by two of the researchers working on it, that the rock was contaminated with seeds (found in their sample) deliberately; since the meteorite landed shortly after Pasteur's public attack on spontaneous generation, this might have been an attempt to show extra-terrestrial

the rock – microscopic holes whose characteristics had several features pointing towards a biogenic

origin, indicating that microbial life had existed at some point in the history of Mars (McKay et al.,

1996). The holes were of a small diameter, on the very verge of the minimal size of known or

hypothesised microbial life, but they exhibited mineral magnetite formations, similar to terrestrial

mineral magnetite formations of known biogenic origins (they are deposits left by magnetotactic

bacteria, a class of microbes sensitive to magnetic fields, discovered a few short years previously), that

were found in ALH84001.

It should be stressed that the techniques used for examining the ALH84001 meteorite were

advanced microscopic and analytical methods only recently made available. Members of a class of

molecules called polycyclic aromatic hydrocarbons (PAHs) were discovered in the meteorite using

microprobe two-step laser mass spectrometry ($\mu L_2 MS$). Originally developed at Stanford University,

this new analytical method had the advantage of not requiring any sample preparation, which

minimised contamination problems, and was therefore ideal for analysing the meteorite sample

(Clemett, 1996). PAHs are organic molecules; therefore this discovery provided the first indication of

organic material on Mars since the Viking lander experiments (see chapter 3) provided inconclusive

results tending to the negative side. However, as critics were quick to point out, PAHs are ubiquitous

throughout both the terrestrial atmosphere and interstellar environments, and can be the result of

abiotic chemical reactions.

The McKay paper was not easy for the scientific community to process. It presented its case

not as a cohesive argument, but as four separate lines of evidence (morphological similarity to

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spontaneousgeneration; if that was indeed the case, the forgery was a dud, since it was not noticed until a century
later (Anders 1964).

terrestrial microfossils; presence of magnetite and sulphide 'biominerals'; presence of PAHs; presence of reduced carbon), each of whom was indicative of biological activity on Mars in the past, but none strong enough to stand alone. The final paragraph of the paper thus reads:

None of these observations is in itself conclusive for the existence of past life. Although there are alternative explanations for each of these phenomena taken individually, when they are considered collectively, particularly in view of their spatial association, we conclude that they are evidence for primitive life on early Mars. (McKay et al., 1996)

This 'additive' way of presenting a scientific argument raised more than one scientific eyebrow; to compound the problems, the ALH84001 findings were first announced not in the context of the scientific paper, but via a special press conference given nine days prior to its publication. This reversal of the accepted way of announcing findings was not well received by the scientific community at large; the McKay research team was accused of "grandstanding" and letting outside considerations override scientific ones. To a large extent that was true, although the researchers themselves were perhaps less at fault than might be suspected: as figures in the upper echelons of government suddenly and unexpectedly became interested in the findings, the hurried press conference was largely the result of political considerations, both inside and outside NASA (Strick and Dick 2004). Then-head of NASA Dan Goldin saw the "life on Mars" announcement as both a potential embarrassment to the agency's reputation (if the work turned out to be shoddy) and as an opportunity for rekindling interest and underlining the importance of its objectives, in particular future Mars missions. Then-president Bill

Clinton as well as vice-president Al Gore took an interest in the finding[49] (Strick, 2004b). All of this

ensured that the ALH84001 report would be received critically from the start[50].

And indeed, as might be expected of such a revolutionary paper, however carefully worded,

every one of the abovementioned four lines of reasoning, as well as several other weak points in the

paper, drew criticism from experts in the field. The most persuasive objection to the McKay paper

conclusions was to the size of the proposed ancient Martian organisms and the concept of

nanobacteria.

This was a new class of organism, whose relationship with the ALH84001 findings was very close

indeed: The existence and prevalence of nanobacteria have been a much-debated issue both then and

since. Initial reports by Folk in 1992-1993 (Young and Martel, 2010) were the result of the examination

of (terrestrial) geological rock specimens dating back hundreds of millions of years with a Scanning

Electron Microscope (SEM). He found the microfossils and proposed that they might be the remnants

of ancient life forms "nannobacteria" (his preferred spelling, in accordance with geological

conventions). It was the Folk figures who first gave the McKay team its first hint that their structures

may be of biogenic origin. Also in 1993, Olavi Kajander and Neva Çiftçioglu reported finding

nanobacteria in bovine blood serum.

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[49] The hurried press conference was to a large extent the result of the findings being amongst information leaked by a White House political adviser. The "Dick Morris scandal" resulted in copies of the confidential ALH48001 report finding its way to newspapers weeks before publication, and NASA management decided to hold the press conference 8 days earlier rather than let the information continue to circulate without any official response.

[50] It should also be noted that the press conference made much more use of images of formations strikingly similar to terrestrial life forms than did the subsequent paper.

The initial Folk reports were made in specialised geological publications and conferences, and did not arouse much general curiosity; the Kajander paper fared likewise. But the 1996 McKay article made both Folk's and Kajander's reports much more interesting. In 1998 Kajander published a more comprehensive paper regarding nanobacteria in the respected journal *Proceedings of the National Academy of Sciences* (Kajander and Çiftçioglu, 1998). Described as a new type of organism, they are purported to be 10-500 nanometres in size, and exhibiting markedly different properties to established classes of organisms. Nanobacteria are supposed to be independently replicating in a cell-free medium (distinguishing them from viruses), with several types being pathogenic, causing problems in blood and kidney tissues.

Since then, research on nanobacteria has been an active if marginal field, although criticism is widespread: detractors point to the gaping lack of reliable evidence of nanobacteria as recognisable living entities (such as isolation and culturing, DNA evidence[51], etc.) and to the inherent difficulties in the maintenance of biological cellular activities within such a diminutive volume. The critics claim that "nanobacteria" are in fact artefacts of SEM, more readily explained as crystalline growth[52] (Urbano, 2007, Young and Martel, 2010, Martel and Young, 2008), or, in the case of terrestrially-occurring nanoparticles, possibly traces of some other organism's metabolism.

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[51]Kajander and Çiftçioglu reported a DNA sequence for their nanobacteria, but this was later found to be most likely a result of reagent contamination.

[52] The fact that Kajander and Çiftçioglu have started a private company, Nanobac Life Sciences, in 2000, and that much (though not all) of "pro-nanobacterial" research emanates from this company, which sells nanobacteria diagnostic kits, does little to alleviate the scientific community's wariness. Here is Drancourt answering Kajander's claim that nanobacteria require a different approach for detection and study:
My coworkers and I tried to reproduce their technique without success. Since 1998, we have tried to obtain the strain from Kajander. Here we failed to confirm their work. The putative "Nanobacterium" strain is protected and not available, but they sell products to detect nanobacteria...The main problem

Advocates say the new class of organism are not identifiable by standard microbiological or molecular methods, since they constitute a type of life that is significantly divergent in its form and function (Aho, 2003)[53]. Countering the size issue, Çiftçioglu has raised the intriguing possibility that nanobacteria are a highly communal type of life form, with the different individuals joining together in order to perform certain processes. This, however, presently remains a purely hypothetical notion. In more recent years, Kajander et al. have taken to referring to the subjects of their studies as "calcifying nanoparticles", acknowledging the difficulty in labelling the entities as any recognised form of life[54].

Everyone agrees that the McKay findings, whatever they eventually turn out to be, had significant impact: the scientific debate made everyone involved think much more thoroughly about the field, its methods and possibilities. Public and organisational interest in the study of extra-terrestrial life received a significant boost, allowing NASA to carry forth its plan (initially suggested in 1995, before the McKay results were known) for its new Astrobiology program.

Clinical aspects of these miniscule formations (now usually more conservatively referred to as nanoparticles) may well turn out to be important. Additionally, nanobacteria might turn out to be an unconventional type of life form after all – perhaps even a 'living fossil', the long sought-after 'bridging entity' between living and non-living. The fact that no real success has been made in isolating specific

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is that in science, the exact method and the obtained strains should be exchanged to allow other investigators to reproduce and confirm the work. Author's reply, (Aho 2003).

[53] In 1997, a team at the University of Queensland found "nanobes", a distinct type of purported miniscule organism, in sedimentary rock (Uwins 1998). No further reports have been issued since.

[54] Compare: "Prof. Burke did not quite feel like calling things bacteria that were soluble in warm water. Eventually he made a name for the puzzling things, and called them 'radiobes,' which, being partially interpreted, means things produced by the action of radium." (1905).

DNA or RNA sequences from these particles does not, obviously, rule out the possibility of their answering to at least some useful definitions of 'life'.

For now, however, the idea of nanobacteria as organisms, either contemporary or ancient, seems to be following the same trajectory as Nagy's 'organized elements' from the 1960s, Lipman's 1930 findings and Hahn's 1870s organisms: morphological findings in meteorites based on improved microscopy technique are the cause of initial excitement followed by public fanfare, then harsh scientific criticism, and ultimately oblivion.

The McKay team's findings followed the route we have seen previously in claims to findings of remnants of life in meteorites: public attention and even a measure of excitement (this time it stretched to a presidential press conference), and much criticism by the scientific community. The critics pointed out the various weak points in the claim (temperature, the "microfossils" being possible artefacts of microscopy technique, possible non-biogenic origin of the holes in the rock and their chemical characteristics, etc.)

2.7.d. Richard Hoover

Recent claims of evidence for panspermia have come from long-time NASA scientist[55] Richard B. Hoover, who in 2011 published a paper in the *Journal of Cosmology* describing microfossils he has found in Orgueil meteorite samples that correspond closely to terrestrial bacteria (Hoover, 2011).

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[55] Hoover is referred to as an "Astrobiologist" in NASA publications of previous years; after his 2011 paper appeared, commentators within and outside NASA pointed out that being an Astrobiologist does not mean that one is a biologist: Richard Hoover is an engineer at Marshall Space Flight Center, and not a biologist by training. In fact, there are professional microbiologists at Marshal…but I don't believe they were in any way involved with this work. Lynn Rothschild, quoted in (Redfield 2011).

The paper is explicit in its support of an extra-terrestrial origin of life. Current NASA viewpoint is by no means opposed to panspermic theory, but Hoover's claims appear to be too radical for NASA's taste at this time, and NASA officials distanced themselves from Hoover's results, stating:

While we value the free exchange of ideas, data, and information as part of scientific and technical inquiry, NASA cannot stand behind or support a scientific claim unless it has been peer-reviewed or thoroughly examined by other qualified experts(AFP, 2011).

The Journal of Cosmology is an open access, online-only journal founded in 2009, and the Hoover paper triggered a controversy over this paper in particular and over the journal in general which is still ongoing at the time of writing: the journal's editors defend it as a bold publication, upholding the true spirit of science and of pioneering scientists of the past, in the face of institutional adversary; its many detractors denounce it as a pseudo-scientific publication led by a small fringe group who are obsessed with the idea of panspermia to the exclusion of scientific integrity and sense. Allegations and accusations are flying fast and furious.

Beyond the particulars of the case (which touches on broad themes and questions of the peer-review system in the digital age and scientific discourse, among other things) it is interesting to observe that NASA, which has repeatedly had to defend itself from accusations of over-enthusiasm and willingness to go down radical pathways levelled at it by the scientific community and the public, now had to face vocal criticism accusing it as being too conservative, a part of the faceless bureaucracy stomping down on free thought. This demonstrates the problematic situation of NASA, whose objectives as a government agency necessitate a balance between serious scientific credibility and far-reaching notions.

2.8. Conclusions

In a biographical note (Fox, 1972), Joan Oró recalls that when he first started to experiment at Origin-of-Life, he had no idea that others, past and present, were working in the field. This state of affairs was over; the 1960s saw Origin-of-Life research established as a coherent research discipline. Although it was still highly interdisciplinary, it was now a scientific community with its own conferences and peer-reviewed journal, and the appearance of NASA as a major funding body meant that Origin-of-Life researchers no longer had to resort to channelling funds and equipment from their 'proper' experiments in order to work on Origin-of-Life, as Stanley Miller had for his 1953 experiment (Lazcano and Bada, 2003).

The period was by and large optimistic; research seemed to be heading vigorously in the right directions towards an answer to the Origin-of-Life question. The problem, in retrospect, was that while the answers were being puzzled out, the question itself was getting more detailed – and at a more rapid pace. The staggering advances in molecular biology, and the progressively more dominant voice of molecular biologists, meant that the biochemically-oriented studies in Origin-of-Life were lagging in their attempt to explain the beginnings of life on earth. Here is Crick in 1966 again:

...the origin of life, an event that took place a very long time ago and about which at the moment it is not very easy to say very much of scientific value (p.17).

...The present state of this subject is moderately encouraging. Chemists can already explain how many of the similar organic molecules that would be needed – the amino acids, the sugars, the bases, and so forth – could have come into existence by a variety of plausible mechanisms. It seems

likely that before long we shall be able to explain the origin of the simpler molecules making up the soup. It is not yet clear how the slightly more complicated activated forms of these molecules were made, but this again is a problem that chemists will be considering in the next few years, and we may hope that a number of interesting possibilities will be discovered by doing model experiments in the laboratory.(Crick 1966)

As we surveyed the 1960s Origin-of-Life developments (and later developments in RNA research and in meteorite analysis) we saw several instances of the remarkable effect of technological advance on Origin-of-Life study. The improved tools allowed researchers to find types of evidence that could not have been searched for without it (as in the case of the Murchison meteorite and of ALH84001).

We also saw how theory relates to experimental capabilities: initial 'RNA world' thinking emerged immediately after discoveries in RNA suggested the theoretical possibility. Then it stopped, because the technology wasn't ripe for experimentation. In the next chapter we shall see how RNA world thinking was allowed to mature.

McKay's ALH84001 SEM findings also provide us with a demonstration the role of microbiological discovery in informing Origin-of-Life (and in this case, exobiology) theorising: had McKay never heard of nanobacteria, it is most likely he would have thought the meteorite's 'microfossils' a purely physical phenomenon rather than evidence of biological activity. The fact that nanobacteria most likely do not exist at all, only demonstrates just how eagerly microbiological discoveries are used for theorising in Origin-of-Life and exobiology.

Chapter 3:1968-1976: The Viking mission, Extremophiles, and Extinct Worlds.

3.1. NASA in the 1970s and the Viking mission

3.1.a. The Viking mission objectives and general outcomes

The Viking missions, their planning and outcome, formed a large part of NASA's activity during the 1970s. They were also a major influence on Origin-of Life research of that period.

Viking was NASA's Mars planetary mission, a continuation of the 1960s Mariner flyby missions. Its planning stages began in late 1968, and the mission was executed in 1975-1976. Viking's primary focus was the search for evidence of life on Mars. The spacecraft consisted of two landers and two orbiters which were constructed to provide data about the planet that previous flyby missions could not supply. The landers included several types of experiments, developed over several years by separate teams of experts, which were performed upon landing, as well as a camera supplying visual images.

Overall, the missions were classified as a triumph (Soffen, 1976). In terms of technical achievement that was undoubtedly true – the spacecraft reached Mars and managed to land both landers safely. The landers remained operative for several years, long after the mission planners estimated they would. Viking's other mission objectives (obtaining high-resolution images of the surface and collecting data regarding its surface and atmosphere) (Williams, 2006) were successful.

Furthermore, the life-detection experimental machinery performed remarkably well considering the enormous technical difficulties involved in devising equipment – in effect complete automated miniature laboratories – that could perform multi-step collection and manipulation of Martian samples after crossing interplanetary distances.

The results of the life-detection experiments were initially encouraging. Ultimately, however, they were far from conclusive, and the question of the possibility of life on Mars remained unsettled even after the billion-dollar mission came to its end.

3.1.b. NASA's organisational thought at the Viking time and before, and their influence on the life detection experiments of the Viking mission

Rocket science enjoyed the fruits of the surge in technological advance that occurred in the wake of the World War II. Fortunately for NASA, exobiology was enjoying a similar surge in enabling technology just when NASA needed it to.

In the period leading up to the launch of the Viking missions, the exobiology community and NASA's organisational rationale and motivation were a match made in heaven. The prevailing mood was one of optimism: the Origin-of-Life research community was taking form; experimental results were showing promise; research funds were relatively plentiful. The research community interested in the origins of life on earth and elsewhere was receiving support from NASA, and – astonishingly – was being given the opportunity to actually, physically go and search for evidence of life on another planet, a possibility that would have sounded ludicrous even a generation before.

NASA was putting a lot of time money and effort into exobiology research. What it was asking in return was justification. NASA's rockets were becoming increasingly ambitious – but what they were lacking was a goal. NASA needed a reason for its projects, and exobiology provided it.

At the time the Viking missions were initiated in late 1968, NASA was enjoying a string of largely successful and high-profile achievements, most notably the Apollo manned lunar missions. However, the tides of support were starting to turn: the cold war was becoming less of a factor in the United States' national considerations. The economic situation in the US, including the cost of the Vietnam War and the American public's increased demand to increase federal spending on socially-centred areas, caused NASA's budget to drop significantly from its mid-1960s peak[56]. Due to the prominence of the Apollo projects, the budgetary constraints were especially felt in other areas of NASA, the Mars projects were among them. Viking was originally supposed to launch in 1973, but the combination of technical challenges and the lack of finance delayed it by over two years[57]. Indeed, the entire mission was nearly cancelled (Ezell and Ezell, 1984).

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[56] NASA's budget, initially comprising about 0.5-1% of the overall USA federal budget, increased dramatically during the Kennedy administration, reaching 4-4.5% of the federal budget in the mid-1960s - but then took an equally dramatic tumble, and by 1974 had gone down once again to the 1% level, and in subsequent years the value fluctuates at the pre-Apollo 0.5-1% area (Source: US government Office of Management and Budget historical tables).

[57] The delay time could more accurately be defined as "one launch window" - the most favourable time for launching a spacecraft from the Earth to Mars comes once every 780 days. This delay, forced by administrative constraints and the laws of physics, though it did present difficulties to the project teams, may also have been beneficial:

While the story of these instruments is a tale of amazing accomplishment, the facts also indicate that if Viking had flown in 1973 it probably would have been launched without the gas chromatograph-mass spectrometer and the biology instrument.Without those experiments, Viking would have been a vastly different mission.(Ezell and Ezell 1984).

Scientifically, the Mariner flyby missions starting in 1964 and ending in 1969 provided a wealth of data, but some of it was dispiriting to those who hoped that Mars could support earth-like life:

Robert Leighton [Team Leader at the Jet Propulsion Laboratory (JPL) for the Imaging Science Investigations on the Mariner missions] described [in 1969] the results of the television experiment at the September science briefing. 'Before the space age, Mars was thought to be like the Earth, polar caps, seasons. . . .rotates in 24 hours, etc.' This view of the Red Planet 'was largely the legacy of Percival Lowell who popularized the idea of reclamation projects to get the water supposedly from the polar caps down to the equator where the farmers were.' Although scientists had rejected the Lowell ideas of an inhabited Mars long before Mariner 4, they were not prepared for the stark, lunarlike images acquired during that mission. Pictures from Mariner 6 and 7, according to Leighton, showed that Mars was 'like Mars', with its own characteristic features, 'some of them unknown and unrecognized elsewhere in the solar system.' (Ezell and Ezell, 1984)

The Viking mission planners were sufficiently accepting of the possibility of extant life on Mars that one of the scientific teams assembled for the development of experiments for the mission was to be a 'biology team', and 1969 project estimates allocated a fourth of the lander budget (and a sixth of its payload) to 'active biology' experiments (as differentiated from organic chemistry experiments), which sought to identify organic molecules which might indicate either extant or ancient life activities.

3.1.b.1. Norman Horowitz, NASA, and life on Mars

Biochemist Norman Horowitz of Caltech was appointed as the director of the Jet Propulsion Laboratory (JPL) Biology Division for the Mariner and Viking missions from 1965 to 1970, and was also

the co-developer of the "Pyrolytic Release Experiment" one of the four experiments that were ultimately included in the Viking mission.

Horowitz at that point was already an eminent scientist well-known for his work in genetics, and had written before on Origin-of-Life and exobiology. He was something of an outsider in NASA culture, but his appointment landed him in the midst of NASA's huge project. Subsequently, his views on the state of mind at NASA at the time are illuminating. A comprehensive biographical interview (given in 1982, near the end of his scientific career) provides an exceptional look into the thought processes at work at Viking-era NASA. Of course no auto-biographical account should be taken at face value, but even so, Horowitz's views serve as a good starting point for discussing the Viking exobiology experiments. In the following pages, I will quote at length from the relevant parts of this interview, stopping to discuss points as they appear.

Horowitz gave this description of attitudes towards life on Mars in NASA:

Q: Why did you think that there was a possibility of life on another planet?

A: Well, at first it was a plausible idea. Everything that was known about Mars at the time later turned out to be wrong, but everything suggested that there was a good possibility of life on Mars....It's hard to convey in a few words the total commitment people had in those days to an Earth-like Mars. This was all an inheritance from Percival Lowell. It's amazing: In the pre-Sputnik I days – in fact, up until 1963 , well into the space age – people were still confirming results that Lowell had obtained, totally erroneous results. It's simply bizarre!

Q: And life on Venus, too.

A: Yes, a lot of people thought Venus was covered by an ocean. But that was speculative; in the case of Mars, they were making measurements and coming up with the wrong answers —I mean, these were supposedly objective measurements... And this was all based on the desire of people to believe that Mars was an Earth-like planet. It wasn't until 1963 that this began to unravel: the first step in the de-Lowellization of Mars occurred in 1963.

Q: What was that?

A: It was one infrared photograph taken at Mount Wilson. It was an unusually excellent photograph, showing the infrared spectrum of Mars. ...They showed, first of all, the total atmospheric pressure on Mars, which back around 1900 Lowell had estimated was 85 millibars. All through the 1900s, up until about 1960, people were making new measurements of the surface pressure that averaged out around 85 millibars. And these were by respectable people! So when the space program started, it was generally accepted that the surface pressure on Mars was 85 millibars, and that carbon dioxide was a small fraction of this; the rest of it was assumed to be mostly nitrogen, as on the Earth.

[The new readings gave the surface pressure of Mars at around 25 millibars; later measurements concluded that the figure is less than 10 millibars; I.BB.]

...Q: How much of NASA's willingness to go along with the possibility of life on Mars after, let's say, '63, do you suppose was because of the firm conviction, since Lowell, that there was life; and how much do you suppose it was because this was a way to get money because it was easier to get money if you could say you were looking for life?

A: Well, I think there was some of the latter. But I think most of it was that people didn't want to give up the idea. And I agreed that, now that we had the capability, we would never solve the problem

by just looking at Mars from the Earth. This was a classical problem, part of Western culture, the idea of life on Mars has been around for three hundred years. And here was the first time we had the ability to test it. I think if it hadn't been for Mariner 9 . . . Mariner 9 found an objective argument for flying to Mars, because Mariner 9 saw that Mars once had water on it. There are dry stream beds, obviously cut by water. All the geologists agree they're water cut; there was water on Mars at one time. And you could say that, if there was water on Mars, then there may have been an origin of life, and that life may still be surviving. Now Mariner 9 was an orbiter, it orbited Mars in 1971; and up to that point, up to the time Mariner 9 took its photographs. I would have said the *a priori* probability of life on Mars was close to zero. It would have really been an irrational act to fly to Mars before 1971 to look for life. But, you know, I think it would have been done anyway, because people were irrational about Mars; some still are. Not only that, but these big space enterprises are planned and paid for long before they're launched.

… we would have had a spacecraft, or at least parts of a spacecraft, and a whole big apparatus set up to build the spacecraft and fly it – and no place to go.

Q: And in a sense, scientifically, you really had to get there and prove that there actually wasn't any life.

A: That's tight. And there are other reasons, too. I mean, planetologists are interested in Mars, whether there's life on it or not. There are a lot of interesting questions about Mars and about all the planets. So it wasn't as if it was only a matter of looking for life and doing nothing else. But after the Mariner 9 orbit of Mars – it was in orbit for a year– there was no question, we had to go to Mars to look for life, because it was clear that Mars once had rivers. And so that's how it happened.

(Prud'homme, 1984)

As Horowitz mentioned, the Mariner missions produced strong indications that Mars did once have water. What the present situation was like was unknown. Some indication of the expectations of the mission planners can be surmised from looking at the types of expertise they were looking for:

Four kinds of biology expertise were sought for the Viking lander biology team:

A microbiologist is the essential ingredient, one familiar with soil growth conditions and the problems of demonstrating viable organisms from natural soil.

A photosynthesis specialist. Since part of the experiment is likely to be done in the light, searching for the photosynthetic reaction, it is important that someone familiar with these conditions be included.

A cellular physiologist-biochemist. This is usually the same individual as the microbiologist, but in addition it is desirable to find a specialist familiar with intermediary metabolism and the internal biochemistry of organisms...

One versed strongly in biological theory, evolution, genesis, chemical de nova synthesis, genetics. This theoretical job is likely to give the very fabric to the biological goals of the mission. An appropriate person could become the [team leader]. (Ezell and Ezell, 1984)

Two of the biology experiments – the Gas-exchange (GEX) experiment and the Labeled-Release (LR) experiment – were in essence generalised microbiological metabolism experiments[58], attempting to test whether microbial activity could be found on Mars. Having both of these experiments on board

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[58] The idea of macro-organisms on Mars, so alluring for previous generations, was by that point considered too optimistic for scientific consideration.

the first-ever Mars landers (each experiment having been chosen out of dozens of submissions, and each costing a significant sum of money to perform) indicates that the possibility of finding Earth-like organisms on Mars was far more than a theoretical hypothesis.

The planners and supporters of these experiments pointed out the logic of searching for familiar characteristics using familiar methods:

It is difficult to imagine what conditions would be necessary for the maintenance of completely novel life forms, such as forms based on silicon, or existing, say, in solid state. We can only guess at the types of instruments that might best be used to detect such forms-forms which even a human observer might fail to recognize. Hence, since we know that the many life forms on our planet are basically similar to one another in biochemistry and in structure at the cellular level, and since we know how to look for them, it is only logical that the first extraterrestrial life probes should seek life of an aqueous and carbonaceous nature. Of course, the possibility remains that alien life which evolved independently, isolated from our own, may have nothing in common with earth forms, but current knowledge dictates that the familiar be sought first.(Levin et al., 1962)

In contrast, Horowitz's Pyrolytic Release (PR) experiment was designed under the assumption, or rather suspicion, that if extant life on Mars does exist, it might be sufficiently different in its characteristics as to render biochemical assays designed for identifying terrestrial microorganisms unhelpful[59]. Horowitz relates:

Q: But you were still out to prove that there was some possibility for life.

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[59] Horowitz worked alongside Gilbert Levin on the latter's LR experiment until their paths diverged, and Horowitz constructed his experiment on nearly opposite assumptions to Levin's (Strick, 2004).

A: There was. The main point up until Viking was water. And there were enough theoretical mechanisms for getting some water on the surface of Mars to maintain the remote possibility – although by the time we launched Viking, it was very remote– that there were either pools of brine or, after snow or frost there might be enough meltwater at sunrise to sustain a population of microorganisms. By then, no one except Carl Sagan was talking about higher forms of life on Mars; the real interest was in the possibility of having microbial life. And there are organisms on Earth that will actually grow slowly on just water vapor; lichens can do that, though they need quite a lot - they need 80 percent relative humidity at a warm temperature to do that.

The point is that in spite of all these new discoveries, people were still building instruments to fly to Mars that were based on the terrestrial environment, and they were eventually approved by NASA.

NASA was supporting these efforts. Around 1960, I got involved in one of them, one that actually flew later on Viking. We called it Gulliver at the time. It was invented by an engineer in Washington, named Gilbert Levin. It depended on an aqueous medium. Two other experiments that were being supported by NASA also involved aqueous solutions into which you would put the Martian soil and then use various ways of measuring the metabolism of the organisms. But after 1965, after the Mariner 4 flyby, it was obvious that the chance of liquid water on Mars was so remote that one had to plan for the contingency that there was no water– that if there was any life on Mars, it was living under the surface...

In those days, if you talked to someone about looking for life on Mars it just seemed the most natural thing in the world to send a medium with a yeast extract, an aqueous medium, and plant it down on Mars and put some Martian soil in it and watch everything grow. I mean, it never occurred to them that this was totally inappropriate. (Prud'homme, 1984)

Horowitz's scepticism was reflected in the nature of his PR experiment, which relied on detection of any synthesis of organic compounds in the Martian soil samples tested, making minimal assumptions about the properties of the organisms being searched for. It was the only one of the three that did not include adding water to the Martian soil samples, and the only one that used environmental conditions resembling those on Mars itself.

As we can see, two of the three experiments on board the Viking were reliant on the assumption that Martian life, should it exist, would be generally similar to terrestrial life in its properties[60].

A point that should be emphasised here is that, were it not for the unambiguous detection of extremophilic microorganisms a few short years before (see Section 3 of this chapter) it is highly questionable whether anyone would have suggested bothering to look for life on Mars at all. The Mariner data presented humanity with a harsh picture of Martian planetary conditions, dispelling all the fanciful notions that had previously held humanity in thrall[61]. It would have taken a prescient thinker to predict the existence of terrestrial extremophilic organisms, but that would not have been beyond the capabilities of some scientists. However, there is quite a distance between a theoretical

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[60] A fourth life detection experiment, known as the "Wolf Trap" after its originator Wolf Vishniac, was also operating under similar operational assumptions. It was dropped from the Viking mission at an advanced stage of planning due to budgetary constraints (Strick and Dick 2004).

[61] The idea of life on Mars had fascinated Western culture for many years. Percival Lowell's popular writings on Mars from the turn of the 20th century are undoubtedly the most influential work. A more scientifically careful example, Richard Proctor, in his 1870 book Other Worlds than Ours, speculated on the possibility of life on other planets (Cercau 2010). Taking Darwinian concepts of adaptation to different environments into consideration, he considered life in extraterrestrial environments in relation to terrestrial life. The fact that his was a fairly scrupulous attempt at describing what alien life might look like while sticking to the known facts and making careful assumptions of what constitutes a different environment to Earth's, brings into sharp relief the difficulties people normally face when trying to comprehend the degree to which an alien world is alien.

suggestion of life forms with extraordinary qualities (however convincingly made) and government

investment of the huge sums necessary to go forth and look for these theoretical life forms.

3.1.c. the life detection experiments' results and their interpretations

The results of the Viking biology experiments proved to be ambiguous: the LR experiment gave

positive results (Levin and Straat, 1979), while the PR and GEX experiments gave positive results both

for the test samples and the control (heat-sterilised) samples (Horowitz et al., 1976, Margulis et al.,

1979, Strick, 2004b), meaning that some activity was occurring, but it was difficult to attribute it to

biological activity, since any organisms should have died during sterilisation of the control sample.

To most analysts, the results therefore suggested that chemical processes of non-biological

origin were responsible for the seemingly positive results that were obtained. Subsequent

experimentation – on earth – demonstrated the possibility of such reactions. Several mechanisms

were proposed for the reactions, including active clays or other components of Martian surface soil

which could have acted as catalysts to produce the results seen by the PR experiment.(Banin and

Rishpon, 1979, Plumb et al., 1989, Klein, 1979, Margulis et al., 1979). No proposed mechanism was

strong enough to dominate, and all of them had problems that could still form the basis of reasonable

objections; some, most prominent among them Gilbert Levin (who was in charge of the LR experiment,

which produced the most consistently positive results) continued to argue for the feasibility of the

biological activity interpretation of the results (Levin and Straat, 1979, Strick, 2004b).

The episode is an interesting one – the debate between the different researchers was carried

out under heavy public scrutiny and in real time (a very unusual experience for chemists and

biochemists). "Preliminary reports" and "interim results" were published quickly after the data was

obtained (Horowitz et al., 1976, Soffen, 1976, Levin and Straat, 1976, Klein et al., 1976). As Norman Horowitz told the press:

> We hope by the end of this mission to have excluded all but one of the explanations, whichever that may be. I want to emphasize that if this were normal science, we wouldn't even be here– we'd be working in our laboratories for three more months – you wouldn't even know what was going on and at the end of that time we would come out and tell you the answer. Having to work in a fishbowl like this is an experience that none of us is used to. (Strick, 2004b).

As we have seen with the ALH84001 findings in chapter 2, and will see later on in other cases, NASA is often unusually quick to announce results at press conferences. The researchers in such cases perform rapid analysis of the data and present their interpretations before going through the process of writing up the results and submitting them to scrutiny by the wider scientific community. A detailed account of the unfolding of the debate may be found in The Living Universe (Strick 2004).

3.1.c.1. Too early?

It has also been pointed out that a significant problem of the Viking life detection experiments was that the technology was not yet up to the task. Rocket technology was advanced enough to send a laboratory all the way to Mars, but the biochemical techniques were not mature enough to be of much use when they arrived there. Nor was there, at that point, sufficient understanding of the possible variety of life that needed to be taken into account when designing life-detection experiments:

> Ambiguity wasn't the study's only problem. Even if Viking had delivered a definite 'no' to life, this could simply have been because its instruments were too crude. 'There could have been 10 million bacteria per gram of Martian soil, and Viking wouldn't have seen them,' says Andrew Steele of the

NASA Astrobiology Institute at the Carnegie Institution of Washington. Facing such problems, interest in looking for life on Mars waned after Viking, says astrobiologist Christopher McKay of the NASA Ames Research Center in Moffett Field, California. 'The experiments were very hard to follow up on,' he says. But there has been a boom in instrumentation since then – today's detectors can spot a single cell, or molecules at concentrations of parts per trillion. And our understanding of the tenacity of life in extreme environments has grown.(Whitfield, 2004)

This demonstrates, once again, and not for the last time, the importance of technological maturity and of microbiological discovery for searching for basic attributes of life. Note that the person speaking is Christopher McKay, whose own life-detection research involving the Martina meteorite ALH84001 we have discussed in the previous chapter.

3.1.d. Post-Viking:

Following the Viking years, NASA exobiology had lost a significant part of its impetus. Although the Mars missions by no means ruled out the possibility of life on Mars (or, for that matter, anywhere else), and the possibility of finding evidence of extinct life on Mars was still a going concern, to be reinforced in 1996 with the ALH84001 findings discussed in chapter 2, and although NASA exobiology leaders presented the missions as the beginning of the era of planetary exploration (Young, 1979), the ambiguity of the Viking results left exobiology with no definite place to go.

The Viking mission had been the apex of preparation for NASA exobiology, in terms of effort and expectations. I believe it would not be an exaggeration to say that, scientific caution pronouncements notwithstanding, Viking was the ambitious 'make or break' gamble that the exobiology program, with its optimistic attitude towards the possibility of extra-terrestrial life, had been building up to since its

inception. Once the experimental results were found to be inconclusive, the public lost interest; budgets showed no sign of growing, and the focus of the American space program was increasingly shifting towards other areas. NASA's next big project was the development of the space shuttle; Mars missions were not in vogue. Here is Dan McCleese, who arrived at the Jet Propulsion Laboratory during the Viking era (later to become its Chief Scientist and a key worker in subsequent Mars missions), speaking in 2006:

[I]ronically the success of Viking led us to close the doors to further exploration. In fact, it was over 20 years before the United States was to send back another mission. Nobody wanted to hear the life word associated with Mars. Therefore Mars was dead, cold, and low pressure and therefore boring. (2008)

To quote Norman Horowitz one final time:

One of [NASA's Ames Research Center]'s main programs is the origin of life, pre-biotic chemistry. I think they're still talking about the possibility of life on the planets, but I think it's really this cynical attitude. I think they feel that their existence is more certain if they take the position that there's still a possibility of finding life elsewhere in the solar system.

Q: What do you think is going to happen to the space program? The exploration of planets and so on?

A: I think it has slowed down enormously. The only really exciting thing that I can think of now that's coming up is the Galileo mission. But it's slowed down. I think the shuttle is a great mistake. It's taken all the funding that should have gone to planetary exploration. (Prud'homme, 1984)

One result of the Mars experiments was that researchers realised that 'normal' earth-life was not likely to provide a good model for searching for Martian life evidence. This led to a new emphasis on life on earth, and especially on life in extreme environments: initially Antarctica, then the Atacama Desert in Chile, and also hydrothermal vents (Strick, 2004 p.83-99). We shall see the results of this shift in the next chapter. A NASA committee report sums up this shift:

In the 1970s, the major focus of the Committee on Planetary Biology and Chemical Evolution of the Space Studies Board (SSB) centered on the planet Mars. Initially, attention was directed at assessing the prospects for finding extant organisms on that planet and developing guidelines for the biological containment both of terrestrial materials that might be transported to Mars and of Martian material that might be returned to Earth. Later, as data from the Viking spacecraft and from ground-based simulations of the Viking biological experiments were made available, the committee became involved in the analysis and interpretation of the Viking Mars biological data.

In the past decade [the 1980s], the scientific thrust of the committee shifted substantially from solar-system exploration to studies of the Earth with the publication of two documents. The first of these, Origin and Evolution of Life— Implications for the Planets: A Scientific Strategy for the 1980s (SSB, 1981), while discussing the state of knowledge in the field of planetary biology and chemical evolution, proposed as its main recommendation the development of an integrated new program to study the global interactions between terrestrial organisms and this planet. (Committee on Planetary Biology and Chemical Evolution, 1990)

The NASA-supported peer-reviewed journal Space Life Sciences included, in its first four or five volumes, a significant number of articles relating to sterilisation of spaceship cabins, contamination of extra-terrestrial soils and samples, and "space medicine" - issues of human health under space mission

conditions. This reflected the focus of the NASA life sciences branch at the time on preparation for

space missions. By the fifth volume, published in 1975, the Viking mission craft were well on their way,

and the focus of the journal's papers had shifted to issues of Origin-of-Life and closely related

subjects[62].

The direction shift in NASA also manifested itself in the theoretical realm; three of the most

influential theoretical advances relevant to the early development of life on earth were made by

scientists working on NASA projects. The first was Carl Woese's taxonomic revolution (which will be

discussed in the next chapter); the second was Lynn Margulis's development of the modern concept of

symbiogenesis. The third theory was more directly related to Viking: James Lovelock, a NASA contactor

who first developed a gas chromatography electron collection device for the Viking experiments (Strick

2004, p.83) started to rethink the whole concept of detection of life. In light of the new data, a search

for life exhibiting Earth-like properties was not a good idea. Rather, the search for signs of life should

be based in a generalised concept of what life is. This was his first step towards the Gaia hypothesis

(see also section 5.2.b.3.)

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[62] This was most likely due largely to the fact that by that time, considerations of contamination and back-contamination of NASA spacecraft had ceased to be of practical consideration; lunar missions had been completed without incident, and the Viking missions to Mars were already in advanced execution stages. The Viking landers, incidentally, were also sterilised.

3.2. Theories of the origin of life

The late 1960s and early 1970s proved to be a fruitful period for theorising in the Origin-of-Life field. The results produced by the molecular biology research program in the preceding two decades provided clearer details of the basic processes of life. These findings rendered existing Origin-of-Life theories obsolete.

In this section I will examine some of the more prominent theoretical constructs that were suggested throughout this period, and argue that the motivation for creating them may be traced to a large extent on the need to explain the new problems.

3.2.a. Panspermia and Directed Panspermia

Exogenesis is the idea that terrestrial life originated outside of planet earth. When combined with the notion that life in the universe is widely prevalent and is able to spread between worlds, the result is called Panspermia. In many cases, however, the distinction is not made, and 'Panspermia' is used for any theory of exogenesis.

Various panspermic theories have been proposed; as we have seen in chapter 2, claims that meteors contained evidence of life surfaced several times throughout the 19th century, and many notable thinkers, including Lord Kelvin, favoured the general notion (Arrhenius and Mojzsis, 1996), but it was Swedish Physicist Svante Arrhenius who proposed in 1908 the first detailed consideration of Panspermia. The discovery of spore-forming organisms (sporulation was independently discovered

during 1876-7 by Robert Koch, John Tyndall and Ferdinand Cohn), with the protection that the spores afforded the organism against harsh environmental conditions, enabled Arrhenius to suggest that spores could have withstood interstellar travels. Later astrophysical findings ruled out the specifics of his theory, but the basic principle of the theory was by no means refuted. Little more was added to the discussion in the subsequent decades.

Panspermia holds an interesting place in Origin-of-Life studies: Though some fairly level-headed speculation on the subject is done within the mainstream of the Origin-of-Life and Astrobiology communities, Panspermia also draws a fair amount of attention from the outer fringes of scientific discourse, and wild theories abound[63].

Surprisingly, one of the wildest of these theories is the one that was presented by two respected mainstream researchers in the 1970s:

Leslie Orgel and Francis Crick's Directed Panspermia theory was first published as a joint paper in 1973 in the journal *Space Science* (Crick, 1973); for Orgel this was as far as it went; Crick elaborated further upon the idea in *Life Itself* (Crick, 1981), a short popular book devoted to the idea. The essence of the argument is that the appearance of life on earth is highly unlikely within the time frame it is proposed to have appeared, and knowing what was then known about living systems and about the environmental conditions on earth. Since the universe is significantly older than the earth, and

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[63] The most well-known champion of modern Panspermia is unquestionably the astronomer and mathematician Frederick Hoyle, whose work on the subject is being continued today by his former student and collaborator Chandra Wickramasinghe. Never one to shy away from scientific controversy, Hoyle rejected the theory of abiogenesis and argued in favour of a comet-delivered extraterrestrial ancestor, within the larger framework of a "steady-state" universe with no beginning or end in which life exists eternally. Later expansions of the theory make progressively more extreme claims (see Shapiro, 1986 for a critical discussion of the Hoyle-Wickramasinghe theory). Richard B. Hoover's recent claims of evidence for Panspermia have been discussed in chapter 2.

contains many environments, some of which may be more conductive to the formation of life, then it is reasonable to hypothesise that life arrived on earth rather than forming on it. Thus far, Orgel and Crick present the basic panspermic premise, but then go one further: since 'regular' panspermic theories were demonstrated to have serious problems (the main one being the inhospitability of prolonged interstellar movement to even the most hardy of life forms), Orgel and Crick concluded that the solution was that terrestrial life was implanted on earth by intelligent aliens.

Crick and Orgel's paper is initially a most surprising work. Not because of its content – the idea (as noted previously) was not a new one at the time[64] – but because of its originators. Crick and Orgel would not seem to be likely candidates for such a radical diversion from the mainstream of scientific thinking at the time. This seeming discrepancy warrants explanation, and is resolved when we note that Crick and Orgel intended their idea mostly as an inducement to thought, rather than a serious attempt at proposing an Origin-of-Life theory (Shapiro, 1986). Inder M. Verma, Orgel's friend and colleague at the Salk institute, says of Orgel's theory: "It was done in the gesture of something exciting and novel…[Orgel] was trying to be provocative." (Chong, 2007).

In the thirteenth chapter of Life Itself, Crick makes it rather clear that he is proposing the idea of directed Panspermia as a scientific theory – but that he is very far from lending his support to it[65]. The purpose of the exercise was to formulate and consider a scientifically valid alternative to abiogenesis (which Crick considered severely deficient), without trying to speculate on the likelihood of the two

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[64]Orgel and Crick mention Thomas Gold's "light-hearted" suggestion - the so-called 'garbage theory' of Origin-of-Life - that life on earth is the result of accidental contamination of the earth by intelligent aliens not cleaning up properly after themselves after a visit to earth (Crick 1973).

competing theories (terrestrial abiogenesis and Directed Panspermia) – Crick argues that the body of evidence is at present so meagre that it could be taken to support both:

In deciding between the two theories, one soon learns that plausibility alone will not do, quite apart from the fact that it is usually contaminated with unstated prejudices. Directed Panspermia may at first sight seem farfetched, but can we give solid reasons for this initial reaction?... It will not do just to put the nail on end and give it a tap. It is essential to drive it home. To give a theory the degree of certainty we need, we have to hit it hard, again and again. And this, alas, is just what we are unable to do in this particular case (Crick, 1981)

Directed Panspermia was taken no further from that point on, theoretically or experimentally, and it is difficult to see how it could influence further research (other than providing a little more impetus to SETI efforts). Apart from being an intellectually stimulating exercise in scientific theorising, Directed Panspermia is above all an expression of Crick's (and, to a lesser extent, Orgel's) frustration with the state of abiogenesis and the quality of the explanations it provided.

3.2.b. Monod's Chance and Necessity

1971 saw the publication of Jacques Monod's Chance and Necessity (Monod, 1971). We have discussed Monod's views in regards to the general question of chance and necessity in the introduction, but it also merits a mention at this point, since it too came from an attempt to grapple with the problematic state of the Origin-of-Life question at this point in history.

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[65] In this respect Crick echoes Lord Kelvin's sentiments on his theory of (non-directed) Panspermia - he says of it that it "may seem wild and visionary; all I maintain is that it is not unscientific". [Lord Kelvin (William Thompson), Presidential Address to the British Association for the Advancement of Science; Edinburgh, August, 1871].

Monod, one of the most prominent and celebrated molecular biologists of his time and recipient of the Nobel Prize in Physiology or Medicine on 1965, argued in the book for the position, encapsulated in his well-known quote: "The universe was not pregnant with life, nor the biosphere with man", that the appearance of life on earth was a chance event, with an a priori probability of "virtually zero". Life on earth requires no further explanation – it is simply extremely lucky to have emerged.

As with Crick's Directed Panspermia, Monod's position is hardly a very stimulating one for further research, and indeed it is not meant to be. The onus of proof cannot be placed on its shoulders; it is those who try to give other explanations Contrasted with Crick's frustration with the state of the Origin-of-Life question, Monod is expressing resignation with it. Other contemporary theoretical attempts at engaging the question were more optimistic:

3.2.c. Eigen's Hypercycle

In 1971 biophysical chemist Manfred Eigen (who had in 1967 received the Nobel Prize in Chemistry for his work on rapid chemical reactions) published his theory of molecular self-organisation, which he called a hypercycle (Eigen, 1971). Eigen and Schuster continued elaborating on the hypercycle theory, and published a more complete version in a series of detailed papers in 1977-8 (Eigen and Schuster, 1977, Eigen and Schuster, 1978, Eigen et al., 1991). The theory, an attempt to formulate a self-organisational model of chemical interactions, was another attempt at resolving the 'chicken and egg' problem:

As a consequence of the exciting discoveries of 'molecular biology', a common version of the above question is: Which came first, the protein or the nucleic acid? – a modern variant of the old 'chicken-and-the egg' problem. The term 'first' is usually meant to define a causal rather than a

temporal relationship, and the words 'protein' and 'nucleic acid' may be substituted by 'function' and 'information.' (Eigen, 1971).

The hypercycle model extends the Darwinian natural selection principle to interactions between molecules, to produce what is essentially a concept of evolution on a molecular scale, resulting from thermodynamic states. Eigen's paper applies the results emanating from Spiegelman's then-recent Qβ replicase experiments (which he discusses in detail) to the origin of life, suggesting that given appropriate starting conditions, a group of multiply interacting molecules could organise itself into an evolving catalytic cycle.

The hypercycle is a network of replicating molecular species catalysing and repressing reactions between each other in a closed loop. It starts off with molecules replicating semi-faithfully so that a "cloud" of molecules of related sequences, which Eigen called quasispecies, is formed. These share an evolutionary fate due to their close resemblance to each other and their cooperation, and the population as a whole replicates at a higher rate than any single replicator species within it, due to the fact that the fidelity of the replication (which lacks any modern correction mechanism) cannot be high enough to ensure that the 'superior' single replicator sequence maintains itself in unchanged form for an extended time, while the quasispecies population as a whole can maintain a higher mean replication rate due to its higher tolerance for error, as long as each molecule within the quasispecies retains its ability to replicate a sequence reasonably close to itself. As the population's variants replicate and interact between themselves, the hypercycle can grow and evolve. It is a hypercycle because each component molecular species has its own replication cycle. These component cycles are intertwined through the reaction that the products have on each other's activity, making the entire hypercycle function as a single autocatalytic unit of activity; its constituents are co-dependent, thus

restricting competition for resources between themselves and acting in cooperation amongst themselves. Mutation in each component affects the other components and thus the entire system's operation and efficiency (Eigen, 1992)

Self-organisation is a concept with a long history – mainly in physics, but principles of self-organisation have been suggested in various fields, including mathematics, economics, anthropology and others. Beginning in 1968, Physicist Ilya Prigogine put forth his theory of dissipative structures (for which he received the Nobel Prize in Chemistry in 1977). Briefly, Prigogine showed mathematically how energy influx into a chemical system can overcome the limitations exerted on the system by the second law of thermodynamics; rather than settling to a single steady state, the system can go through a series of increasingly complex steady states:

...Prigogine and Glansdorff's principle of nonlinear irreversible thermodynamics. Whenever we have a self organizing system with selection behavior– as defined by certain properties of the reaction system and by specification of external constraints – the occurrence of a new species or ensemble of higher selective value (by fluctuation or mutation) will cause an instability, i.e. a breakdown of the former steady state and a build- up of a new steady state which is dominated by the species or ensemble having the higher selection value. The 'breakthrough' of the new species is subject to certain limitations and can be described correctly by stochastic theory. (Eigen 1971)

Eigen's hypercycle draws much from Prigogine's calculations. The interacting molecules are not specified in Eigen's earlier papers; the scheme is presented in theoretical mathematical terms, and one possible type of hypercycle can be composed of nucleic acid polymer species as well as amino acid polymers of comparable complexity. In subsequent reformulations of the hypercycle (by Eigen and

others), and as the catalytic abilities of RNA became known in the 1980s, the model became more closely associated with RNA, with the protein components considered a later addition to the operating system. Later still (Eigen et al., 1991), Eigen draws on the results showing the relative ease of formation of amino acids in prebiotic conditions, and of Fox's work on the formation of peptides and catalytically active proteinoids to hypothesise that

[E]ven in the prebiotic phase, at least some proteinoids could be formed to catalyse virtually any chemical reaction. However, these catalysts were not optimal, nor was it possible to optimize them, since optimization calls for a stepwise evolutionary adaptation based upon self-reproduction.(Eigen, 1992)

thus giving proteinoids a substantial role in the formation of the hypercycle. The RNA-protein hypercycle then undergoes further development to produce the first stages of a genetic code and enzymatic interactions.

Another important source of inspiration for Eigen came from RNA viruses, whose infection cycles provide an example of an existing hypercyclic interrelationship between the viral RNA and the replication factor it encodes, an RNA-dependent RNA polymerase known as a replicase (Eigen and Schuster, 1977, Eigen et al., 1991, Haruna et al., 1963). Spiegelman's aforementioned Qβ replicase experiments studied RNA and RNA-polymerising enzymes in a cell-free medium; in addition Spiegelman and co-workers showed (Haruna et al., 1963) that a viral replicase has the ability to differentiate between the viral RNA and the 'native' RNA of the host cell, thus assuring that the viral RNA is preferentially replicated.

[The hypercycle's] role in early evolution was analogous to its role in viral evolution today: Hypercyclic coupling provides functional evaluation and evolutionary improvement of the phenotype by specifically favoring the replication of its own genotype. The host's role in virus infections had to be played in precellular evolution by the (eventually compartmentalized) primordial reaction medium.(Eigen et al., 1991).

Eigen uses this existing system to demonstrate his point about the possibility and power of preferential replication in RNA population dynamics – in an environment containing two populations (host cellular RNA and viral RNA) one population is preferentially replicated[66].

Not unlike the systems it describes, the hypercycle model itself has been updated several times. The theory elaborated upon in the 1977-1978 papers differs in certain respects from the original 1971 paper, and the 1992 book offers yet more changes. The hypercycle model is a significant component in the 'replicator-first' tradition of abiogenesis. Its extension of the principles of Darwinian natural selection makes it easier to maintain that life started at the point at which the first replicating molecules appeared.

The hypercycle model is not without its faults. Among them:

- It assumes rather a lot of specific starting conditions for the hypercycle to develop, including (among other things) a large and robust population of replicating polymers with a constant influx of both energy and monomeric building blocks to keep the system operating. Amino acids as well as nucleotides are explicitly assumed by Eigen and Schuster to be present and available,

and they make no claim of addressing the question of whence these starting conditions came to occur.

- The components of the system are supposed to interact with each other within a spatially defined environment, implying some sort of compartmentalisation, a fact which is acknowledged by Eigen and Schuster at several points throughout their work and several possibilities suggested, but the details of the compartment and its influence on the system within are not elaborated upon to any meaningful extent; in addition, the rate at which the components form is assumed to be greater than the rate at which they decompose.

- There are several internal inconsistencies:

  Hofbauer and Sigmund have derived that hypercycles are not dynamically stable for than four types of chemical species… This means that hypercycle catalysis alone cannot support five or more species in long-term-equilibrium existence, without something else being added. The population of one or another of the species in such complicated ecologies soon or later is driven to zero, causing the entire interdependent cycle to unravel. (Padgett 2011)

- The model contains no specific descriptions of what real-world pre-biological hypercycles would look like. One cannot treat the model as a blueprint for constructing a working hypercycle-like reaction series. The way in which proteins are to enter the reaction cycle is especially vague.

- Although attempts to design and create a simple working hypercycle have been made, and even successful (Lee et al., 1997), and the aforementioned viral systems demonstrate the principle's existence in nature, there is scant observational or experimental evidence for the existence of

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[66] Eigen does not consider the viral hypercycle to be descended from the pre-biological one; the link between them is conceptual rather than phylogenetic.

complex hypercycles involving more than two or three constituents, of the type which would be required for a proto-biological hypercycle.

Despite these and other faults, the hypercycle is the most thoroughly worked out model demonstrating the action of natural selection on the molecular level, which has had much influence on later ideas and experiments in Origin-of-Life, starting with Eigen himself (who, true to his dictum of "no theory without experimentation, no experimentation without theory", performed experiments with RNA systems in the following years) and carrying on to researchers such as Wächtershäuser, Luisi, and Lancet. The hypercycle also foreshadows later theoretical attempts at a 'law of emergence' advocated by Stuart Kaufmann and others of both the metabolic and the genetic approaches (see section 4.6.c. for a discussion of this topic). It also sits well beside the RNA World models, although it had little influence on its emergence and the experiments devised within the RNA World perspective.

3.2.d. The Chemoton

The chemoton, another model of an autocatalytic chemical network producing a minimal proto-metabolism, was developed and published by Hungarian biochemist Tibor Gánti and was published (in Hungarian) in 1971 (Gánti, 1971), coinciding almost exactly with Eigen's first hypercycle paper. The two models share some important and interesting attributes. A more detailed examination of the theory will be given in the next chapter, but it should also be noted here as a legitimate though less well-known member of the group of Origin-of-Life theories originating during this short chronological period.

3.2.e. The RNA World

The discovery of the catalytic function of RNA proved a major boost for the idea that an RNA-like

molecule was the original replicator, since a catalytic capability meant that since it could hypothetically self-replicate, thus providing a way out of the interdependency problem of DNA and protein and potentially solving the confounding 'chicken-and egg' problem.

The RNA world hypothesis states that RNA molecules were hypothetically both the 'genetic' information-storing and the 'functional' catalytic entities at an early stage of life's evolution, while the development of the protein-DNA system is a later development, proteins being a class of molecules better suited for catalysis, and DNA a more efficient and reliable data-storage vehicle.

The theory is further supported by the observed properties of RNA in present-day cells, such as catalytic RNA functioning as a key component of ribosomes (rRNA). RNA World theorists suggest that such phenomena constitute 'molecular fossils', indicative of the historical role of RNA.

Since the first suggestions of the RNA World, and up to the present day, numerous labs are attempting to discover a suitable 'first replicator' molecule (or molecules: the concept of 'cross-replication' – the idea that several molecules can do to each other what one molecule cannot do to itself – has been gaining momentum) and give a possible description of the conditions that could have made these initial RNA replication events possible.

3.2.e.1. Origin of the RNA World theory

As molecular research was carried out throughout the 1950s and 1960s, the RNA molecule was found to be performing a diverse spectrum of functions, some of which are embedded in the fundamental genetic processes of the cell – messenger RNA (mRNA), transfer RNA (tRNA) and, perhaps most surprisingly at the time, ribosomal RNA (rRNA). In addition, RNA plays an important part in gene regulation, as well as other cellular activities. As we have mentioned previously, RNA was also

found to be genetic material in and of itself, in RNA viruses. RNA is now known to have even more natural functions (snRNA, iRNA, etc.).

Unlike DNA, RNA is not a passive, inert information-bearing molecule waiting to be 'read', as DNA is often described, but a type of molecule capable of acting on other molecules. It is also relevant that RNA is a chemical precursor of DNA, but not vice versa. All of these have led to the widespread belief that RNA is a prime candidate for the role of the first genetic molecule – or at least a precursor to the 'DNA-Protein World' extant in nature today.

The theoretical model which later came to be known as the RNA World is often said to have been first suggested by Carl Woese in 1967 (Woese, 1967) and, independently, by Francis Crick (Crick, 1968) together with Leslie Orgel (Orgel, 1968)[67] in the following year[68] (five years before their joint espousal of the Directed Panspermia theory). The more informed accounts correctly attribute the first suggestion of the concept to molecular biologist Alexander Rich, who contributed his thoughts on the origin and evolution of life to a 1962 volume dedicated to physiologist Albert Szent-Gyorgyi:

We postulate that the primitive polynucleotide chains are able to act as a template or a somewhat inefficient catalyst for promoting the polymerization of the complementary nucleotide residues to build up an initial two-stranded molecule. . . It may be reasonable to speculate that the hypothetical stem or parent polynucleotide molecule was initially an RNA-like polymer. . .(Rich, 1962)

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[67]Harold White III suggested in 1976 that nucleotide enzyme cofactors (enzyme cofactors are small non-protein molecules which are necessary for some types of cellular enzyme function) can also be viewed as historical relics, evidence that RNA enzymes had previously existed, and whose catalytic sites were replaced over time by protein enzymes (White 1976).

[68] Crick and Orgel discussed the idea between them, but had written papers on it independently, and so their papers appeared back to back in the same issue of the Journal of Molecular Biology (Orgel 1993).

In a biographical account, Rich writes of his 1962 paper:

It was apparent by that time that RNA molecules could contain genetic information, as in the RNA viruses. They also were known to play a central role in the synthesis of proteins. DNA was thus regarded as a specialized derivative molecule that evolved later in a form that contained specific information and carried out the molecular replication inherent in propagating living systems. (Rich, 2004)[69].

Significantly, none of the papers suggested finding catalytic activity in extant RNA molecules. Here are Crick and Orgel, discussing their ideas in retrospect:

How clearly did we anticipate the exciting experimental discoveries of the last decade? We must confess that we did not anticipate them at all! We discussed a number of hypothetical schemes for the origins of our genetic system and touched on each of the major features of the RNA world hypothesis. However, we did not ourselves search for, nor did we encourage others to search for, relics of the RNA world in contemporary organisms. We took it for granted that RNA-based catalysis was necessarily less efficient than protein-based catalysis, and consequently that RNA catalysts had been superseded by protein enzymes in every case. The same assumption led us to underestimate the potential complexity of an RNA world.(Orgel, 1993)

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[69] Rich was an acquaintance and colleague of both Orgel and Crick, and had even lodged at Crick's house for some months in 1955 (Rich 2004). It is reasonable to suppose that there had been some mutual discussion on the issue, though the extent of the influence of Rich's ideas in the 1960s is doubtful. All four were heavily involved in the study of the structure and function of RNA. All three were members of the loose, light-hearted but by all accounts intellectually stimulating professional circle known as the 'RNA tie club'. Established in 1954 by physicist George Gamow, it comprised many of the earliest thinkers and workers in molecular biology.

It seems as if the RNA World (not yet under that name) was proposed as a hypothetical model by four well-known, even eminent, researchers, actively working at the forefront of their discipline – and then lay dormant for a decade and a half, only to spring forth in the mid-1980s to become one of the most discussed, investigated, and arguably the foremost theory in Origin-of-Life research, even unto the present day. What was the reason for this 'gap'?

3.2.e.2. Non-Enzymatic RNA Replication

One important fact to consider is that the description in the preceding paragraph is not entirely correct. It might perhaps have been more convenient for the purposes of this narrative if the years from 1968 to 1982 had been devoid of all experimentation pertaining to the RNA World, but it is a fact that a few researchers, by far most prominently among them Leslie Orgel and his group, worked from the mid-1960s onwards on the study of non-enzymatic systems of ribonucleotide replication. They initiated the study of non-enzymatic template-directed oligonucleotide synthesis.

It was discovered that oligonucleotide strands composed of RNA can spontaneously align their complementary sequences with the help of mineral catalysts such as metal ions and clays, without the need for enzymatic intervention (Orgel, 2000)[70].

The reactions were experimentally well established; there were, however, severe limitations on their efficiency as models of prebiotic reactions; to no-one's surprise, non-catalysed nucleotide polymerisation is a slow process (hence the metabolic need for catalysts in the living cell), and thus the

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[70] These results showing that RNA can polymerise on a template but without an enzyme were nicely complemented by Eigen and co-workers' results showing that RNA can form polymers in a reaction with a polymerase enzyme but without a template (Biebricher, Eigen et al, 1981, Biebricher, Eigen et al, 1981, Biebricher, 1986).

reaction rate of non-catalysed hydrolysis of nucleotides was extremely slow: reaction times were measured in days, as compared with catalysed RNA polymerisation reactions which are measured in minutes – compare, for example (Inoue and Orgel, 1982) with (Been and Cech, 1988).

[the reaction rate of the ribozyme Ribonuclease P] is small by the standard of many enzyme reactions, but represents an enormous acceleration over the rate of noncatalyzed hydrolysis of other phosphodiesters. (Orgel 1986)

Other problems of the non-templated reactions were no less significant: the polymers produced were very short (the longest ones were 10 nucleotides long, and these were simple strings composed only of Cytosine rather than any more complex sequence); the reaction conditions also did not adhere to plausible prebiotic conditions; what's more, once the product was formed on the template, strand separation would not take place, which meant that the template could not undergo a full replication cycle, something that would be crucial to the inclusion of such reactions in a viable model of abiogenesis.

When reading the papers describing these experiments up to 1982, one can notice that they contain repeated caveats to the effect that the reactions described therein are not presumed by the authors to be representative of what might actually have happened in the prebiotic environment; the reactions are only regarded as experimental steps towards that goal, which seems, at that stage, to be rather far away.

To sum up: the search for a plausible prebiotic reaction that could start off replication cycles involving RNA was limited to a very small number of researchers, attracted very little attention at the time, and was proceeding – not unlike its subject matter – very slowly indeed.

3.2.e.3. Discovery of ribozymes

The major boost for RNA World research arrived in 1982 with the announcement of the

discovery of ribozymes, actual, naturally-occurring catalytic RNA molecules discovered independently

by Cech and co-workers studying the ciliated protozoan Tetrahymena thermophila (Kruger et al.,

1982), and Altman and Guerrier-Takada studying the formation of tRNA molecules in bacteria

(Guerrier-Takada and Altman, 1984). These studies, unrelated to Origin-of-Life[71], were employing

molecular techniques and tools that only became available to researchers in the preceding few years[72]:

restriction enzymes, nucleic acid sequencing, and reverse transcriptase reactions capable of creating

DNA sequences from RNA templates. Without these new tools, it is hard to think of a way in which

ribozymes would have been discovered in either existing or artificial biological systems.

The Origin-of-Life research community was immediately appreciative of the value of ribozymes

to their field; a flurry of papers espousing the concept of the "RNA World" (a term coined by Walter

Gilbert in his cornerstone 1986 paper) and debating various aspects of it, appeared within a

remarkably short period (Gilbert, 1986, Maizels, 1987, North, 1987, Nisbet, 1986, Mehta, 1986,

Benner, 1987, Benner and Ellington, 1987, de Duve, 1988, Robertson, 1988, Joyce, 1989, Pace and

Marsh, 1985). Christian de Duve summed it up well when he wrote in 1988: "What was only a

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[71] Cech recalls that he did not know of the theoretical suggestions for the RNA World, and in fact was largely ignorant of the entire Origin-of-Life field in general (Dick and Strick 2004, p.126).

[72] 1970 saw the isolation of first restriction enzyme and of the reverse transcriptase enzyme, both crucial to manipulation of genetic material. In 1972 the first gene cloning was performed; the Southern blot technique for detection of DNA fragments was developed in 1975. Fred Sanger published his DNA sequencing technique in 1977. Methods for manipulation and detection of genetic material were fast becoming available to researchers, and thus the mid-seventies saw a significant rise in the capabilities of scientists to work with it. These developments, and the concerns they engendered in scientific and public circles, brought forth the famous Asilomar Conference on Recombinant DNA in February 1975 - a useful indicator of the emergence of genetic engineering.

cautiously advanced hypothesis some years ago has now gained so much credibility as to go largely unquestioned. It is even presented to students as 'almost certain'." (de Duve, 1988)[73]

Origin-of-Life research has never been short of interesting theoretical suggestions; the RNA World had been one of these. What had made the difference between 'yet another theory' and widespread acceptance was the real-world discovery of catalytic RNA.

A review of Origin-of-Life experiments leading to the mid-1980s reveals little utilisation of molecular techniques (with the exception of phylogeny tracing); Origin-of-Life is at heart a chemical research field, not primarily a biological one. Although it might have been the case that, had ribozymes not been detected when they have, or indeed had nature aligned with Crick and Orgel's assumptions and ribozymes not existed at all in contemporary organisms, then somewhere along the line an enterprising researcher would have attempted to construct – from scratch – a catalytic RNA molecule. As it was, however, the discovery of ribozymes in nature followed relatively quickly at the heels of the technical advances that made it possible.

3.2.e.4. PCR and the second age of in vitro evolution experiments

Sol Spiegelman's original experiments in the 1960s relied on the use of Qβ replicase enzyme. We have already mentioned the fact that this enzyme is viral in origin, and has the characteristic of preferring the replication of viral RNA over other RNA polymers it interacts with. This enhances the efficiency of the viral replication cycle in vivo, but these selective properties significantly limit the scope of in vitro molecular evolution experiments available to researchers.

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[73] It will come as no surprise that, immediately following this passage, de Duve goes on to present a critical appraisement on the RNA World theory and to put forth his own ideas.

The powerful molecular technique of Polymerase Chain Reaction (PCR) changed all that. Gerald

Joyce, in an article reviewing the history of this type of experiment, writes his description of the start

of the 'modern' era of in vitro molecular evolution experiments under the telltale heading And Then

Came PCR. (Joyce, 2007). He writes:

The breakthrough for in vitro evolution came with the development of the polymerase chain

reaction (PCR) and related methods for amplifying nucleic acids of almost any sequence. This allowed

RNA (and DNA) molecules to be selected based on properties other than their ability to be amplified by

a replicase protein. (Joyce, 2007)

The availability of PCR (initially developed in 1983, and, after the introduction of Taq Polymerase

and other refinements, coming into widespread use by 1987) as well as related techniques, dovetailed

with the concurrent discovery of ribozymes to bring forth the second age of in vitro evolution

experiments.

It became possible to control the selection process, and thus use in vitro evolution itself as a tool

for producing different types of ribozymes that are not designed beforehand, but emerge via a series

of selection and amplification cycles from a random pool of RNA sequences (Bartel, 1993, Joyce, 2007,

Oehlenschläger and Eigen, 1997).

PCR could be used as a means of selection (amplifying particular sequences determined

beforehand) and also as the means for mutation (using 'error-prone' PCR, which produces random

variations from substrate sequences), thereby providing artificially both of the necessary elements of a quasi-Darwinian process of evolution operating on nucleotide sequences[74].

(It's important to point out a distinction between two types of *in vitro* evolution experiments: the first, attempts to recreate to some extent plausible prebiotic formation; the second and currently more prevalent type, use the experimental setup to produce ribozymes with interesting functions, without bothering to limit the reaction conditions to assumed prebiotic conditions. The latter type of experiment understandably yields a wider array of ribozyme types.)

By artificially selecting for particular traits and capabilities of ribozymes, the spectrum of catalytic functions that RNA polymers can be shown to perform is continually expanding to include different types of ligation and polymerisation reactions.

The first order of business is to evolve an RNA polymerase ribozyme – an RNA polynucleotide capable of catalysing the polymerisation of other RNA molecules – and a ligase ribozyme. In one recent development, the Joyce lab has developed a system containing two ribozymes that are able to cross-replicate - they catalyse each other's formation, as well as undergoing selection (Lincoln and Joyce, 2009). This, RNA World proponents hope, is the first step towards an *in vitro* demonstration of an

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[74] For example: In Bartel and Szostak's pioneering protocol, one of the two primer sequences necessary for amplification was added to the start of an RNA template sequence; the other primer sequence was at the end of each of a series of random RNA sequences. The two types of molecules were then allowed to mix, and a subsequent PCR amplification produced a polynucleotide which had a primer sequence at each end, thus selecting for an RNA sequence that could catalyse its own ligation reaction to the template sequence - a ligase ribozyme (Bartel 1993).

RNA-based system evolving to generate novel catalytic functions and bring forth something resembling Eigen's hypercycle.

Critics of this approach make the point that this achievement may well turn out to be about as far as this approach could take, and that expectations of an interesting evolution of the system are unrealistic; they also point to the highly artificial conditions in which the system operates, and ask whether it has any true bearing on the issue of the primordial RNA World, or whether it is destined to remain a demonstration in principle only.

3.2.e.5. Difficulties of the RNA World theory

The RNA World provides a theoretical solution to the "chicken and egg" problem, which, as previously noted, arose upon the elucidation of the details of genetic machinery. It is not the only solution, and faces many difficulties. Some of the more prominent ones are:

- RNA nucleotides are complicated molecule, far more so than, for example, the simpler amino acids, and the functional properties they exhibit as building blocks and genetic material are dependent on the specific configuration of the different component atoms. The numerous other plausible possibilities for the atoms to join up would produce variants of a nucleotide, any of which would 'ruin' an RNA oligonucleotide, preventing it from aligning correctly.

- Ribose is not the main product of the reaction that forms it. The larger amount of "flawed" molecules created chemically would interfere with any formation of RNA.

- Ribose is not chemically stable under most plausible prebiotic environmental conditions.

- Ribozymes, being RNA polymers, decompose in water after performing a limited number of reactions.

- Calcium phosphate, required for the formation of RNA polymers, isn't very water soluble.

- Although purines can be synthesised relatively easily under presumed prebiotic conditions, as we have seen, pyrimidines are far more complicated, and it is less plausible to suggest their spontaneous prebiotic formation in any significant amount.

- Nucleotide polymerisation requires active nucleotides.

- The problem of balance between length and fidelity, discussed previously in the "Hypercycle" section.

- Enantiomeric cross-inhibition: template-directed polymerisation involving one enantiomer of RNA is inhibited strongly by the presence of its mirror image.

(Fry, 2010, Shapiro, 2007, Joyce et al., 1987, Joyce and Orgel, 2006)

Solutions to the various problems are being sought; The ribonucleotide synthesis problem, to take another example, has been addressed by a series of *in vitro* evolution experiments producing (once again, under stringent artificial conditions) ribozymes that can specifically catalyse the formation of purines and the more challenging pyrimidines from simpler substrates (Unrau and Bartel, 1998, Unrau and Bartel, 2003, Lau et al., 2004). This was also a demonstration that ribozymes can in principle catalyse small organic molecules, an important requisite for a primordial ribozyme.

Recent work goes some way towards addressing the problem of RNA's structural stability under prebiotic conditions. A 2009 paper from the Sutherland research group at Manchester made some headway as well as some headlines due to their success at constructing RNA pyrimidine nucleobases– the hard-to-produce individual cytosine and uracil (the 'C' and 'U' units of RNA, respectively) by challenging the assumption that because nucleobases are composed of 'base' and 'sugar' components,

then this was also the order of their prebiotic formation[75](Powner et al., 2009). Sutherland and co-workers demonstrate a chemical pathway that starts off with the same precursor molecules as the ones for free ribose and separate nucleobases, but proceeds via a different intermediate – all this under conditions that the authors maintain are consistent with primordial prebiotic conditions (Cheng, 2010). Sutherland:

Experimentally, there have been several notably successful reactions that ostensibly support this nucleobases ribosylation approach…Indeed, for many years, a prebiotically plausible synthesis of ribonucleotides from ribose 3, the nucleobases, and phosphate has been tantalizingly close but for one step of the assumed synthesis – the joining of ribose to the nucleobases. This reaction works extremely poorly for the purines and not at all in the case of the pyrimidines.(Sutherland, 2010)

Regarding the Sutherland pathway, it should be emphasised that the RNA World theories and explanations all hinge on the possibility of prebiotic formation of RNA polynucleotides of sufficient length and stability to be able to maintain their structural integrity and to interact with each other over time. Since this is not, as we have seen, particularly in keeping with what is known of the RNA molecule's properties, this theory is therefore not a 'bottom-up' continuation and development of findings in Origin-of-Life research, but a back-extrapolation of findings in existing systems to primitive ones.

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[75] One's first impulse is to applaud this fine example of the researchers thinking 'outside the box' and ignoring the categorisations, imposed by chemistry conventions, on arrangements of atoms. However, we should bear in mind that these conventions are not arbitrary - not in the chemical context, and especially not in the biochemical context. The living cell does metabolise sugar and base as distinct units rather than in Sutherland-type composites. This is not to mean that the prebiotic pathway to RNA subunits can be ruled out on the grounds of "argument from present biochemistry", but it should be pointed out that "RNA World" supporters regularly invoke present biochemistry to lend strength to its historical claims.

3.2.e.6. Pre-RNA Worlds

The 'RNA World' school of thought is itself divided in two. The first views RNA as the original replicating molecule, the one first formed by pre-biotic processes. The second camp claims that RNA is far too complex a molecule to emerge from prebiotic sludge. Although the RNA world did exist, they maintain, it was preceded by 'worlds' of other, more rudimentary, types of replicating molecules

A good demonstration of the differences between the two camps can be made by comparing the two first papers of the latest (2006) edition of the definitive RNA World book. Benner et al. end their contribution thus:

A decade ago, the absence of mechanisms for synthesizing and stabilizing RNA precursors such as ribose, combined with the promise of alternative molecules for storing genetic information, would have inclined us to doubt an RNA-first model for the origin of life. This would encourage the believers in the RNA World to also believe in a pre-RNA World that used a genetic system.

Today, given the limitations of alternative genetic polymers, the lack of evidence for a pre-RNA World or genetic takeover, and a clearer understanding of the details of the prebiotic synthesis of ribose, its stabilization by minerals, the availability of these minerals in natural geology, and the example found on Mars by the Opportunity rover, this encouragement is no longer as strong. Although far from compelling, the RNA-first hypothesis appears to be more defensible today than it was a decade ago, and provides a useful starting point for more hypothesis-driven research into the origin of life." (Benner et al., 2006)

In the immediately following paper of the same volume, Orgel and Joyce write:

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[A]thorough consideration of this 'RNA-first' origin of life inevitably triggers 'The Prebiotic Chemist's Nightmare,' with visions of the intractable mixtures that are obtained in experiments designed to simulate the chemistry of the primitive earth. Perhaps this continuing nightmare will eventually have a happy ending, but our view is not optimistic. Instead, we believe that it is fruitful to consider the alternative possibility that RNA was preceded by some other replicating, evolving molecule, just as DNA and proteins were preceded by RNA. (Joyce and Orgel, 2006)

To engage with the problem of the highly improbable spontaneous formation of a functional RNA molecule or set of molecules from prebiotic substrates, other 'worlds' preceding the RNA World, leading to it and which have subsequently been 'overwritten' by it, so that no traces of them can be found at present, have been suggested, some of them more plausible than others, some more empirically supported than others.

Supporters of the hypothesis that RNA was the first genetic material must explain where the nucleotides came from and how they self-organized. Those who believe in a simpler precursor have the difficult task of identifying such a precursor, but they hope that explaining monomer synthesis will then be simpler.(Orgel, 1998)

To be considered successful, a pre-RNA World model has to present a molecule type capable of performing what RNA can – base pairing, faithful replication, catalytic abilities, etc. Another highly regarded attribute would be an indication of some way by which it could lead to the RNA world (such as the capability to base-pair with RNA). It should also satisfy another condition: that it exhibit some chemical rationale for the system's ultimate transfer from the simpler precursor to RNA.

Apparently the physical and chemical properties of RNA were advantageous for its primitive role

as information carrier and catalyst and eventually allowed it to usurp the function of some precursor

genetic material during the early history of life on earth. (Joyce et al., 1987)

Several such alternatives to RNA have been suggested[76]: a leading candidate is peptide nucleic

acid (PNA), a DNA analogue with a peptide backbone replacing the sugar-phosphate one of RNA or

DNA (Nielsen, 2007, Nielsen, 1993, Nelson et al., 2000, Nielsen et al., 1991). Originally conceived for

clinical uses (Nielsen et al., 1991)[77], it is simpler than DNA or RNA, a-chiral, and since its backbone is

composed of amino acids (which readily appear in Miller-type experiments), rather than the elusive

sugar-phosphate backbone, a prebiotic formation is easier to envision – although no detailed prebiotic

scenario has been laid out. Also easier to envision is PNA's compartmentalisation, as it is a

hydrophobic molecule (Rasmussen et al., 2003). Other possible progenitors of RNA include alanyl-PNA

(ANA) (Diederichsen, 1998); threose nucleic acid (TNA) and its analogue glycerol nucleic acid (GNA)

(Ying-Wei, 2007), and also p-RNA (Eschenmoser, 1997, Eschenmoser, 1999), a modified variant of RNA.

Of all the above alternative molecular species, none has yet been demonstrated to form

abiotically. They are all artificial derivations of RNA or DNA, synthesised using modern automated

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[76] Alternative base-pairing molecules can be constructed with the explicit intention of modelling RNA precursors in a prebiotic or newly biotic world, but that does not have to be the case; DNA/RNA alternatives have been constructed with little or no attention to Origin-of-Life questions, being of interest as a tool for exploring questions regarding DNA and/or RNA's chemical structure and function, as well as what might be termed nature's rationale for selecting the genetic material it did (Eschenmoser, 1999).

[77] Due to its ability to hybridise with DNA and RNA, PNA is considered for use as a diagnostic tool, as well as having rationally-designed PNA oligomers and catalysts act as induced antisense gene regulators (Nielsen, Eghom et al, 1991; Gaglione, 2011).

oligonucleotide synthesisers; an acceptable stepwise pathway leading from the inorganic world to an RNA one via these or other genetic intermediates is yet to be proposed.

3.2.e.7. rRNA

Ribosomes are crucial and ubiquitous components of every living cell's genetic machinery. It is they who carry out the cell's translation processes: the ribosomes attach themselves to a messenger RNA molecule and proceed to polymerise amino acids, in an order determined by the mRNA sequence, into polypeptide chains to create the cell's proteins. Ribosomal structure is highly conserved throughout nature, a fact whose implications to phylogeny we will be dealing with in greater detail in the next chapter.

It has been known since the early 1970s that ribosomes are composed of both RNA and protein, forming ribonucleoproteins. It was not known what role each component plays in the translation process, but the straightforward and most popular assumption was that it was the protein moiety that catalyses the peptidyl transferase reaction (the reaction responsible for creating the peptide bond linking one amino acid to another) that creates the elongating chain of amino acids.

The ribosomal RNA was supposed to perform supporting structural roles[78], but evidence that something else was happening began to accumulate. In 1992 Harry Noller indirectly demonstrated that rRNA is elemental to the peptidyl transferase reaction (Noller et al., 1992), but it was only late in

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[78] "...the overwhelming preponderance of opinion in the translation field was that the functions of the ribosome were determined by the proteins..." (Noller 2006).Noller was among the first to challenge this opinion, and here he is writing after his challenge was proven successful, so his pronouncement could perhaps be taken with a grain of salt. Be that as it may, the discovery of the true way the ribosome functions did indeed prove to be a surprise.

the year 2000 that a long and laborious project of mapping out the atomic structure of the ribosome, initiated by Ada Yonath in the 1980s, came to fruition.

The discovery of the role of ribosomal RNA in translation was significant to thinking about the RNA world. The ribosome's protein component's role is a structural one – it orients and stabilises the molecules involved – whereas the core 'informational' sequence-specific action of the ribosome is performed by the ribosome's RNA component. Thus, it is the RNA component which is the component of the ribosome. It is therefore highly plausible that rRNA was the original component of this 'machine', with the supporting ribosomal proteins evolving later:

Evidence for an earlier biosphere on Earth that relied on RNA before the emergence of encoded proteins comes from the structure of the ribosome. An RNA component of the ribosome appears to be in direct contact with reacting atoms as the peptide bond is formed (Moore and Steitz 2003). Given the homology among all ribosomal RNA, one can infer from the ribosomal structures from even a few organisms that the synthesis of all peptide bonds on Earth is catalyzed by RNA (Harms et al. 2001), and that their common ancestral ribosome also used RNA to catalyze peptide bond synthesis. This completes the use of structural biology to define the concept of the RNA world, a use that began with the structure of transfer RNA (Kim et al. 1974), which prompted Francis Crick to comment that tRNA looked like a molecule trying to be a catalyst (Crick 1968).(Benner et al., 2010)

3.2.e.8. 'Paleogenomics'

A main attraction of the RNA World hypothesis lies strongly in the fact that it is traceable back from the present conformation of life. RNA is found at all the critical junctures of the molecular processes, and therefore RNA can be seen as a sort of molecular 'living fossil'; its various forms being

modern variants of the original RNA molecules which held these roles exclusively in the prebiotic and early biotic past, and were later modified by natural selection: the ribosome 'grew' a protein scaffold around its core RNA unit; RNA genes gradually separated into a more chemically stable form (DNA) and a more dynamic short-lived type (messenger RNA), and so on.

By the end of the 1980s, sufficient sequence data were available to take the next step. Here, comparative genomics was used to infer the entire genetic complement of the organism that is represented in the universal tree as the organism connecting the archaeal, bacterial, and eucaryal kingdoms (Benner, Kim et al. 2010)

Advanced molecular sequencing techniques made comparative genomics feasible. Comparison of ribosomal RNA (rRNA) sequences from different organisms and genera reveals the remarkable degree of similarity between them. This attribute made the reconstruction of taxonomic relationships through examining the differences between the rRNA sequences, as we shall discuss below, but in addition, there was considerable legitimacy gained by the RNA World hypothesis from the similarities themselves. It became evident that in addition to the delivery of genetic information to the cellular protein-production machinery, RNA molecules were embedded within the machinery itself – and that this was true across the entire spectrum of taxa and therefore (one may reasonably assume) true for the Last Universal Common Ancestor.

3.2.e.9. The RNA World – Summary:

The RNA World hypothesis emerged as one of several ideas regarding the origin of life. A host of molecular tools developed throughout the 1970s and reaching maturity in the 1980s provided it with accessibility to experimental testing; these same tools enabled discoveries in the natural domain that

highlighted the crucial roles that RNA plays within the genetic processes. Thus the RNA World, though it does not lack its critics, is currently the most well-received theory in the Origin-of-Life field. Despite its many extant problems, for its proponents, the RNA World has become something closer to a historical fact than a suggested model. Szostak et al. open their review of developments in the field with the pronouncement:

The reality of the 'RNA World'….has been firmly established by recent structural studies of the ribosome…With the reality of the RNA World so strongly supported, the questions being asked about this early stage or life now focus on the transition from prebiotic chemistry to the RNA World, and then from the RNA World to the world of modern biochemistry.(Chen, 2006)

The next Origin-of Life theory has not fared quite as well:

3.2.f. Mineral Life

The initial idea that inorganic clays might have had a role in the origin of life was first proposed by J.D. Bernal in 1949 in his influential lecture titled The Physical Basis of Life¸ which was published in book form shortly afterwards (Bernal, 1951).

Chemist Alexander Graham Cairns-Smith of the University of Glasgow proposed a theoretical system of mineral-based self-replication (often referred to as the Clays Theory): that an intermediate step between inorganic matter and organic life might be provided by the self-replication of clay crystals in solution. The resemblance between inorganic crystal growth and the growth of organic living forms was not new at the time – Schrödinger's 1944 description of an 'aperiodic crystal' forming the stuff of genes (Schrödinger, 1944) is a familiar example of the use of the analogy, but we can find

references to crystals in the origin of life at least as far as A.E. Schäfer's presidential address to the British Association for the Advancement of Science's annual meeting in 1912 (Schäfer., 1912)[79].

Bernal did not treat mineral clays just as analogies, but suggested that clays provided chemically active sites at which the first prebiotic reactions could take place. Cairns-Smith's theory, which he initially put forth in the mid-1960s (Cairns-Smith, 1966) and continued to develop in a series of papers culminating in a scholarly book (Cairns-Smith, 1982) followed by a readable popular work (Cairns-Smith, 1985), went one further to suggest that the clays themselves can be seen not only as catalysts, but as prebiotic genetic systems in their own right, formed by a prebiotic version of natural selection, and that the origin of life included what he called a genetic metamorphosis (later normally replaced by the term genetic takeover) – a stepwise[80] transfer of 'informational' systems from these primitive inorganic clay systems to the present mechanism.

Cairns-Smith's theory is an elegant one; one of its intellectually attractive features is that it starts from inorganic materials that can be safely assumed to have been present in adequate amounts on the prebiotic earth, and moves from that point on, thus bypassing (or at the very least delaying to a later stage) many of the difficulties experienced by other Origin-of-Life theories attempting to explain how the constituent molecules of the first replicators came to form. Its strength lies in the fact that organic chemistry comes in after the genetic system had been established and is already in operation. Cairns-Smith writes:

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[79] Schäfer's talk apparently espoused a quite boldly materialist viewpoint of the origin of life; it stirred up some critical responses from his peers, including Alfred Russel Wallace.

[80] Interestingly, Cairns-Smith does not rule out the possibility that the shift from the inorganic system to the present DNA-RNA-protein system could have taken place with a single step.

[T]his is the question that should be the first focus of our attention: What are the simplest genetic memories that we can imagine working in a primitive geochemical milieu? The RNA world idea has been a great inspiration, but this system is already too sophisticated and too far from ordinary geochemistry to be a likely beginner in the evolution game. I have suggested that the mineral world provides us with several candidates for more primitive genetic materials (Cairns-Smith 2005, 2008 and references therein). I will argue against the usual approach to the puzzle of the origin of life, which looks for ways in which the present molecules of life might have arisen as a prelude to a Darwinian evolution. I think that this puts the cart before the horse. I will suggest rather that natural selection came first, based on inorganic materials, and that "the molecules of life" were a crucial but later part of the story.(2009)

This 'crystalline genes' concept is discussed in nearly all overviews of the Origin-of-Life field – and beyond. As a strictly Darwinian theory, and since it is decidedly placed within the 'replicator-first' framework and places such emphasis on the centrality of genetic information, it is not surprising that Richard Dawkins had chosen it as a representative example of a plausible abiogenetic theory in both The Selfish Gene(Dawkins, 1976) and The Blind Watchmaker(Dawkins, 1986), joined by, among others[81], Daniel Dennett in Darwin's Dangerous Idea (Dennet, 1996). It would be hard to think of an Origin-of-Life theory that would conform more closely to Neo-Darwinian gene-selectionist thinking.

Thus far we have looked at the development of the ideas; what experiments have been performed?

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[81] A literary example (found in Hazen 2005, p.155): novelist John Updike references the Clay Theory in Roger's Version (Updike 1986), wherein a character proclaims "I happen to know exactly how lifearose....Clay is the answer...all life did, you see, was take over the phenotype that crystalline clays had evolved on their own.".

Bernal's clay concept has been lent strength by experiments starting in the late 1970s; though no conclusive pathway can be shown, this approach now forms a significant part in some other theories. In their review of the origin of the RNA World (Joyce and Orgel, 2006), Joyce and Orgel explain how minerals are something like a 'poor man's enzymes' (not their phrasing). The ability of charged minerals to catalyse chemical reactions, combined with the large variety of possible minerals which ensures that a suitable candidate can be found for just about every reaction that 'needs to be' catalysed, makes it possible to envision chemical reactions taking place in non-enzymatic environments. Thus, and due largely to work by Ferris and co-workers (Ferris, 1996, Ertem, 1996, Ferris et al., 2004), minerals have become an important part of some abiogenetic models (including some variants of the RNA World hypothesis).

Some view this flexibility in more critical terms. The fact that an Origin-of-Life model can include a hypothetical clay-based explanation for any desired catalytic reaction makes it perhaps too convenient for comfort. As Robert Hazen (whose research touches on clay issues regularly) writes: "these 'magic powder' aspects of clays leave me frustrated" (Hazen, 2005)

In contrast to these advances in the clays-as-catalysts approach, experiments testing Cairns-Smith's concept of crystalline genes are much less prevalent. The previously mentioned discussions of Cairns-Smith's theory in Origin-of-Life reviews are followed by the caveat that, however ingenious the theory, experimental verification for it is lacking:

It has been claimed that the redox and binding affinities of montmorillonite clays can be propagated from preexisting to newly grown layers of clay (Weiss 1981). But efforts to define and reproduce these observations have not been successful (Arrhenius et al. 1986). Thus replication of clay

"information" has remained hypothetical, and transfer of replicated clay properties to nucleic acids even more so. (Yarus, 2011)

It is only very recently that Kahr and co-workers have performed an experiment attempting to observe–- using advanced dyeing and microscopy techniques – gene-like dynamics in an experimental setting (which, the authors scrupulously note, was not aimed at replicating any plausible pre-biotic earth conditions). As the authors write:

Herein, we have presented an experimental test of [Cairns-Smith]'s hypothesis of defect-laden crystals as analogs of prebiotic genes. Our goal was not to solve the problem of the origin of life but was much more modest: to rescue the proposals of CS from the 'limbo of uninvestigated hypotheses'(Bullard et al., 2007).

The results of this preliminary experiment and a few others (Schulman and Winfree, 2011) are, to no one's surprise, only a first step towards validating or rejecting Cairns-Smith's theory. The fact that this first halting step was taken only after over four decades had passed since the inception of the theory (four decades, moreover, of the most intense and large-scale overall scientific activity in history) stands in peculiar contrast to the theory's popularity both within and (arguably to an even larger extent) outside the Origin-of-Life community and its laboratories.

I maintain that it is precisely this unique combination of characteristics of the crystalline gene theory – its close fit to a dominant trend within evolutionary theory, combined with its pristine status, unsullied by experimental tinkering – that has enabled it to survive for so long on the list of viable Origin-of-Life scenarios.

A compelling reason for this practically unique status of the Cairns-Smith theory within the myriad collection of Origin-of-Life theories is that it posits a form of genetic system that is technically extremely difficult to decipher. The structure of the DNA double helix was revealed by X-ray crystallography, and the details of the code later deciphered via nucleic acid sequencing techniques. Due to the physical properties of the molecules that would be involved in crystalline gene formation, the comparable capacity for reading the 'sequence' of a presumed crystalline gene is still beyond the capabilities of labs today.

In addition to these physical limitations, there is also the issue of effort: most Origin-of-Life theories are concerned with organic molecules and their precursors; these have been extensively studied due to their importance in biochemistry and biomedicine in general, and analytical equipment and techniques are easily found. In contrast, the range of inorganic reactions is both wider, as it is not confined to known biochemical reactions and constituents, and less closely examined. This is a direct result of the Clay Theory's starting position: since it explicitly resists taking any hints from existing biochemistry, and starts from scratch, the path to a crystalline gene begins at an unknown point somewhere within the little-explored inorganic realm. It may well be that this point (assuming it exists, of course) has been of no particular previous interest to anyone, making any experimental attempt at analysing the chemical pathway a formidable task indeed.

An optimistic view of this state of clay theory would compare Cairns-Smith to the early formulators and supporters of the gene concept in previous centuries; like them, his theory will also have to wait 'in limbo' for however long it may take until the technical know-how for testing it is in place.

3.3. Extremophiles

Another significant development of the late 1960s was the discovery of microbial species known as extremophiles. These are microorganisms capable of survival and reproduction in 'extreme' terrestrial environmental conditions (including temperature, salinity, desiccation, acid and alkaline pH, radiation, pressure, and virtually every other measurable environmental factor), and they went largely unnoticed by humanity until the 1965 isolation of a heat-resistant bacterium (named Thermus aquaticus) from the hot springs at Yellowstone National Park by microbiologist Thomas Brock of Indiana University (Brock, 1997, Brock, 1995, Setchell, 1903, Brock, 1967)[82].

This event marked the start of modern extremophile research; soon more extremophile species, occupying all kinds of inhospitable ecological niches, were being discovered.

There are several important implications this discovery had on Origin-of-Life studies. The discovery of extremophiles:

- Informed, as we have discussed, the Viking life-detection efforts.

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[82] Studies suggesting the existence of organisms in temperatures up to 89 degrees Celsius were carried out at Yellowstone National Park around the turn of the 20th century (Setchell, 1903), but received scarce notice. The radiation-resistant Deinococcus radiodurans was isolated in 1956 (Anderson, 1956) and was likewise largely ignored at the time. Brock, who came to microbiology via a circuitous route - he was originally educated in botany - was interested in microbial ecology and the study of microorganisms in nature rather than under laboratory conditions. As he writes:

The study of microbes directly in the natural habitat led to the discovery of extreme thermophiles. A reliance on enrichment culture techniques and standard incubation temperatures of 55°C had caused investigators working up to that time to miss them. (Brock, 1995).

- Made Carl Woese's phylogenetic revolution (see chapter 4) possible. Although it is now known that archaeal species can be found living in all sorts of conditions and environments, including those that we would not consider 'extreme', it was extremophilic species of Archaea who were first recognised as such.

- As a technical side effect, it made the Polymerase Chain Reaction a common technique: it so happens that a thermostable DNA Polymerase enzyme, isolated from the thermophilic Thermus aquaticus, was the crucial element needed to transform PCR from a fairly laborious process into one that is very easy to perform. This helped PCR to 'take off' and become the ubiquitous and multifunctional technique it is today, with significant effect on genetic and genomic sequencing and manipulation and other uses, including the more advanced experiments relating to the RNA World.

- Enabled the advancement of extreme environment Origin-of-Life theories – the Iron-Sulphur world, black smokers, etc. – as will be discussed in the next chapter.

3.4. Conclusions

Arriving at the mid-1970s, the prospects for the Origin-of-Life field were not at their best. Although humanity had reached outer space, it (or, to be precise, the two small patches of the surface of Mars that had actually been examined with any care) had not yielded solid evidence for life. The 'chicken and egg' problem refused to go away, and although several suggestions, some of them highly ingenious, and some of them highly relevant to research in later decades, had been made to resolve it, the ones who were suggesting something other than either 'aliens did it' or 'it was a lucky fluke' still lacked any empirical backing. The right way forward for researchers was less clear than it was at any point since 1953.

Some of the problems brought to the fore during this period are still plaguing the field today: extra-terrestrial planets remain a difficult-to-reach and hugely expensive place in which to search for evidence of life, and the move from prebiotic chemistry to an operating cellular or pre-cellular protobiological system is still waiting for a robust explanation. However, advances in laboratory techniques and in biological (and especially microbiological) discovery which were happening during that difficult time, would open pathways for research efforts in the following decades. These will be the subject of the next chapter.

Chapter 4: 1976-Present

4.1. Introduction: Planetary Considerations and the Fossil Record

The current age in Origin-of Life research traces its roots to three realisations that emerged starting in the late 1970s and early 1980s, which forced some changes in the working assumptions held by most practitioners (though the most fundamental assumptions of abiogenesis remained unchanged). An in-depth discussion of each of these lies outside the scope of our review, but the essence is as follows:

First, the time frame for the appearance of life was severely constricted by findings of microfossils. Evidence was found that microorganismal life was stable and flourishing 3.5Gy ago – about 300 million years after environmental conditions had stabilised (see below). The preliminary microfossil findings emerged in 1954, acquired strength in 1960s findings, and were generally accepted following a 1977 paper in Science by Barghoorn and Knoll (Knoll and Barghoorn, 1977, Schopf, 1999)[83].

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[83] The debate over the age of the oldest fossils is far from settled; key findings made in 1993 by William Schopf, have been challenged in 2002 (on a similar basis to the challenge made to the ALH84001 evidence- a non-biological explanation for the "fossil" indentations was offered; in the ALH84001 affair, Schopf was arguing against a biogenic origin of the Martian fossil evidence). Very recently a counter-challenge was made. (Schopf, 2002; Brasier, 2002; Wacey 2011)

Second, the Earth's atmosphere was no longer generally considered a reducing atmosphere, a consideration that was central to the field of prebiotic chemistry since the time of Oparin and of Miller. A growing body of evidence and argument brought to the fore the concept of a neutral or weakly oxidising atmosphere, with high levels of carbon dioxide and atmospheric nitrogen, rather than the reactive ammonia and methane (Levine et al., 1982, Walker, 1977, Chyba, 2005, Kerr, 1980, Kasting, 1993). This would allow for a much less chemically active atmosphere, and one that would be much less favourable to Miller-Urey type reactions, as Miller himself argued (Stribling and Miller, 1987).

The transition from one mode of thought to the other was by no means sudden, or complete; in the geochemical community the idea of the reducing atmosphere was contested since before the Miller-Urey experiment; the debate on the nature of the primitive earth's atmosphere never disappeared, and today is far from settled, with several competing models – including a reducing atmosphere – under consideration (Zahnle et al., 2010).

The third realisation was a growing consensus, that the early earth had passed through an era of 'heavy bombardment' – a period when large asteroids and other cosmic debris would slam into the earth, disrupting atmospheric conditions and causing evaporation of surface water and turning a large portion of the earth's oceans to hot steam. This realisation was fuelled, among other things, by observations of impact craters on planetary bodies, and radioactive sampling of impact craters on the moon and the earth.

An era of heavy bombardment was a state of affairs that would considerably weaken the case for the development and continual survival of life on or near the earth's surface (Sleep et al., 1989). Since this period is assumed to have ended about 3.8Gy and life was probably extant by 3.5Gy, there were about 300 million years for life to develop unless shielded from the impacts of heavy bombardment.

The combination of these three constrictions robbed Origin-of-Life mainstream theories of both a sizeable chunk of time for life to form, and of an accepted atmospheric source of reactivity to drive this formation. It thus became necessary to seriously rethink the (by now traditional) view of a steady, unhurried, gradual formation of prebiotic compounds and their coming together driven by atmospheric reducing forces, a view that had been central to the field from its earliest days (Wald, 1954).

One important element in the new equation was a growing appreciation that carbonaceous meteorites, such as the Murchison meteorite, could have been the source for a significant amount of prebiotic molecules (Chyba and Sagan, 1992). The original findings of organic molecules in the Murchison and other meteorites, as well as comets, whose contribution was suggested (as noted in section 2.3) by Joan Oró as early as 1961 (Oró, 1961), were initially highly interesting because they suggested that conditions enabling such molecules existed beyond the earth; now these meteorites were viewed as a major source for the terrestrial scenario of the emergence of life. This was in addition to terrestrial sources of organic molecules (from the earth's crust, atmospheric reactions, as well as Miller-type discharge reactions) (Hazen, 2005).

At sufficiently high energy fluxes, such mixtures of reduced gases generate hydrogen cyanide and formaldehyde, which in turn react by Strecker synthesis to produce amino acids, purines, and a variety of simple sugars. The proposal that organic compounds could be synthesized under prebiotic conditions

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was given additional weight when it was convincingly shown that carbonaceous meteorites contained amino acids, hydrocarbons, and even traces of purines [13–15]. If such meteorites represent samples of the primitive solar system components that underwent synthetic chemical reactions, it was reasonable to assume that similar reactions may have occurred on the Earth's surface.

This view was challenged in the late 1970s when lines of evidence emerged that the early atmosphere was composed of carbon dioxide and nitrogen rather than the mixture of reducing gases assumed by the Miller–Urey model. Carbon dioxide does not support synthetic pathways leading to chemical monomers, so interest was drawn to the second potential source of organic material: extraterrestrial infall in the form of micrometeorites and comets…The total organic carbon added by extraterrestrial infall over $\sim 10^8$ years of late accretion can be estimated to be in the rage [sic] of 10^{16}–10^{18} kg, which is several orders of magnitude greater than the total organic carbon in the biosphere. From such calculations it seems reasonable that extraterrestrial infall was a significant source of organic carbon in the prebiotic environment. (Wächtershäuser, 1990b)

Due to the new findings, prebiotic chemistry now had to shift location – it was now searched for not only in prebiotic simulations, but also beyond the confines of planet earth. This is one reason for the advent of NASA's astrobiology program.

It should be noted that, in retrospect, the geochemical evidence for a strongly reducing atmosphere was never as compelling as one would have believed from reading Origin-of-Life material generated between 1953 and the late 1970s. There are grounds for arguing, as some have (Kerr, 1980, Gribbin, 1982), that the strength of the Miller-Urey results (and the prebiotic experiments following them) provided a substantial disinclination for the Origin-of-Life community to consider non-reducing

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alternatives. More speculatively, these compelling results may even have reached beyond the Origin-of-Life research community to influence geochemists themselves. The existence of past and present life on earth is a geological fact, and can be applied in arguing for or against a historical geological scenario.

4.2. Changes in the Microbiological Landscape

The late 1970s were also the time of significant findings in microbiology, and they in turn changed the Origin-of-Life field. As we have seen in previous instances, discoveries of hitherto-unsuspected existing forms of life strongly influence theories of possible life.

In addition to the Woese findings I shall discuss below, the results of a pioneering exploration of deep-sea hydrothermal vents, undertaken in February 1977, were published in 1979 (Corliss et al., 1979)[84]. Prior to this expedition, the deep ocean floor was assumed to be a barren, sparsely populated wasteland. Any organisms to be found there would subsist on nutrients and energy reaching the ocean floor from surface plant life. Hence the surprise engendered by all when it was discovered that entire ecosystems were flourishing around the vents. These ecosystems were fuelled not by plant life, with sunlight as a source of reducing power (the ultimate source of energy of every ecosystem then known), but by nutrients and energy derived from these vents by thermophilic, chemo-autotrophic bacteria feeding on the dissolved minerals bursting from the vents, and producing organic material via a metabolic system reliant on sulphur compounds, particularly hydrogen sulphide.

A model for the origin of life based around these findings followed quickly thereafter from Jack Corliss, the marine geologist who first glimpsed the hydrothermal vents, and co-workers (Corliss,

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[84] Note that the idea of the existence of these hydrothermal vents wasn't around for too long before that, with the plate tectonics model only being accepted in the early 1970s.

1981)[85]. This Corliss-Baross-Hoffmann model of life developing near hydrothermal vents made it easier to explain the origin of life given a non-reducing primitive earth environment, provided a safe and stable environment, unaffected by ultraviolet radiation or meteor and comet strikes, and tied in with the newly emerging ideas regarding the antiquity of extremophiles (as opposed to the traditional view of extremophiles being a late adaptation – see below) and provides us with another instance of a discovery of a type of life followed very shortly by a general theory of Origin-of-Life.

As expected, the model was a subject of criticism, and was published only in a minor geology journal. Stanley Miller and Jeffery Bada, protective of their reducing atmosphere/surface origin model, dismissed Corliss et al.'s idea, arguing that the excessive heat involved would be a contributing factor to the disintegration of organic compounds of increasing complexity, rather than their synthesis, and moreover that the idea was too speculative and had not been demonstrated experimentally. This last criticism held true – the Corliss-Baross-Hoffmann model was rather generalised and lacked experimental support.

However, over the years more hydrothermal systems have been found. Organic molecules under high pressure and temperature conditions in an aqueous environment have been found to be chemically reactive (Hazen, 2005, Hazen et al., 2002, Bassez, 2003, Orgel, 2004); meanwhile, the development of the Wächtershäuser model (to be discussed below) in the late 1980s, posing an alternative to a reducing general environment due to its iron-pyrite surfaces acting as a chemically

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[85] The history of the paper is a contentious one. Sarah Hoffmann, then a student, claims to have come up with the model in consultation with John Baross, and to have sent it to the more senior Corliss for review, whereupon Corliss added his name to theirs and submitted it. Corliss claims that the idea was originally his (Hazen, 2005, p.97-8).

active environment enabling chemical reactions to proceed, provided a rather more solid theoretical foundation to the concept of a hydrothermal origin of life.

Today the 'hydrothermal vent' theory of the origin of life is considered a legitimate contender in the field, and has sprouted several versions. It has also not been lost on Astrobiology workers that a hydrothermal vent model, with its novel chemo-autotrophic metabolic pathways not reliant on sunlight, is a promising avenue for the emergence of life elsewhere in the cosmos; the liquid oceans of Europa, submerged below a sheet of ice, have been proposed as a promising site in which to search (Barry, 2001)

Finally, before moving on, we should note that Corliss et al. had not been the first to speculate of a deep-sea origin of life:

Degens hypothesized [in 1968 and 1971] that hydrothermal systems, like the ones of Lake Kivu in the East African Great Rift Valley, would be perfect environments for primitive life forms to evolve. He considered three criteria necessary for any model on the origin of life. The system must: 1) be thermodynamically feasible, 2) have a high yield, and 3) allow for chemical evolution towards a primordial cell. (Holm, 1992)

Although Weyl (1968) did not discuss abiotic processes in hydrothermal systems he preferred deep water environments for modelling the origin of life. The reason for doing this was that newly formed organic aggregates would have been shielded from hazardous ultraviolet radiation at depth. Solar ultraviolet light is quenched by only a few meters of water. However, the necessity of a protective screen for early life from radiation and impacting objects from space has become a major argument lately in favour of the hydrothermal model." (Holm, 1992)

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But there was no impact of these speculations on Origin-of-Life research until the 1979 evidence

of actual organisms living in hydrothermal deep ocean systems.

4.3. Carl Woese's influence on Origin-of-Life research

Carl Woese of the University of Illinois is one of those researchers who are not considered a part of the Origin-of-Life research community (by himself or by the community), but whose name nevertheless tends to emerge when discussing Origin-of-Life issues. A biophysicist by education, his research was a significant factor in revolutionising thought regarding the roots of the evolutionary tree.

We have previously seen that Woese suggested the possibility of an RNA World in 1967. We will now have a look at two additional contributions he has made to the Origin-of-Life field. The first and major one is his work in molecular phylogenetics; we will look into the various implications of this work. The second item is Woese's 'cloud model' – his only attempt to suggest a 'bottom-up' prebiotic Origin-of -Life scenario.

4.3.a. The three-domain revolution

On the 3rd of November 1977, NASA and the National Science Foundation (NSF) released a joint press release announcing a "third form of life". The announcement made the front page of the New York Times. The scientific community was more critical, with several prominent scientists rejecting the idea (Pace et al., 2012), which was put forth by Carl Woese.

Woese's shake-up of the foundations of the taxonomic tree has been extensively documented. Briefly, with the development of amino acid and nucleic acid chain sequencing methods came the ability to compare these sequences between different organisms. Woese, who as we saw in chapter 3

was actively pursuing RNA research, recognised the potential of these sequencing methods to bring forth a major advance in taxonomy. He suggested (Balch et al., 1977) that ribosomal RNA sequences would provide a good molecular clock with which to compare organisms. The nucleic acid sequencing techniques that were by then available made it possible to make these comparisons. The 5S and 16S bacterial ribosomal RNA subunits were discovered to be extremely conserved throughout nature; 16S rRNA sequencing provided Woese and his co-workers with an excellent classification tool. The work initially focussed on the 5S rRNA component of the bacterial ribosomes (due to technical sequencing constraints), and later shifted to the 16S component. The method used was the laborious (and somewhat dangerous) sequencing technique named "oligonucleotide cataloguing", derived from the Sanger method (and introduced to Woese by a postdoctoral worker from the Sanger laboratory)[86].

Woese's ideas of these times were retrospectively summed up by himself in a recent paper:

Woese foresaw the unique possibilities for molecular biology, through Sanger sequencing specifically, to address questions about the evolutionary process. For Woese, molecular biology was more than just a tool to expose the workings of the cell machinery. (Woese and Goldenfeld, 2009)

Woese's motivations for [a research program to determine the universal phylogenetic framework] at the time are perhaps best captured in a letter written to Francis Crick, dated June 24, 1969. In that letter, Woese writes: 'If we are ever to unravel the course of events leading to the evolution of the prokaryotic (i.e., simplest) cells, I feel it will be necessary to extend our knowledge of

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[86] Woese's Herculean sequencing effort has been justifiably lauded; but it is a sobering thought, and one that I have not seen expressed, that, had he not undertaken it, the introduction of PCR a decade later (its development independent of Woese's work) would have made the task infinitely easier - as indeed it had for subsequent sequencing projects.

evolution backward in time by a billion years or so –i.e., backward into the period of actual "Cellular Evolution". There is a possibility, though not a certainty, that this can be done by using the cell's "internal fossil record" – i.e., the primary structures of various genes. Therefore, what I want to do is to determine primary structures for a number of genes in a very diverse group of organisms, on [sic]the hope that by deducing rather ancient ancestor sequences for these genes, one will eventually be in the position of being able to see features of the cell's evolution –i.e., by knowing what features of the primary structures are "locked-in", what regularities (repeats, etc.) existed, and how one ancient primary relates to another ancient primary structure(s) [sic] (which gave rise to some different cellular function).'(Woese and Goldenfeld, 2009)

The molecular approach to taxonomy was not entirely new – Francis Crick first suggested it (regarding amino acid sequences rather than nucleic acid ones) in 1958 (Crick, 1958), and Linus Pauling and Emile Zuckerkandl gave the matter more serious consideration from 1962 onwards (Zuckerkandl and Pauling, 1965), but sequencing technology had to achieve a certain level of efficiency before a meaningful and even partially representative comparison between equivalent genetic elements from several different samples were to be made. Before Woese, Zuckerkandl and Pauling's 1965 paper was cited by only two papers (Bellett, 1967, Storck 1970), and both were advocating molecular taxonomy by estimating nucleic acid composition in different species rather than by sequence.

Molecular tools proved to be the "great equaliser"; Woese's approach provided the possibility of classifying the entire prokaryotic realm, hitherto approached by taxonomists only with difficulty:

When dealing with molecular sequences an evolutionist feels a sense of liberation; he is no longer confined to the world of "higher forms." From the vantage point provided by molecular data, he

now gazes over the Cambrian "wall" that had obstructed his temporal perspective...It is not only the evolutionist who has benefited from our exploration of the molecular world. One has only to look to microbiology to see this. Here was a science that, devoid of an evolutionary framework (a natural system of classification), had developed in a stunted way. Microbiology's condition was captured well in Stanier and van Niel's 1962 complaint: "Any good biologist finds it intellectually distressing to devote his life to the study of a group that cannot be readily and satisfactorily defined in biological terms" ...To understand that organism, to define it "in biological terms:' one has to know about its evolutionary history and its relationships to other organisms. Microbiologists had been unable to do this. Bacterial morphologies, physiologies, and most other whole cell properties are too simple or too volatile to be reliable phylogenetic indicators. Thus, although microbiologists had tried valiantly to infer a natural bacterial classification in terms of the characters available to them, they had relatively little to show for their efforts (2, 3) – a frustration that led Stanier and van Niel to continue their lament by adding, the abiding intellectual scandal of bacteriology has been the absence of a clear concept of a bacterium" (1). (Olsen and Woese, 1993)

However, the approach pioneered by Zuckerkandl and Pauling (1965), the reading of the historical trace retained in macromolecular sequence, holds great promise for the bacteria, in spite of their antiquity and in spite of the fact that they possess a relatively rapid biological clock, i.e., they fix mutations at a relatively rapid rate (Drake, 1974). All bacteria contain macromolecules, the constraints on whose primary structures are sufficiently complex that evidence of extremely ancient events are still retained therein. It was suggested several years ago that the ribosomal RNAs might be the proper "semantides" through which to approach bacterial phylogeny (Sogin et al., 1972). Not only is the translation function ubiquitous, but ribosomal RNAs appear functionally equivalent (interchangeable)

over a wide range of bacteria (Nomura et al., 1968; Lee and Evans, 1971; Bellemare et al., 1973; Wrede and Erdman, 1973), implying considerable sequence homology. The conjecture has proven correct. (Olsen and Woese, 1993)

The classification of microorganisms shifted from a reliance on cellular organisation (such as the 'eukaryote/prokaryote' dichotomy) and morphology, to biochemical and genetic criteria – metabolism, membrane composition, and rRNA sequence[87]. The results of this approach provided the now-famous revolution in classification – a new class of species (initially known as archaebacteria, later renamed Archaea) were pronounced in the late 1970s to be a distinct taxonomic kingdom (Balch et al., 1977, Fox et al., 1980, Woese and Fox, 1977)[88].

This upheaval of the recognised order of nature did not go unchallenged or uncriticised (Morell, 1997), but the following years saw a growth in its acceptance, until it reached a state approaching consensus by the mid-1980s[89]. At the same time, these rRNA sequencing results indicated that the

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[87] After comparing the rRNA sequences of the methanogens, Woese sent them off to a lipid expert in Thomas Brock's laboratory to see if they exhibited the same unusual lipid structures as Brock's thermophiles (Friend 2007). The result was positive. Brock previously noted the lipid irregularities but attributed it to convergent evolution (Brock 1978).

[88] In a March 1977 paper co-written by Woese and George Fox, they point out differences between "eucaryotic" and "procariotic" translation mechanisms - at this point Woese's famous challenge of the prokaryote/eukaryote dichotomy is yet to emerge in full - and suggest that these indicate that the split between the two lineages had occurred before the genotype/phenotype distinction had been fully consolidated; thus, the universal common ancestor was not a primitive prokaryote but an even more primitive progenote, a rapidly developing entity wherein protein and nucleic acid roles were still emerging (Woese and Fox 1977, Pace 2012).

[89] Some prominent biologists stuck to their guns; Ernst Mayr and Salvador Luria were among the especially staunch critics (Brock 1978; Friend 2007).

ribosome was involved in translation processes in the Last Universal Common Ancestor in a form not too far removed from its present ones. This fit nicely with RNA World theorisation.

Woese's subsequent 16S rRNA sequencing findings in 1990 and 1994 (Woese, 2004a) established extremophiles (especially thermophiles) at the root of the tree of life. Many of the most well-known species belonging to the domain Archaea are widely known to inhabit 'extreme' environments. Formerly viewed as relatively late adaptations to extreme conditions, having been established as a separate domain of ancient origin, and with a number of Archaean families exhibiting autotrophic metabolism,

Archaean species were now beginning to offer grounds for some intriguing possibilities for the origin of life: if 'extreme' organisms were ancient, then life may originally have emerged not in the tepid, 'normal' primordial Oparin Ocean, but in an 'extreme' environment of one type or another. The variety of possible environmental conditions at the origin of life was now radically expanded.

4.3.b. Woese's cloud model

In a short 1979 paper, Woese proposed a general model for the origin of life which rejected the accepted model ("Oparin's Ocean"). Woese rejected the 'Oparinistic' view that the appearance of the first living organisms radically shifted of the dynamics of the prebiotic earth. Instead, he postulated an environment on the prebiotic earth which was more conducive to the formation of autotrophic organisms, which continued the prebiotic dynamic rather than utilising and usurping it.

…the course of experimentation in prebiotic chemistry is a de facto rejection of Oparinism. Basic biochemical reactions by and large are dehydrations; they cannot reasonably happen in an ocean. As experimentation has progressed the prebiotic chemist has found it necessary to invoke increasingly

severe, dehydrating primitive environments in order to effect primitive syntheses – which environments are always viewed somehow as adjuncts to the Oparin ocean. These ptolemaic revisions of Oparinism should be recognized for what they are, and the question put squarely: It is not a matter of how to modify Oparinism, but whether to replace it. (Woese, 1979)

To back his critique, Woese brings the recent discovery of microfossils and the previously discussed radical reappraisal in microbial taxonomy for which he was largely responsible, and was at that time still a controversial issue:

As recently as 20 years ago the biologist believed life to be a relatively recent arrival on the planet, the first cells arising, say, a mere one billion years ago. This view reflected both the fact that the macroscopic fossil record becomes scant to nonexistent prior to 600 million years ago, as well as the prejudice that evolution of a cell must have involved a series of highly improbable events – a euphemism for miracles – and so took a long time. With the discovery and study of microfossils and with the capacity to determine ancient evolutionary relationships among organisms from properties of their extant descendants, this picture has changed completely. The oldest known sedimentary rocks – 3.4 billion years – contain what are almost certainly fossil bacteria; the oldest known limestones – 3.1 billion years – contain stromatolites, i.e., fossilized algal mats. (Woese, 1979)

Woese drew on recently acquired astrophysical data from observations of the moon and (especially) Venus to postulate a prebiotic earth that is a radical departure from the Oparin Ocean – Woese's prebiotic earth has no oceans at all! Woese's prebiotic earth is under the influence of a "runway greenhouse effect", similar to Venus'. Under such conditions, the heat generated by the lithosphere causes water vapour to condense into droplets around ubiquitous dust particles blown up

by the powerful winds to form clouds. These clouds' droplets are the scene for the formation of the first living cell.

Woese does not enter into any specifics regarding the formation of early macromolecules or of the genetic mechanism (and does not mention his 1967 ideas regarding the origins of the genetic code and RNA's proposed role in the origin of life) but does suggest that the earliest living forms were methanogens – a suggestion with a clear connection to his prior pronouncement that methanogenic microorganisms are among the most ancient lineages if not the most ancient of them all. In addition, he provides a global biogeochemical role for these methanogens, suggesting that it is their metabolic activity which drains the atmosphere of carbon dioxide and molecular hydrogen, converting it to methane and water, thus eventually releasing the earth from its greenhouse state and allowing oceans to appear, and forming the earth as we know it.

Whatever we might say about the scientific validity of his ideas –Woese freely acknowledges that "the value of the scheme outlined here lies neither in truth nor completeness" and that "[i]ts main function is to force a relization [sic] that there may exist genuine alternatives to Oparinism" – it is interesting to note here the central role Woese assigns to what we might be tempted to call 'his' methanogens. Methanogenic microorganisms were discovered in 1971 (Wolfe, 1971), and it is Woese (prompted by Wolfe to study them) who placed them a few short years later, as we have seen, at the root of the phylogenetic tree. In this 1979 paper he not only argued for a methanogenic Origin-of-Life, but ascribed to it a central role in the very creation of the same oceans which were commonly held to

be the setting for the scene of the emergence of life; we can imagine that this provocative model was a highly satisfying one for Woese to put forth[90].

The model put forth in Woese's 1979 paper was not taken further by him or anyone else; I could find no experimental work influenced by it. His later papers pertaining to the early period of life's history make no mention of the 1979 paper, and are much more closely related to his aforementioned work on the origin of genes and of the progenote(Woese, 1998, Woese, 2004b). For instance, a 1998 paper in PNAS in which he does not concern himself with planetary conditions or the formation of the protobiont and the genetic mechanism, but focuses on the universal ancestor (Woese, 1998), challenging the idea that a universal ancestor existed as a single, defined, discrete entity, and drawing a distinction between a lineage of organisms and a lineage of genes[91]. I suggest that the 1979 paper is something of an offshoot, a 'reverse-engineered' scenario originating in his thoughts regarding methanogens that do not conflict with, nor overmuch concern, the main lineage of his long-term scientific work.

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[90] In going over the list of feats that Woese ascribes to the humble methanogen, one cannot help but draw a parallel between it and the biblical God who creates order from chaos, separates the sea from the land, and brings forth all manners of life. Other than separating light from dark and setting the sun and the moon in their orbits, it seems the methanogen is fulfilling every traditional "creator" role, with an added bonus for basing the entire operation up in the clouds.

[91] In this paper, Woese bases his thoughts on the discovery of the mechanism of lateral gene transfer, whose importance and prevalence has been found (not least, once again, due to his own work) to be progressively growing.

4.4. Compartments, Lipid membranes and the Lipid World:

4.4.a. Compartments

The critical event which may best be called the origin of life was the enclosure of several self-reproducing polymers within a semipermeable membrane. (O'Malley et al., 2009)

The 'naked gene' hypothesis enjoyed, as we have seen, some early popularity with the genetic school of Origin-of-Life; a main argument for its primacy was that compartments are also necessarily barriers, and thus would constrain the possibilities for prebiotic chemical reactions (Eigen, 1981). Another option for genes-first Origin-of-Life researchers was to simply not mention compartmentalisation at all in their papers, or devote to the issue a brief mention at most. This is understandable; for the genes-first researcher, the question of compartmentalisation is one of several important but nevertheless secondary problems requiring explanation, along with chirality, bioenergetics, and so forth. A researcher could be justified in assuming that these problems are 'down the road', both for the original abiogenetic process, and for the research effort attempting to recreate it.

(Compartmentalists, on the other hand, tend to stress the fact that any Origin-of-Life experiment is an experiment in compartmentalisation since it is conducted within a compartment – test tubes and beakers are simply inert artificial compartments used for defining the chemical reaction space.)

The lipids composing modern cellular membranes are not (at least as of yet - see section 4.e. below for recent developments) considered to be a type of informational molecule in the sense that DNA, RNA and proteins are. Current biological membranes exhibit hundreds of types of lipid molecules; in the bio-membrane, they have no sequence composed of a small, fixed, repeating set of sub-units. From the perspectives of heredity and molecular biology, they are detail rather than essence. In contrast to the limited number of more-or-less universal components of genes and proteins (four nucleobases in both DNA and RNA; twenty-something amino acids in proteins), cellular compartments in organisms can take a very large number of forms. They are composed of lipids of many kinds in diverse configurations (phospholipids, lipoproteins, etc.); to which are added proteins (embedded in the membrane, forming an additional layer as in the bacterial S-layer, or, in the case of viruses, composing the entire viral shell) and sugars (as in the ubiquitous lipopolysaccharide, or LPS, layer of the bacterial cell wall). Viewed in this way, it is difficult to find a core set of molecules on whose formation an origins-type research effort should concentrate.

All this is not to say that Origin-of-Life research has been totally inattentive to compartments, even in its early days; the importance of compartmentalisation had pointed out by Haldane in his landmark 1929 paper (Haldane, 1929), while Oparin, as I noted, saw compartmentalisation as an essential part of his coacervate model. The conception of a cellular compartment as the basic entity of life is even older, of course, and dates as far back as the first observations of living cells – long before the advent of modern abiogenesis. A number of research efforts are dealing with the problem of compartmentalisation – and to a growing extent, these are not just concerned with compartmentalisation as simply another aspect of the transition from non-life to life, but as a fundamental way of understanding the Origin-of-Life event. The idea of a passive enveloping bubble

serving mostly to define a space in which the interesting actions are taking place is challenged by researchers claiming an early and active role for membranes in the formation of the first living cell.

4.4.b. Lipids

Current research focuses mainly on membranes composed of molecules of the lipid group (including fatty acids, sterols, phospholipids, glycolipids, lipoproteins, etc.). However, the question of whether the original proto-cellular compartments were indeed composed of lipids is still open. Although lipid research makes good sense, there is no guarantee that a shift from one class of compartment to another could not have occurred in the distant past. The original compartments could have been composed differently, and replaced gradually by lipid structures throughout evolutionary time (in much the same way that DNA is now normally accepted as having replaced earlier form or forms of genetic material, as discussed earlier). Sidney Fox, as we have seen, argued for proteinoid microspheres –proteinaceous compartments. Michael Russel (see below) suggested that 'compartments' on the microscopic scale may consist of microscopic pores in rock, clays or solidified volcanic ash. 'Cubic Phases' – regular small cubic solid formations in rock – have also been suggested. (Luisi, 2006)

Lipids do, however, exhibit some remarkable qualities which, added to the fact of their present roles in all cellular membranes, make their study in the Origin-of-Life context a good bet. A defining moment in the story of compartmentalisation was the 1964 discovery (discussed below) that small, amphiphilic molecules in an appropriate aqueous environment can and do spontaneously associate (due to the hydrophobic forces exerted on the hydrophobic component of each molecule) into defined structures, including globular bodies – a direct equivalent of soap bubbles forming in air. Due to their

physical properties, lipid membranes (even ones containing no membrane proteins) act as a selectively permeable barrier able to maintain ion gradients – a critical property for membranes both current and prebiotic, and one that is missing from non-lipid compartments such as Fox's.

The major strength of the lipid vesicle concept is that it offers a true barrier function. That is, if certain conditions were established which permitted ion gradients to form, lipid membranes would be able to maintain the gradients for significant lengths of time. An early life form would be able to take advantage of these gradients either as a source of energy or as a source of components for the replicative process.(Deamer and Oró, 1980)

4.4.c. The history of membrane research and Origin-of-Life

The importance of membranes in the very first steps of the evolution of living entities was already stressed by Oparin (1957; also see Lazcano 1992). A prebiotic model of such a membrane was suggested only much later, however, by Deamer and Oró (Deamer 1980). Because most molecular evolution research was traditionally focused on peptides and nucleotides, and because the specific incorporation of membranes into these models was not clear, the study of the role of membranes in the origin of life was delayed compared to that of biopolymers. This may have influenced the hypotheses on the primordial entities involved in origin-of-life processes. Today the importance of membranes in the study of origin of life is recognized by most researchers. (Lahav, 1999)

Lipids appearing in living organisms form an extremely diverse class of biomolecules, with constituent monomers from varying types. There is a marked difference between the lipid composition of modern eukaryotic cellular membranes, bacterial membranes, and archaeal membranes. Even within a single typical eukaryotic cell there are numerous distinct types of membranes; the variety

within the biological realm is large, and the possible lipids that can be chemically synthesised is much

larger still. Thus, the study of cellular membrane structure, function and formation is markedly

different from molecular research on nucleotides and proteins, and does not progress in the leaps and

bounds that the latter has exhibited in the last few decades. It is a smaller field, concerned not with

sequence but with overall structure and function; as there is no fundamental 'code' of cellular lipids to

be cracked (at least, none that has so far been recognised as such), technical progress and discovery

follow in a more linear fashion.

The major enabling technological event in lipid research was the introduction of the electron

microscope during the late 1950s and early 1960s. In combination with X-ray diffraction studies, it

brought forth a series of discoveries and understanding regarding cellular membranes (Robertson,

1967). The bilayer structure of bio-membranes was ascertained, internal compartmentalisation of

eukaryotic cellular membranes was detected, as well as other aspects of membrane composition.

During the 1970s, the fluid mosaic model of bio-membrane structure became well accepted; the

macromolecules comprising the cellular plasma membrane, rather than being in fixed positions, are in

a state of constant fluid movement.

4.4.c.1 Peter Mitchell – chemiosmotic theory

In 1961, Peter Mitchell published his chemiosmotic theory – chemical energy provided by proton

gradients across cellular membranes. (Mitchell and Moyle, 1967, Mitchell, 1961) This was Mitchell's

solution to the problem of ATP generation by cells, which was a significant puzzle for mid-20th century

biochemists (Deamer, 1969). The working hypothesis was that of a 'high-energy intermediate', a

hypothesised molecule linking cellular respiration (or photosynthesis) with ADP phosphorylation, and

research efforts concentrated on identifying it. Mitchell's theory did away with the hypothetical

chemical intermediate entirely, replacing it with the physical concept of the proton gradient. This idea

ran counter to the assumptions and intuitions of biochemists at the time (Orgel, 1999)[92]; needless to

say, it was highly controversial at first, but it slowly gained acceptance during the 1970s, with a 1974

experiment demonstrating, using a model system containing only two enzymes (bacteriorhodopsin, a

light-driven proton pump, and a mitochondrial ATPase) within a reconstituted membrane vesicle,

providing a convincing demonstration of the theory (Racker, 1974). In 1978 Mitchell received the

Nobel Prize for Chemistry for his chemiosmotic theory, which is now known to be used by cells to drive

cellular respiration (in mitochondria and microorganisms) as well as photosynthesis.

From a design point of view, this buildup of a proton gradient for driving chemical ATP-

producing reactions is hardly a straightforward method; nevertheless, it is shared by cells of organisms

with radically different metabolic systems. This provided researchers interested in the origin of cellular

metabolism with a relatively simple, though counterintuitive (Orgel, 1999), mechanism for energy

production, shared by all organisms and therefore arguably present in the common ancestor.

An early outline of Mitchell's ideas regarding membrane function in the cell – and its origin –

was presented at the first international conference devoted to the origin of life in 1957 (Mitchell,

1957). The detailed chemiosmotic theory still lay in the future, nor did Mitchell present any specific

Origin-of-Life scenario, but the general idea of the membrane as an active participant determining the

relations between the constituent systems of organisms and the external environment (and, in the

context of the talk, their origin) is there:

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[92] For a discussion of Mitchell's personal intuitions, see (Prebble 2001).

The feedback which can occur by the coupling of the internal catalytic and genetic systems with the osmotic linkage systems regulating membrane permeability and transport, will give rise to types of stabilization or adjustment ...and they would be expected to play a dominant and essential role in the regulation of the relationship between the organism and its environment. (Mitchell, 1957)

Mitchell did not thereafter work on, nor speak specifically of, Origin-of-Life issues; this was left to those who followed in his footsteps. The paper was included in the conference proceedings, and received very little attention thereafter.

4.4.c.2 membrane self-organisation

As well as elucidation of the bilayer structure of the membranes themselves, in 1961 Alec Bangham at Cambridge discovered that amphiphilic molecules in solution can, as we have discussed above, self-organise into lipid vesicles which were named liposomes (Bangham, 1995, Bangham and Horne, 1964); "osmotically active, relatively impermeable to ions and non-polar compounds like glucose, and can be given selective permeability functions by appropriate additions of other materials" (O'Malley, 2009), they quickly proved themselves excellent model systems for studying bio-membrane properties, as well a finding commercial and therapeutic applications (Heap, 2011, 2000).

From an Origin-of-Life perspective, the self-organising nature of liposomes meant that the problem of polymerisation and organisation into superstructures, a problem so prevalent in protein and nucleic acid research in Origin-of-Life, in a sense doesn't come up at all in the case of lipids. This leaves only the questions of lipid origin, replication (such as it may be), and interaction with other cellular entities. Note that high calcium and magnesium ion concentrations in water (such as seawater)

prevent formation of vesicles. Also note that vesicles can be of any number of different formations and lipid composition.

This evidence, along with the planar bilayer models being developed at the same time, established that lipid bilayers are the primary permeability barrier of all cell membranes. It was the membrane equivalent of finding the double helix structure of DNA. (Deamer, 2010)

Bangham or his collaborators did not at the time publish any Origin-of-Life scenario, but the subject did not have long to wait before being breached again: in 1977 David Deamer, then at the University of California at Davis, was inspired by conversations with Bangham, especially a talk Bangham gave a few years prior titled "Membranes came first!" (Deamer, 2010), to find with his postdoctoral student Hargreaves that lipid vesicles can form under simulated prebiotic conditions (Hargreaves, 1977). To show the formation of the membranes, they used the electron microscopy freeze fracture technique (Deamer, 1974, Wells, 2005).

Modern cells have 16-18 carbon phospholipids in them. Hargreaves and Deamer showed that shorter phospholipid chains (9-12 carbons), which are significantly more likely to have been prebiotically assembled, are more permeable, and can form vesicles spontaneously.

In 1981 Deamer, who has since become a central figure in Origin-of-Life related lipid research and one of the most prominent figures in the entire Origin-of-Life community[93], received a small sample of the Murchison meteorite, and upon its analysis discovered water-insoluble amphiphilic molecules capable of self-organising into compartments. Thus, this class of molecules joined amino

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[93]Deamer, too, is a recipient of substantial and ongoing financial support for his work from NASA sources.

acids and other organic molecules in the list of materials that can presumably be synthesised

abiotically, outside terrestrial environments. In 2001 Allamadola performed a similar experiment using

a sample from a simulation of interstellar dust acted upon by UV light. The experiments generated

lipid compartments, supporting the hypothesis of an extra-terrestrial origin for lipids (Dworkin,

2001)[94]. It was, Deamer writes, "just a curiosity" until NASA's Astrobiology program started[95] (Deamer,

2011).

Evidence for the plausibility of lipid involvement in early prebiotic processes has been

accumulating at an invigorating pace since Deamer's initial experiments: Pierre Luigi Luisi (yet another

Nobel prize winner) showed in the 1990s that lipid micelles can, given the appropriate conditions and

substrates, perform self-replication (Bachmann, 1992, Bachmann, 1990). Two vesicles are able to

'fuse' or join together, and they can also exhibit rudimentary self-replication (Buhse, 1997, Buhse,

1998) and even environment-specific variation, to a degree. Robert Hazen, as mentioned in the

previous section, showed lipid formation in simulated volcanic or hydrothermal vent conditions (high

temperature and pressure).

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[94] Regarding prebiotic origin of lipids: in 1967, Allen and Ponnamperuma synthesised long-chain fatty acids in a Miller-type spark discharge experiment (Allen and Ponnamperuma 1967). This (they noted) was the first experiment of this sort. They produced mainly short and branched fatty acids, not the longer, straight ones found in modern cells. This was not a heavily-cited paper.

[95]Deamer is also conducting experiments in volcanic pools - an interesting break from laboratory-based, strictly controlled prebiotic syntheses. Deamer's experiment under volcanic conditions, he claims, shows membranes do not form readily under high-temperature conditions. Deamer favours origin scenarios more conducive to membrane formation, and currently suggests something not dissimilar to Darwin's 'warm little pond'. Speculations aside for a minute, this is the only recorded instance I have found of an Origin-of-Life researcher stepping outside the lab not for observation or sample collection, but for conducting actual field experiments. There is a declaratory element in this experiment, serving to highlight the 'all experiments are compartmentalised experiments' point noted above.

4.4.d. Encapsulation; lipids and genes operating in concert; protocells

In recent years, the issue of compartmentalisation has been forming an alliance between the different approaches: Deamer's lab, in conjunction with RNA researcher Gerald Joyce, generated simple cell-like structures by mixing RNA polymerase enzymes and amphiphilic molecules; the result: polymerase enzymes encapsulated within lipid vesicles (Chakrabarti, 1994). Oberholzer (of the Luisi lab) showed polymerisation of nucleic acids within liposomes (Oberholzer, 1995, Oberholzer, 1999, Oberholzer, 2002). In 1999, Yarus and co-workers showed an interaction between RNA molecules and phospholipid bilayers. Certain selected RNA sequences can form ion-conducting channels within the membrane (Khvorova et al., 1999). Another series of experiments showed that phospholipid membranes can act as a suitable site for non-enzymatic oligomerisation of RNA nucleotides (Janas and Yarus, 2003).

These studies, which hint at the possible formation of a hybrid model of gene and membrane cooperation in a prebiotic scenario, were followed by a number of studies attempting to join together a version of the RNA World hypothesis and contemporary understanding of membranes. In the Jack Szostak lab[96], which started out firmly in the genetic tradition (Bartel, 1993), work is now being done on models and scenarios of RNA incorporation into lipid vesicles; an influential theoretical paper (Szostak, 2001) complements experiments (Chen, 2004, Hanczyc, 2003, Mansy et al., 2008, Hanczyc and Szostak, 2004). In the 2003 paper, a mechanism of RNA adsorption into micelles via its attachment to clay particles is discussed. In the Chen 2004 paper the argument is that RNA encapsulated in the lipid vesicle exerts an osmotic pressure on the membrane that leads to the uptake of additional

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[96]Szostak was awarded the 2009 Nobel Prize for Physiology or Medicine for his contributions to genetics.

membrane components (in relation to non-RNA-containing vesicles), thus giving a Darwinian-type selection for vesicles containing RNA – an intriguing proposition that adds weight to the scenario of RNA being encapsulated by lipid vesicles[97]. Support for this finding has come from the Luisi lab (Thomas, 2005).

The compartmentalist approach is the one that appears to lend itself most naturally, at both the conceptual and experimental levels, to attempts at creating a working protocell, a functional, operating protobiological cell , created from the 'bottom-up' (i.e. not by using existing biological cells or cellular components) (Rasmussen, 2009). The Deamer, Bachmann and Luisi groups are working on self-replicating micelles, lipid vesicles (Hargreaves, 1977, Hargreaves, 1978, Bachmann, 1990, Bachmann, 1992, Luisi, 2004, Peretó, 2004, Deamer, 2005, Luisi, 2006, Deamer, 2011).

The researchers taking this approach have progressed over the decades from establishing the properties of membranes and vesicles suitable for proposed protocells, to recent attempts at constructing systems within these vesicles that exhibit some features of a working protocell. Luisi's experiments with differences in the rate of fresh surfactant between two populations of vesicles, constituting a type of prebiotic 'competition' (Cheng, 2003).

A membrane-gene configuration leads one step closer to a working protocell. Following the Deamer-Joyce construct noted above, Many groups, including Yu, Walde, Chakrabati, Fischer, and Ishikawa now work on expression of nucleic acids and proteins within lipid vesicles (Chakrabarti, 1994,

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[97] It should be noted that thus far, a natural scenario is yet to be found:

Although vesicle growth by processes similar to that demonstrated here might occur in a natural prebiotic setting, our use of membrane extrusion to mediate division is artificial, and the possibility of a natural analog of this process seems remote. (Flow through porous rock should be evaluated, however.)(Hanczyc and Szostak 2004).

Walde, 1994, Yu, 2001, Fischer, 2002, Tsumoto, 2001, Ishikawa, 2004). Nomura encapsulated a gene-expression system within a lipid vesicle. (Nomura, 2003).

As discussed in chapter 3 in the section discussing peptide nucleic acids (PNAs), Rasmussen & Chen have developed a theoretical design for a simple, minimal protocell. Using three interacting basic elements: a 'container', 'genes' and a 'metabolism', but proposing that neither the gene or the container are to be self-replicating before the event of their convergence in a single system (Rasmussen et al., 2003). The PNAs, which they suggest as the genetic material for this model protocell, are non-naturally-occurring molecules that are easier than RNA to couple with lipid layers. This project can also be considered to belong under a 'Synthetic Biology' heading, in that a successful end result of this project would result in a working artificial cell, available for numerous practical applications. This, however, along with every other model discussed above, is still a possibility rather than a reality.

4.4.e. "Lipidia", a theoretical 'Lipid World' model.

In a 2001 paper, Daniel Segré and Doron Lancet proposed a Lipid World model for the origin of life. They argued that lipid micelles and vesicles are important "players" in the prebiotic scenario because catalytic properties they display (Segré et al., 2001), if taken together with their aforementioned self-aggregation properties that provide an environment with an enhanced concentration of organic compounds, can provide a plausible site for initial chemical interactions to take place. As an alternative to the popular scenario of genetic information carriers' being internalised into lipid vesicles, they put forth a more extreme version of the hybrid models discussed above, suggesting that lipid-like molecules alone could have been responsible for many of the crucial steps

leading up to a viable cell, as lipids can themselves be viewed as 'information carriers' of a sort. Nucleic acid-based information-carrying systems could have been, by that view, a later development[98].

The final touch, explaining "why lipids" was through studying the papers of Luigi Luisi, which describe replicating lipid vesicles. This is elegant because lipids can spontaneously form supramolecular structures – micelles and vesicles. What was missing in Luisi's treatise was storable, transmittable information, which Luisi has added in the form of RNA within the lipid vesicles. I developed the idea that lipids themselves could store information, not through sequences but through compositions. (Lancet)

Lancet et al. proposed a theoretical model named GARD (for Graded Autocatalysis Replication Domain) wherein Composomes–non-covalent proto-cellular aggregates – were generated by catalysed recruitment of diverse amphiphilic and hydrophobic compounds, which could, they assert, have constituted the first systems capable of preserving information, and undergoing inheritance and selection[99]. (Nomura, 2001, Segré et al., 2000, Segré et al., 2001, Shenhav et al., 2005, Nomura et al., 2008) .

One of the main problems of this model – a problem it shares to some extent with all attempted comprehensive models of the Origin-of-Life – is that experimental vindication of it would be extremely difficult to achieve. The researchers write: "Most likely the proof will come in the world of in-silico chemistry and biology, huge supercomputer simulations." (Shenhav, 2004)

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[98] It should be noted that the details of how such a "takeover" could have taken place are still lacking, and therefore the 'Lipid world', even if it does suggest a workable explanation of the origin of life, has yet to bridge the gap between the prebiotic world and the present situation.

Nevertheless, the concept in itself is an intriguing exercise; independently of its scientific merits, it can be viewed as an attempt by lipid research to claim a legitimate, active role in the informational narrative that has been dominating the life sciences for the past decades, and as an attempt to reformulate and expand, once again, the conception of the gene.

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[99] The GARD model was a development of an earlier model simulation (Lancet, Sadovsky 1993) originally developed for modelling olfactory system receptors.

4.5. Metabolism-First approaches

4.5.a. Early theoretical formulations

The metabolism-first tradition in Origin-of-Life studies has a history that stretches back to Oparin's original scenario. It maintained a lower profile during the first years of the modern era of Origin-of-Life research, which, as we have seen, occurred within the expanding wave of the molecular revolution in the life sciences. Metabolic conceptions of the origin of life did occur, but it was not until the late 1980s that any significant attention was given to the idea.

A metabolism-first model of the origin of life is rooted in the biochemical research tradition rather than the molecular biology one, and is based on the notion that metabolic cycles perpetuate and regulate each other. Martin Ycas, who was among the first to envision an early, theoretical formulation of metabolism as the origin of life, described it thus in 1955, shortly after the Miller-Urey experiments (in a paper communicated by Urey):

Now consider the following case: a product of [metabolic] cycle A catalyzes a rate-limiting reaction in cycle B, and conversely a product of cycle B catalyzes a rate limiting- reaction in cycle A. In such a case the quantity of matter passing through these two cycles will increase at the expense of other reaction cycles. A kind of "natural selection" based on reaction rates will result. Eventually (and automatically), a system of interlocking cycles will be selected which operates at the maximal rate. Such a system of self-generating catalysts meets the minimal definition of life. In this initial stage,

however, there are no discrete organisms, and there exists only one living thing, the metabolizing ocean. The further evolution of this system presumably led to the production of catalysts of a high molecular weight and peptide nature. These may have agglomerated, and eventually the system would have become delineated into small discrete masses, the individual organisms. A better understanding of the biosynthesis of proteins and the nature of enzymatic catalysis may eventually make it possible to speculate in more detail on the nature of the above process. (Ycas, 1955)

Ycas then goes on to state:

This proposal has the advantage that it is not necessary to invoke a series of highly improbable events to account for the origin of life. Furthermore, since the metabolism of such a primitive system is primarily determined by the catalytic properties of compounds rather than by their initial concentrations, metabolic systems of a similar kind might arise in any large solution of organic compounds, relatively independently of the exact initial composition of the system, given a suitably coupled energy source. If bodies similar to the earth occur elsewhere in the universe, the occurrence of life with very similar properties may therefore be cosmologically a common event. (Ycas, 1955)

And indeed, since the models propose simpler molecules, reactions, reaction chains and networks gradually creating increasingly more complex versions of themselves, rather than relying on the random emergence of a single genetic entity, the metabolic tradition in the Origin-of-Life field has always been closely associated with the idea of a likely rather than improbable origin. Also note that in this view, a rudimentary form of natural selection is already at work, thus extending the concept of evolution into the chemical realm.

Proponents of the metabolic approach point to the fundamental cycles of modern metabolism –

the reductive citric acid cycle is a prime example (Morowitz et al., 2000) – in much the same way that

RNA World model points to the fundamental roles of RNA in the modern genetic array (as discussed in

chapter 3). To them, the universality of many metabolic pathways across all classes of organisms

suggests (though they allow that this is not a logical necessity) the antiquity of metabolism and its

presence, at least in rudimentary form, in much the same way the common genetic code suggests

these things.

Aside from the popularity of the gene, a problem facing early metabolic Origin-of-Life theories

was their dependence on a stable influx of both energy and molecular substrates to feed the cycles.

The dilute soup environment that was the scene of Origin-of-Life theorising could not provide these

conditions; a biochemical reaction network also requires a reasonable concentration of organic matter

– i.e. some sort of compartment or another means of spatially anchoring a host of participating

molecules. As we have discussed above, lipid vesicles were known to self-organise and thus could

create that space, but it was difficult to imagine a membrane that could afford the appropriate

selective permeability, allowing a steady stream of the right substrates and energy to enter and

unwanted molecules to exit, while holding the molecules participating in the cycles inside; the further

question of the replication of such an entity was an additional difficulty.

An early and consistent advocate of the metabolic approach is biophysicist Harold Morowitz of

Yale University, whose work on mycoplasma we have discussed in chapter 2. Beginning in 1964, and

over a period spanning four decades, he published a series of over a dozen books discussing and

advocating his ideas, under the central tenet he expressed as: "the energy that flows through a system

acts to organize that system," (Morowitz, 1968). His ideas were favourably received[100], but no detailed scenario or experimental efforts were forthcoming.

In 1974, Cairns-Smith and Walker suggested a theory of mineral surfaces adsorbing and concentrating organic molecules, thus aiding in the first formation of life. (Cairns-Smith and Walker, 1974). As we have discussed in chapter 3, the ideas Cairns-Smith was developing at the time were mostly to do with the formation of the informational genetic entity rather than an energetic metabolic model; however, he deserves mention here. In 1982, theoretical physicist Freeman Dyson proposed a "double origin" theory of Origin-of-Life (the "duality" being that of nucleic acid polymers and proteins developing concurrently), which he described as

a simple abstract model of the transition from disorder to order in prebiotic structures...not intended to be a theory of the origin of life. It provides only an empty mathematical framework within which questions about the origin of life can be posed with some degree of precision. (Dyson, 1982, Dyson, 1985)

In Dyson's model "cells came before enzymes, enzymes before genes." He later expanded the idea in a book (Dyson, 1985).

In 1988 Morowitz joined with David Deamer to put forth a theoretical proposal for a minimal cell in the metabolic tradition (Morowitz et al., 1988). The model builds on Deamer's 1977-8 findings to propose a phototrophic original cell, wherein protein gradients are generated by a simple pigment capable of utilising light energy to generate a trans-membrane proton motive force. The idea is

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[100] Morowitz, too, as discussed in section 2.6, enjoyed NASA support for a considerable period. He was also involved in decisions regarding the Viking missions.

sometimes referenced in discussion, but is much less popular than the Wächtershäuser model discussed below – most likely because it is still an 'organic broth' scenario rather than a hydrothermal vent one.

4.5.b. Wächtershäuser, Russel and other 'ventists:

…[the metabolism-first approach] received a large boost in popularity from the dramatic discovery of life in the late 1970s at the very bottom of the ocean, around thermal vents oozing from deep inside the earth…this was life based on sulfur and iron. Thermal vents reminded geochemists of early conditions on earth, when volcanoes interacted chemically with oceans with much greater frequency than today. This discovery, moreover, dovetailed nicely with the earliest application of genome sequencing to evolutionary questions, which placed thermal archaebacteria at or near the root of the evolutionary tree. Far-from-equilibrium energy throughput obviously is not a problem with thermal vents. (Padgett, 2011)

Günter Wächtershäuser, an independent chemist (working outside academia as a patent attorney), proposed in a series of publications starting in 1988 a mineral-based (pyrite) chemoautotrophic origin of life in an 'Iron-sulphur World' (also known as the 'Iron-pyrite World') – autotrophic chemical reactions taking place in the intensely active geothermal environment rich in iron sulphides – as the key first step to the first self-reproducing lipid systems (Wachtershauser, 2000, Cody et al., 2000, Wächtershäuser, 1998, Wächtershäuser, 1988a, Wächtershäuser, 1988b, Wächtershäuser, 1990a, Wächtershäuser, 1990b, Wächtershäuser, 1997, Wächtershäuser, 2003, Wächtershäuser, 2006, Huber et al., 2012).

The theory is currently quite well-known– any review of the field from the mid-1990s onwards is

bound to mention it. It is, for an Origin-of-Life theory, very detailed– a meticulously charted series of

hundreds of proposed chemical reactions – and, uniquely for an Origin-of-Life model, covers the

spectrum of development from elemental chemistry to biology. The autotrophic origin of life it

postulates is an idea that has not been seriously entertained since the early 20th century, having been

dethroned by Oparin's concepts of a heterotrophic origin of life.

Wächtershäuser's model is, like Ycas's, Morowitz's and Dyson's, a theoretical construct.

Ostensibly, it could have emerged at any time[101]; however, it is no coincidence that it emerged a few

short years after the discovery of submarine hydrothermal vents and their resident ecosystems, and

especially the sulphur-metabolising bacteria. This type of microbial metabolism had been known to

microbiologists since Winogradsky discovered it in the late 19th century, but hydrothermal vents

provide an environment with which the theoretical proto-biochemist can work with.

The vents provide a stable source of minerals, which are also, like the biochemical cycles, a

universal and fundamental part of modern metabolism. There's no compelling a priori chemical reason

for an inclusion of such exotic elements as molybdenum – or, for that matter, sulphur – in metabolic

processes, suggesting that it may be a historical remnant. Iron-sulphur minerals are also found forming

critical components of enzymes converting carbon dioxide to sugars (using hydrogen gas) in modern-

day methanogens and acetogens (Lane, 2009). Vents also supply a reliable flow of heat energy, and

stable proton gradients, which are, as we have seen, a primary energy source for the cell. It is

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[101] According to Wächtershäuser, the emergence of such a system on the primordial earth is proposed to have
been quite rapid - "maybe two weeks" (Hazen 2005, p.113). Almost needless to say, the theory belongs firmly in
the necessity camp - an origin of life scenario dependent neither on a chance meeting of molecules, nor on a
fortunate supply of high-end organic material floating in an ocean for a heterotrophic proto-organism to chance
upon.

hypothesised that what we see today as a strange mechanism for energy transfer is a historical relic –

an internalisation of the proton gradient from an ancient environment.

This stability is central to the acceptance of metabolic theories – it provides for a stepwise

accumulation of reactions and products. A metabolic approach cannot rely on a chance aggregation of

elements to create a replicating unit; instead, the network of reactions has to stay stable and evolve

over time.

Another element essential to Wächtershäuser's theory is the presence of mineral surfaces: the

reverse citric acid cycle discovered in bacterial metabolism in the 1960s enables them to synthesise

organic cellular constituents out of gas and water. This should lie at the heart of metabolism-first

theories. The general problem is that several steps of the cycle are not spontaneous and require

enzyme catalysts to function in the cell. Wächtershäuser's Iron-pyrite theory, relying (much like Cairns-

Smith suggested) on mineral complexes to provide the catalytic activity in the absence of enzymes in

the prebiotic environment, solves the core difficulty. The mineral surfaces can also catalyse the

aggregation of lipid molecules to form proto-cellular compartments.

Iron sulphide minerals are to be found in ample quantities in hydrothermal vents. The surface of

Pyrite (a crystalline mineral composed of iron sulphide) is positively charged. When hydrogen sulphide

reacts with iron, the reaction can act as an electron donor, providing a favourable energetic

environment for chemical reactions. Wächtershäuser proposed this as the first step towards

metabolism (later to be encapsulated within a proto-cellular compartment, which was also to be

synthesised with the aid of the mineral surfaces).

In short, hydrothermal vent systems provide the conditions required for the "iron-sulphur" reactions to take place. It is possible that their discovery has influenced Wächtershäuser's thinking; it is certain that it has been instrumental in its acceptance.

[W]here is this original homestead of life?

By the various aspects of my theory, it must be a place with liquid water having a nearly neutral pH and high salinity; a place with a high temperature and a high pressure; a place where hydrogen sulfide, carbon dioxide, and nitrogen are pressured into reaction in the presence of ferrous and other catalytic metal ions; a place where hot volcanic exhalations clash with a circulating hydrothermal water flow; a place deep down where a pyrite-forming autocatalyst once gave, and still is giving, birth to life. (Wächtershäuser, 1988a)

Wächtershäuser, himself not an experimental scientist, was (he says) highly influenced by the ideas of philosopher of science (and Wächtershäuser's personal friend) Karl Popper, and has from the outset insisted that a prime requirement for his theory needs to be its experimental testability and possibility of falsification (Wächtershäuser, 1988a). The theory therefore makes a number of testable chemical predictions, and they have since provided the basis for experiments. Huber and Wächtershäuser published a paper in 1998 detailing experiments simulating Wächtershäuser's theory, and demonstrating the surprising formation of peptides from amino acids in vents – amino acids formed peptide bonds due to the high temperature and pressure conditions to create thioesters and

acetic acid (Huber and Wächtershäuser, 1998)[102]. A large number of experiments followed (Cody et al.,

2000, Hazen et al., 2002, Hazen, 2005, Cody, 2004). The iron-sulphur model has subsequently

undergone revisions, by Wächtershäuser as well as others (Kundell, 2010, Lindahl, 2004),

The Iron-sulphur World attracts its (considerable) share of criticism (Orgel, 2000, de Duve and

Miller, 1991, Bada and Lazcano, 2002). The Miller faction of the Origin-of-Life community is holding on

to the concept of the primordial ocean environment, and genes-first proponents are not satisfied with

the model's reliance on the ability of minerals to catalyse reactions satisfactorily and to organise

sequences of macromolecules; a frequent criticism is that the Wächtershäuser model does not deal

adequately with the 'side-reaction' problem[103], so prevalent in prebiotic chemistry theories.

Faults and unproven conjectures have been pointed out, and not even the most fervent admirer of

the Iron-sulphur World would currently claim it as an adequate explanation of abiogenesis. However,

no-one disputes that the theory is exciting; it has at present firmly established the possibility of a hot,

anaerobic, chemoautotrophic, high-pressure origin of life, a radical departure from the traditional

heterotrophic organisms forming gradually in a cool ocean.

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[102] It should be noted that the experiments are often not easy ones to carry out - the chemical reactions require high-temperature, high-pressure conditions simulating those in the vents, and hydrogen sulphide, a central component of the metabolic models, is a troublesome and dangerous gas.

[103] Briefly: for any proposed chemical reaction, it should be shown how not only how this particular reaction takes place, but that it, and not competing chemical reactions, will indeed take place.

4.5.c. Other metabolic models

The Iron-sulphur World is not the only metabolic model to have emerged in recent years. In 1988, geochemists Michael Russell and Alan Hall published a preliminary theory of Origin-of-Life, to have taken place at a different type of hydrothermal vent system, which he had been developing since the late 1970s (Whitfield, 2009; Russell et al., 1988). A more detailed version followed a decade later (Russell and Hall, 1997).

At that point such vents, characterised by an alkaline pH and lower temperatures (100ºC at most), and therefore more conducive to organic chemical reactions than the acidic, super-hot type found by Corliss et al., were unknown to exist. Russell and Hall had developed their ideas based on geological formations Russell had found in 1981 in mineral deposits in Ireland (Boyce et al., 1983), formations which resembled a much smaller version of hydrothermal vents. The theory was strengthened immensely by finding exactly such an active submarine vent in the year 2000 (Kelley et al., 2001), with more following soon after.

An expansion of the model (Martin, 2003), proposes metabolic cycles catalysed by iron-sulphate and nickel-sulphate precipitates to create proto-organisms. Rather than on two-dimensional surfaces, the proto-metabolic reactions are to have taken place inside stationary metal-sulphide-walled compartments (with lipid compartments, and thus free-living cells, being a later development):

Other models, not necessarily confined to hydrothermal vents, have emerged: cell biologist

Christian de Duve, another Nobel laureate (physiology 1974), developed starting in 1988[104], his

metabolic model of a "Thioester World" (de Duve, 1988, de Duve, 2007)[105] as an intermediate step in

the formation of RNA world, thioesters being a class of relatively simple molecules that could have

played the energetic role held by ATP in modern cells, as well as forming a part of the synthesis of

lipids and peptides.

Meanwhile, Harold Morowitz carries on refining metabolic models – he, too, now argues for

chemoautotrophy as the original metabolism (Morowitz et al., 1988, Morowitz, 1999, Morowitz et al.,

2000, Copley et al., 2007), and has recently, with colleagues, suggested a model for the emergence of

an RNA World through a series of co-dependent steps merging the metabolic and genetic traditions.

(Copley et al., 2007).

All of the modern metabolism-firsts theories share a fundamental critique of the "out of chaos –

order" view that has been dominant in the Origin-of-Life question since the days of Oparin. For

Wächtershäuser (who is outspoken on this matter) as well as for others, life proceeded to emerge in

an orderly fashion from the very start as soon as the environmental conditions allowed it.

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[104] 1988 appears to be a veritable annus mirabilis for metabolism-first theories, reminiscent of the near-simultaneous appearance of RNA World theories in 1968. This is for no particular reason that I could find; no groundbreaking technical achievement or observation had occurred just before. It seems that it simply took that long for the hydrothermal vent discoveries and the findings and analyses that followed in their wake to mature in their separate ways.

[105] de Duve is also known in the Origin-of-Life community for his position on the contingency debate: he holds that the emergence of life was a deterministic process, certain to occur. His phrase, "The Universe is pregnant with life" (de Duve 2007) is a deliberate direct contradiction of Monod's famous proclamation.

4.6. Autocatalytic models

A number of theoretical constructs relevant to Origin-of-Life studies have appeared over the years. Although their focus on interrelations between elements within a network would initially lead us to favour placing them within the metabolism-first approach, it would be more correct to say that they form a subset, one might even say a lineage, within the phase space of ideas in the Origin-of-Life debate. These models are much less concerned with the details of prebiotic chemistry of simple metabolites under supposed real-world environmental conditions; instead, they attempt to model, usually in mathematical terms, the behaviour of more abstract entities to explain the emergence of complexity, information and of the existing interrelations in modern cells.

A detailed analysis of the contents of these models is far beyond the scope of this work; what I would like to do is make a few points regarding the common characteristics of these models and their history.

Most of the models I will describe began taking shape in the minds of their authors on or about 1968. I suggest that, much like the preliminary RNA World and other genes-first theories we have examined in the previous chapter, the holistic autocatalytic models came into being as an attempt to resolve the newly emergent chicken and egg problem. Of these models, the more speculative and overarching ones still await experimental testing; the more technically feasible models waited until the mid-1980s due (I believe) mostly to technical constraints: the ability to produce a rationally designed sequence-specific peptide or nucleotide oligomer, and accurately measure and analyse the reaction

rates and compositions was not readily available (see chapter 3 section 2.e.2). Even today, autocatalytic network models are still highly artificial; relying on carefully maintained reaction conditions and a steady supply of monomer substrates[106].

4.6.a. Gánti and the chemoton

Manfred Eigen's hypercycle concept, discussed in the previous chapter, is arguably the most influential autocatalytic network model. Significantly less well-known is Hungarian Tibor Gánti who from 1968 onwards proposed and then developed the chemoton, a theory of organisation of matter not too far removed from Eigen's hypercycle. Both proposals were published, independently, only days apart. Both describe self-sustaining, autocatalytic and self-reproducing chemical systems (Gánti, 1997, Gánti, 1971, Gánti, 1975, Gánti, 1979). The chemoton model postulates the basic unit of life to be a minimal chemical reaction system, a network of autocatalytic fluid automata (familiar to us from the work of Prigogine) that can reproduce itself and retain an identity separate from its environment. It requires a compartment, within which a metabolism consisting of a cyclic subsystem and a proto-genetic subsystem arises, necessitating non-enzymatic template-directed nucleotide polymerisation (Gánti, 2003).

The comparison between the respective fates of Gánti and Eigen's theories provides us with another opportunity for examining the factors determining these fates. The chemoton is a carefully thought out idea; it foreshadows conceptions that are today much more seriously considered. Nevertheless, it has received, and continues to receive, comparatively little attention. The hypercycle

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[106] Autocatalysis in membranes is, as section 4 of this chapter has shown, more easily achievable, due to their self-assembling properties and lack of reliance on sequence.

is a mainstay of Origin-of-Life scholarship, while the chemoton, though by no means forgotten, is currently in the 'also ran' rubric of Origin-of-Life models. Why should this be so?

Let us try to answer that by considering three passages from Gánti's (2003) book, which contains a detailed description of his theory as well as contributions from two of his admirers:

...why did the Anglo-Saxon world miss these results? The obvious answer is that they were not published in internationally known journals. Why not? There are a number of reasons. Gánti seems to have chosen a bad publication strategy. He has always tried to promote the grand scheme first, and to derive specific points from that. Now, the more revolutionary an idea is, the more difficult it is to sell it, unless it focuses on one timely and specific aspect. The second reason is that Gánti has not been well funded in Hungary, to put it mildly. He has been almost completely denied the possibility of attending meetings. It is true that his English (partly as a consequence of that) is not very good, but he has been a marvellous speaker in Hungarian and an acceptable one in English. More opportunity could have helped. (From the preface by Eörs Szathmary. p.vii)

Three features of Gánti's model are of fundamental importance philosophically. First, it is a chemical model. The importance of introducing a seriously chemical way of thought into the philosophy of biology should not be underestimated. These days, molecular biology is prominent in the thinking of many philosophers of biology, but we know from the many and various critical reviews of molecular biology as a history of 'informational macromolecules' that this molecular biology sustains a curiously un-chemical philosophy. Gánti's work opened my eyes to the real possibility of a philosophical reapproachment of biology and chemistry far more sophisticated than the tired debate over whether biology is 'reducible' to chemical laws or not. (From the preface by James Griesemer. p.viii)

In 1971 nobody had a clear idea of how one could construct a living chemical system. However, everybody assumed that such a formulation must incorporate the genetic code and enzymes. Gánti showed that this assumption, taken for granted by almost everyone (including Eigen) is unwarranted, and then solved the problem that nobody was able to solve. It is no exaggeration to state that Gánti is a visionary. He was a quarter of a century ahead of his time. (Szathmary, in Gánti 2003 p.162).

Based on the above, we can propose three non-conflicting explanations for Gánti's relative obscurity. The first is that Gánti, a chemical engineer who had spent many years in industry, although by all accounts an established man of science, was not and is not a high-profile academic (let alone a Nobel Prize winner)[107]. Most crucially, Gánti was based in Hungary, which at the time he proposed his theories, was essentially cut off from the "west". The political divide at the time was significant, and seriously affected links between scientific communities. Gánti had serious trouble contacting academics, attending conferences, and even writing for English-speaking audiences.

Second, Gánti was proposing a theory which belonged to the metabolism-first school of thought, at a period when, as we have seen, the genetic approach was much more prominent[108]. Gánti explicitly rejected the primacy of the gene in the origin of life, at the height of the concept's popularity. In that respect, the chemoton was truly ahead of its time.

The third drawback of the chemoton is that it is a theoretical exercise, however ingeniously

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[107] It is interesting to note the similarities between Gánti and Günther Wächtershäuser, not particularly in their respective theories (although there too we can find room for comparison) but in that they are both scientific people doing scientific jobs, but are not part of the mainstream academic milieu (in Gánti's case - he was a working academic - this remove was largely due to the political barriers between Hungary and the West). Their ideas are theoretical, comprehensive, scrupulously worked out and start from first principles.

worked out. Gánti does not 'name names' –"the chemoton is a virtual chemical network and does not promote any specific chemistry" (Popa, 2004)– and experimental evidence in its favour is not readily available in the literature[109]. To an extent (as mentioned in chapter 3) this is also true of the hypercycle, especially of its earlier formulations, but the hypercycle model did evolve rapidly at Eigen's and Schuster's hands to the point where it was explicitly associated with a specific molecule – RNA. Moreover, whilst the hypercycle starts out from a real-world problem encountered, involving mutation in RNA polymers, Gánti starts out *ab initio* – he begins from first principles with a definition of life, then sets out to build the minimal unit of life based on that definition, and then constructs the model around that. I would suggest that the chemoton theory was, when it was first published, too far away, in more ways than one, for the Origin-of-Life community to take notice.

It would be beyond me to pass a quality judgement on the chemoton theory. However, circumstantial drawbacks aside, the hypercycle looks to be a more useful concept with better applicability and explanatory power regarding the real world. It fits more closely to the known, and therefore it had received more attention. Conversely, the chemoton, less relevant to its time and developed outside the mainstream of its field, could prefigure several important themes which were to emerge fully only decades later.

The notable exception to the statement that the chemoton is not the basis of experiments is that of computer simulations, which appear remarkably early on in Gánti's own work (Gánti, 1975), at a period when no other Origin-of-Life research was utilising that novel tool, and are still continuing

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[108] The first formulation of the theory dates back to 1952, before Watson and Crick and the impact of the molecular revolution (Gánti 2003, p.xi).

today (McCaskill, 2012, 2005, Fernando, 2004). The issue of whether and to what degree a computer simulation can be regarded as an experiment in the natural sciences is an interesting and debatable one, and raises the general issue of the relations between computer simulations and Origin-of-Life studies. The chemoton may be an instance of an abstract model – being favoured by abstract experiments.

4.6.b. Autopoesis

Humberto Maturana and Francisco Varela of the University of Chile in Santiago coined the term Autopoesis and developed the main ideas during the late 1960s and early 1970s (Luisi, 2006), with the first paper appearing in 1974 (Varela et al., 1974). Autopoesis is a philosophically interesting concept that regards cellular life (among other things) as an autonomous network of interacting elements. Autopoesis does not centre on genetic material, and to an extent rejects reproduction as a defining attribute of life, preferring to focus on homeostasis. Life in this view is defined as a cyclic, self-perpetuating process:

...the living organization can only be characterized unambiguously by specifying the network of interactions of components which constitute a living system as a whole, that is, as a 'unity'. We also claim that all biological phenomenology, including reproduction and evolution, is secondary to the establishment of this unitary organization. Thus, instead of asking 'What are the necessary properties of the components that make a living system possible?' we ask 'What is the necessary and sufficient organization for a given system to be a living unity?' (Varela et al., 1974)

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[109] In his 2003 book, Gánti writes: "To the best of my knowledge, direct experiments proving the existence of these reaction networks have not yet been performed" (p.137).

From these premises, Maturana, Varela and others have reached some rather radical and far-reaching statements, extending autopoesis to social systems, and discussing the relationship of autopoesis with the environment under the heading of "cognition" (Bitbol, 2004). Their work has received some attention, including in the social sciences, but actual experimental work related to abiogenesis using the concept has been sparse, with the Luisi lab producing a solitary attempt at a working autopoetic system (Zepik, 2001).

4.6.c. Autocatalytic peptide systems

Since proteins were initially considered the class of biomolecules most likely to be the stuff of genes, it is not surprising that early considerations of the origin of life focused on a world in which peptide molecules would be the first to form and replicate.

Although, as we have seen, the discovery of DNA and RNA as the physical manifestations of genetic material diverted much attention away from this Peptide World model, it has never quite died out, and recent advances have shown that there is still much potential in this model of Origin-of-Life (as well as possible practical applications for enzyme-free peptide synthesis systems).

We have previously met Alfonso Herrera And Sidney Fox, early workers on peptide systems, with Herrera publishing his experiments producing amino acids, polymers and more in the first half of the 20th century (Fox, 1988, Negrón-Mendoza, 1995) and Fox studying the spontaneous formation of protein structures in the 1950s and 1960s, demonstrating that under plausible prebiotic conditions, amino acids could spontaneously form small peptides, and further, that these could form microspheres, closed spherical membranes which, he argued, could grow and reproduce, thus serving as an intermediate step between simple organic compounds and genuine living cells (Fox, 1988).

Theoretical biologist Stuart Kauffman, then at the University of Chicago (later closely associated with the Santa Fe institute, a stronghold of research into complexity theory) first published his thoughts on autocatalytic peptide networks in 1971: "Momentarily ignoring the DNA molecule may allow us to see replication as a fundamental behavior of a class of matter". (Kauffman, 1971) continuing on Fox's protein reactions and on Manfred Eigen's hypercycle model. In 1986 Kauffman proposed a mathematically-based theoretical notion of catalytic peptides (Kauffman, 1986). He proposed that from any sufficiently complex set of polypeptides it is highly probable that an autocatalytic system will emerge, and that such an emergent process had happened in the prebiotic world, and was not limited to peptide interactions but could have extended to create proto-metabolism.

Also significant is his idea in his At Home in the Universe (Kauffman, 1995) that self-replication is achieved not by a single molecule but by an ensemble. Kauffman and fellow complexity theorists are searching for law-like properties in the emergence of life; the best-case scenario would be the formulation of a so-called "fourth law of thermodynamics", providing the mathematical explication of self-organisation dynamics in nature. So far this has not come to pass.

Kauffman's work is of a theoretical nature; others perform research on physical autocatalytic systems: Reza Ghadiri at the Scripps Institute advanced Fox's notion of self-replicating peptides, producing a simple artificial in vitro model of self-replicating and cross-replicating peptides (Lee et al., 1996, Lee et al., 1997) which may, it is suggested, form the basis of interaction of peptide and nucleotide structures. (Leman, 2004, Saghatelian et al., 2001). This is directly connected to the hypercycle concept (Lee et al., 1997). Their work drew on the efforts of the von Kiedrowski group at Bochum, who pioneered the design of autocatalytic molecular systems – using short nucleotide

sequences (von Kiedrowski, 1986, Sievers, 1994). Jean Chmielewski at Purdue explores more systems of self-replicating peptides (Isaac and Chmielewski, 2002, Li and Chmielewski, 2003, Takahashi and Mihara, 2004. Review: Ghosh and Chmielewski, 2004).

As discussed in section 1.1.m., Troland and others proposed in the first decades of the 20th century that genes are 'autocatalytic enzymes'. Troland and his contemporaries did not know what genes were made of, and by the 1930s it was commonly assumed they would be composed of proteins (Fruton 1999 p.431, Kay 1988 p.111). Today, after a long period in which genes were associated exclusively with nucleic acids, these recent projects may see life scientists re-tracing that path, and redefining autocatalytic peptides as genes. This is yet to pass. As Tirard et al. write:

Unfortunately, complexity models have promised much but delivered little. Evidence for the spontaneous origin of a catalytic system and metabolic replication would indeed be exciting—if it could be demonstrated. There is no evidence that metabolic cycles could spontaneously self-organize, much less replicate, mutate, and evolve." (Tirard et al., 2010)

4.7. Synthetic biology

We have previously discussed protocells – 'bottom-up' projects attempting to recreate a hypothetical Origin-of-Life scenario. In recent years, and with the advent of advanced molecular techniques, a number of top-down projects, some of them attracting considerable attention, have been attempting various goals.

As we have seen in section 2.6, the first indication of an attempt of creating a planned artificial cell was an abortive idea floated by Harold Morowitz and several other researchers interested in, and excited by, the newly discovered characteristics of the minimalist Mycoplasma microbe family. The project did not progress beyond the initial discussion level, and there matters lay for several decades, until the tools were available to start thinking once again on these ambitious goals.

4.7.a. Synthetic biology and minimal cell concepts

Synthetic biology is currently one of the most exciting fields in the life sciences; the name is readily embraced and adopted, it encompasses several different meanings (Benner and Sismour, 2005, A. O'Malley et al., 2008). In essence, it is concerned with advanced genetic manipulation of microbial organisms.

Perhaps the most familiar projects of the last decade are Minimal cell programs, aiming to create a rationally designed microbial cell by paring down a complete existing microbial genome to the bare essentials (Islas, 2004, Luisi, 2002). Due to the significant challenges inherent in 'bottom-up'

protocell research, the minimal cell projects are to a large extent currently the most technically feasible ways of approaching the synthetic life field. In aims they are generally better aligned with practical and commercial measures, geared, as one researcher put it, towards creating so-called "biotechnological workhorses" for producing biopolymers, therapeutics, and so forth (Forster, 2006).

Mitsuhiro Itaya proposed a theoretical "fully permeable minimal cell" – reliant on available supply of nutrients (Itaya, 1995). George Church has recently published a detailed blueprint for assembling a synthetic cell from scratch, needing only 115 genes along with other biomolecules. Such a cell, though, would not be able to live outside a very particular laboratory environment, in contrast to Venter's free-living minimal cell (which, in turn, is derived from an obligatory parasite – see below).

J. Craig Venter and Hamilton Smith have been attempting to create Mycoplasma laboratorium, an artificially produced bacterium. In 2008 they succeeded in synthesising an entire genome from scratch using synthetically-produced nucleotides assembled one by one (Gibson et al., 2008), and in May 2010 announced the insertion of a synthesised minimal genome derived (by knocking out superfluous genes) from Mycoplasma mycoides (Gibson et al., 2010).

In much the same way as for minimal cell programs, projects creating modular genetic devices, known as Biobricks (Baker et al., 2006, Endy, 2005) are highly interesting in themselves and for their engineering potential, but the application of their research to the core questions of the Origin-of-Life debate is not strong.

4.7.b. Impact on Origin-of-Life research

These projects are technically exceptional, commercially promising, conceptually exciting, and no doubt precursors to future endeavours, but conceptually serve only to give a conclusive

demonstration of the long-accepted view that there is nothing special about 'naturally-produced' genetic material.

Synthetic biology is fundamentally an engineering discipline, not an inquisitive endeavour. It does manifest a strong current of conceptual analysis, nicely summed up by physicist Richard Feynman's memorable (and controversial) quote "What I cannot build, I cannot understand"[110]. By inference, any successful manipulation of a working system should – not necessarily, perhaps, but most likely – entail a certain level of understanding by the manipulator, and this holds for systems derived from natural ones. What precisely is or should be that level of understanding, how it can be attained, and to what extent does successful manipulation signify conceptual understanding (can it be said that "what I can build, I understand"?) are questions that synthetic biology provides fertile ground for discussing, as it is one of the most overtly reductionist avenues of research in modern biology. Nevertheless, since its fundamental modules are existing, operational genes, I would hesitate to suggest that Origin-of-Life research is likely to benefit from knowledge gained by it.

4.7.c. A short note on systems biology

A challenge for origins of life research is to understand the minimal interactome that will allow life to begin as a functional system of compartments and large molecules capable of catalysis and replication, together with feedback loops that regulate their functions. Finally, if life is really understood in terms of systems biology, it should also be possible to fabricate artificial versions of life

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[110] Feynman once famously offered a thousand dollar prize to whoever could build a functioning electrical motor of exceedingly small size; he hoped that building such a machine might perhaps lead to some new principle of matter and energy movement. The required motor was finally presented to him, but no deeper understanding came of it -

in the laboratory. This is where systems biology meets synthetic biology, and the result will surely change the way in which life on Earth is viewed, not to mention the real possibility that life has arisen on other planets by similar processes. (Deamer, 2009)

Systems biology is the name applied to the recent attempts dealing with the interactions of genomic and metabolic regulatory pathways in biological systems in a holistic manner, embracing complexity while staying within the boundaries of the scientific method.

From a historical perspective systems biology can arguably (and rather simplistically, perhaps) be viewed as a reaction to the failure of scientific research to produce significant knowledge from the analysis of the large amount of data gathered by the genome-wide sequencing projects of the 1980s-1990s (Powell and Dupre', 2009). Although the principles of synthetic biology are not new, the popularity of its practice is a relatively new trend, since the research is heavily reliant on computerised analysis of large amounts of biological data – both the computing power and the data having become available in sufficient quantities only in the recent past.

For Origin-of-Life research the concept appears promising; systems biology appears to focus on themes that have been the mainstay of the Origin-of-Life debate for decades: emergence, interactions, control and regulation. As we have seen, a number of the more interesting projects in the Origin-of-Life, especially protocell construction attempts, display an affinity to that mode of thought in their studies of cross-catalysis between different classes of cellular or proto-cellular components (Thomas, 2005, Szostak, 2001, Szostak, 2009).

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it was just a very small, ingeniously crafted, version of a regular motor. I would perhaps offer this anecdote as a cautionary tale for taking on engineering challenges for the purpose of facilitating fundamental understanding.

On the one hand, both the approach and the results thus obtained appear very promising, and the more optimistic workers in the field have high hopes. A more critical perspective could suggest that this might be yet another reflection of current trends in the general scientific attitudes and fashions into the Origin-of-Life field. I shall not presume to pass a final verdict on the matter.

4.8. NASA 1976-2012

Any attempt to adequately review over three decades of extensive work is beyond the scope of this thesis, and has been performed elsewhere (Strick, 2004b). Instead, I would like to offer a general outline of NASA's involvement with the Origin-of-Life question since the Viking days:

The late 1970 and the 1980s were, in general, a relatively quiet time in NASA exobiology. The work being done was unspectacular (although some of it led to remarkable developments affecting the entire field of biology); NASA's space efforts were mainly concentrated on space shuttle and planetary probe missions rather than planetary missions; life scientists at NASA and receiving NASA support were doing molecular phylogenetics, identifying and classifying microbes in extreme environments, and rethinking their basic ideas regarding prebiotic chemistry and the sources of organic material on earth.

The mid-1990s saw a resurgence in NASA life sciences: bolstered by the ALH84001 event; encouraged by the new findings emerging from the deep-sea vent systems with their suggestion of radical possibilities of microbial metabolism that could be applied on other planetary systems; and wishing to define the search for life on other planets as an endeavour drawing on several disciplines (organic and inorganic chemistry and biology as well as the geosciences, palaeontology and astronomy), NASA announced the founding of its new Astrobiology institute in 1998.

4.8.a. Earth-like planetary systems

In addition to the abovementioned, a crucial development was the early 1990s discovery of previously unknown extra-solar planets (Angel, 1996, Parsons, 1996, Beckwith and Sargent, 1996). This discovery was due mostly to technological developments in radioastronomy.

The idea that stars other than the sun had planets revolving around them was not a new one, but evidence was thin to non-existent until that period. Until 1995, the only argument for the existence of planets was a probability one, not one based on factual observation (Gross, 1997). With time, evidence of the existence of more and more 'earth-like' planets outside the solar system ('more' both in number as well as in degree of similarity to earth) has bolstered optimism regarding the possibility of life outside earth.

I should mention two problems with this attitude, both stemming from the pesky 'single sample' problem of estimating the probability of the emergence of life:

The first problem is that, until the research community offers up a more-or-less robust scenario for the emergence of life on earth (or under earth-like conditions), the notion that the same ought to happen elsewhere is based on hardly more than unfounded optimism. The second criticism comes from an almost diametrically opposed direction: why, we may ask, do we feel the need to limit our focus to earth-like conditions? The search for life should strive to encompass every possibility rather than just the one we are arbitrarily familiar with. The argument for weird life, or xenobiology, rests on the assumption that life is an emergent, highly probable event given minimal starting conditions (Cohen, 2001).

4.8.b. Arsenic-Based life

In 2010 a NASA-affiliated research team announced that arsenic-based life was discovered, via press conference (the NASA releases announcing the press conference did not give any details, only hints of a "significant finding" related to extra-terrestrial life – which triggered a short but intense burst of speculation in the media and the web, with the familiar 'little green men'-type tropes trotted out once again). A paper followed shortly after (Wolfe-Simon et al., 2010)

The Wolfe-Simon discovery turned out to be not an extra-terrestrial finding, but the isolation (from the arsenic-rich environment of Mono Lake) of GFAJ-1, a new terrestrial bacterial strain which was reported to have integrated arsenic rather than carbon into several locations within its genomic DNA. Apart from the general innovation, it was the first demonstration that arsenic can indeed perform as a carbon substitute in a biological system – a highly relevant finding for those interested in extra-terrestrial biological systems.

The paper was highly interesting – and was almost immediately subjected to criticism. Detractors pointed to several methodological problems in the research, maintaining that the announcement was premature (and, therefore, another case of 'science by press conference'), a state of events reminiscent of the ALH84001 controversy (Hayden, 2011c, Hayden, 2011a, Hayden, 2011b). The final verdict is yet to emerge; however, on balance it now seems that the Wolfe-Simon findings are indeed an artefact rather than the first instance of arsenic metabolism.

This fairly minor episode highlights many characteristics of NASA involvement in the life sciences: NASA is supportive of a wide range of research efforts (many of them to do with microorganisms), and retains a tendency, sometimes verging on the irritating, to announce new

observations (especially regarding evidence of water on known and new planets) as revolutionary news stories. The media, both scientific and general, shoulders some of the responsibility for this; nevertheless, the frequency of 'hyped' announcements is rather high.

4.9. Conclusions

It would be presumptuous to contain within a single narrative the profusion of Origin-of-Life research since 1976. It would be equally presumptuous to attempt to pass judgement on the future fate of these projects and the field in general. However we can see that an emergence of a new consensus brought on by the convergence of phylogenetics, microbial diversity, paleomicrobiology, and new – or at least newly affirmed – notions regarding environmental conditions on the prebiotic earth.

Theoretical Origin-of-Life ideas still tend to crop up whenever an interesting finding comes along; this chapter counts off one of Woese's, one of Mitchell's, one of Deamer's (inspired by Bangham), and the Corliss-Baross-Hoffmann model followed by the metabolic 'ventist' theories.

We can also see a loosening of the molecular dominance over Origin-of-Life thought. Even considering the excitement involved in the emergence of RNA World theories in the mid-1980s, it was getting clearer that the 'naked gene' hypothesis is at a loss to explain the origin of life in its totality, and that there was room for biochemistry to reassert its role in the origins scheme.

In recent years, we can identify a trend towards another type of convergence: previously differing schools of Origin-of-Life research are increasingly offering up hybrid models containing elements of each model. The large amount of work, and the new spirit of collaboration, have sparked a renewed air of optimism in the field; the results seem to be pointing, albeit still uncertainly, towards a unified scenario.

The scientists might argue this surge is a natural development, owing mostly to the objective

process of trial, hypothesis formation, etc. A less charitable interpretation might rephrase this as the result of the continual failure of each single school (and especially the dominant gene-centric approach) to reach a satisfactory working scenario of the origin of life. As mentioned above, it remains to be seen whether this collaborative convergence of ideas and research is a robust and useful perspective.

NASA remains the single dominant organisation operating in the field, involved in nearly every single research initiative (including theoretical models). The emergence of the trans-disciplinary framework of Astrobiology places the Origin-of-Life question ever more firmly within the wider context of planetary exploration.

Chapter 5: Conclusions

5.1. Technology and Discovery in Origin-of-Life

5.1.a. Enabling technology

The origin of life problem appears at present to be one of these pesky scientific problems that are always just beyond our grasp; each time the principles seem to be well worked out, with only some details and a missing step or two that need to be completed before a satisfying stepwise scenario can be formulated. Then our powers of resolution increase, and suddenly, together with the enhanced ability to observe and explain, there appear more phenomena that require explanation and integration into Origin-of-Life theories...and so forth.

We have seen how the availability of analytic techniques has made possible – and simultaneously shaped and guided –advances and directions in Origin-of-Life research:

The Miller-Urey experiment was not only possible before Miller but was actually conducted decades before Miller's, but it required paper chromatography analysis in order to show the proliferation of amino acids in the broth;

As analytic techniques in meteorite analysis progressed, they provided each generation of researchers with a progressively more complete understanding of the composition of carbonaceous meteorites. Finally the careful, 'clean room' analysis of the Murchison meteorite in 1969 enabled the

idea of organic materials from space to be included in our picture of the ancient earth. The more advanced techniques available in the 1980s enabled the ALH84001 event.

The newly available molecular tools in the 1960s enabled the manipulation of nucleic acids and Spiegelman's evolutionary RNA experiments – which had such a major influence on Eigen's theoretical work, as well as the thinking of other theorists such as Crick. Later on, when RNA analysis and sequence construction technology was available, ribozymes were discovered almost immediately, revitalising a dormant RNA World hypothesis.

Sanger's nucleic acid sequencing methods were immediately seized upon and modified by Woese for sequencing the ribosomal subunit. Later on, the ability to elucidate the ribosome's structure gave the RNA World unprecedented grounds for legitimacy.

The electron microscope's availability to lipid research immediately led to findings of self-assembly, and to lipids' progressively increasing place within Origin-of-Life models.

More recently, PCR technique, genomic analysis capabilities and an increase in computation power enable researchers to design, construct and analyse physical tests of abstract models – models which, as we have seen, can otherwise languish unheeded.

This pattern in Origin-of-Life research is hardly unique. Indeed, technological advance is now understood to be a significant driving force of scientific understanding. Scientific research is now understood to be significantly more 'technology-driven' and less 'hypothesis-driven' than was previously thought. As Maureen O'Malley writes:

The early development of the microscope, for example, revealed an invisible world that was then studied extensively in ways that led to entirely new understandings of life and of roles for technology in scientific investigation (Wilson, 1995). Hypothesis testing played only a minor role in this revolution, which involved exploratory investigation of regularities among microscopic phenomena. Again, general questions and the exploration of new technologies, rather than strict hypotheses, have propelled the development of chemistry throughout its history (Caldin, 2002). In biology, despite the efforts of some commentators to reconstruct all of Charles Darwin's work as hypothesis testing (Ayala, 2009), it is clear that Darwin spent over two decades identifying regularities in several biological domains and codifying the phenomena to be explained in the Origin (Hodge, 1983). Similarly, in contemporary molecular biology, the accumulation of high-throughput data and technology-driven developments point to the importance of a diversity of non-hypothesis-driven practices. (O'Malley, 2009)

My review of Origin-of-Life research shows that this is true even when dealing with this highly theoretical and fundamental question. In thinking about the Origin-of-Life problem, one might expect the research to begin from first principles, and then proceed to hypothesis testing. In practice, it is nearly always the other way around: technological advance is the initial trigger for theoretical and experimental work to be done.

5.1.b. Microbiology: Searching for the weakest link

The Origin-of-Life question is normally seen as belonging mostly within the chemical realm; it is, after all, the fundamental assumption inherent to the field that chemical reactions begat the first living entity. In practice this is also largely true. There is, however, a constant influx of input from microbiology that informs and directs Origin-of-Life thinking and research.

I would characterise the dynamics between the Origin-of-Life question and microbiology as revolving around the search for the simplest way to explain abiogenesis. The Origin-of-Life field is tasked with explaining the emergence of life; advances in microbiology continually redefine our understanding of that concept. As a result, in a number of instances, Origin-of-Life research had often – not always successfully – seized upon a new type of organism as a better explanandum, a simpler question to be answered.

We can trace this dynamic to the early days of microbiology, when (as reviewed in chapter 1) microscopy enabled the discovery of microorganisms, and allowed Spontaneous Generation theory to hold on for a while longer. In the early decades of the 20th century, and until viruses were finally confirmed as strictly parasitic entities, they were considered by some scientists as the nearest thing to free-living, non-metabolising organisms – in essence a replicator that is not bound up, as the gene is, within a cellular context (Muller, 1929, Podolsky, 1996), and thus a 'naked gene' whose precursor's abiotic appearance would be infinitely easier to understand[111].

In much the same vein, in the early 1960s the characterisation of species of the Mycoplasma family as minimal free-living organisms inspired an almost immediate call to embark on a project of synthesising an artificial cell; though that expectation was quickly understood to be premature, Mycoplasma-based research has since remained a useful Origin-of-Life research avenue. A little later on, in the 1970s, at a point when Origin-of-Life research was starting to find it difficult to find a way for the first protocell to have formed in the primordial ocean, and exobiology research was having comparable difficulty in visualising what sort of organisms could conceivably exist in the inhospitable

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[111] Eigen's hypercycle, as mentioned previously, owed much to then-recent discoveries in RNA viruses.

environments that were discovered on Mars as well as other planets in the solar system, came the

discovery of extremophiles, with their astonishing array of adaptations, and expanded the imagination

of scientists to redefine and expand the borders of life, its metabolic possibilities and the conditions it

can survive and proliferate in – thermophiles, methanogens, sulphur-metabolising microorganisms –

and come up with different, perhaps much more likely, scenarios of abiogenesis[112].

In a telling example from recent time, the McKay ALH84001 paper would not have come to pass if

not for the characterisation, a few years earlier, of two very different kinds of microorganisms – the

first, magnetotactic bacteria; the second, nanobacteria. The McKay identification of the microfossils in

the meteor relied on a 'nano'-sized organism leaving behind it the ferrous deposits that are

characteristic of magnetotactic bacteria. The fact that the evidence for nanobacteria's existence is

currently shaky in the extreme, and that they are in all probability no more than an artefact, serves to

demonstrate the power of discovery on theory.

Another recent probable false alarm is the arsenic-DNA bacteria from Mono Lake as discussed

in section 4.8.b. – a microbiological finding (whatever its veracity turns out to be) that was

immediately noticed by Astrobiology (for however short a time).

The influence of discovery on Origin-of-Life is, of course, not limited to microbiology; as I

noted, the discovery of ribozymes revolutionised the field, as did the discovery of deep-sea vents with

their ecosystems. Geological and paleontological findings had a profound influence on Origin-of-Life

theories. And so on.

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[112] An earlier example would be Arrhenius's Panspermia theory (ch.3), which required the discovery of sporulation.

5.1.c. The value of in silico models

I have reviewed a number of theoretical Abiogenesis models throughout this narrative. They spread over a continuum: at one end are theoretical models that provide details of actual physico-chemical reactions. Wächtershäuser's iron-sulphur world, Eigen's hypercycle, and Cairns-Smith's mineral theory fit this description. As we have seen, these theories are sometimes, cautiously, tested out in 'wet' labs. Wächtershäuser's theory, the most detailed, is also the most tested (notably by Robert Hazen). Kauffman's peptide autocatalytic sets have seen some tentative experiments, while Cairns-Smith's theory has up until now inspired a single solitary experiment.

Closer to the other end are theoretical models that provide general chemical details, if any. These include Maturana and Varela's autopoesis, Gánti's chemoton, Lancet's GARD, plus several more that I have not mentioned which concern themselves with more abstract mathematical modelling. These models do not cross the border from the computer lab to the chemical lab, and more often than not remain mathematical exercises with no direct influence on 'wet' Abiogenesis work.

5.1.d. What drives research in Abiogenesis?

All this serves to demonstrate a fundamental point relating to 'hypothesis-driven' science: in principle, every single discovery I mentioned could have been hypothesised to exist (and indeed some had). Nothing prevents the theorist from imagining an organism with extraordinary capabilities, as long as it remains within the confines of physico-chemical possibility. Yet in practice, what bolstered research, opened up new possibilities and enabled theories to come forth were real-world discoveries in microbiology.

Günter Wächtershäuser could have come up with the Iron-sulphur World at any time – but he didn't, and nor did anyone else. Exobiologists before Brock discovered Thermophilus could have come to the theoretical conclusion that microorganisms can survive intense heat, cold or acidity – but they didn't. Morowitz could have thought up the minimal cell alone, and perhaps he did, but the fact remains that these theories gained access to the scientific discourse only after real-world 'proofs of concept' were demonstrated.

In summary, I would like to argue that a strong underlying dynamic in Origin-of-Life research is that of discovery-driven and technology-driven research. The various theories, models and ideas of Origin-of-Life are not the prime movers of the Origin-of-Life intellectual ecosystem.

5.2. NASA, Abiogenesis and the utility of Origin-of-Life research

5.2.a. Research and Influence

The shadow of NASA has been looming large over Origin-of-Life research ever since NASA was founded over sixty years ago. Virtually all modern research on the question has been performed since that time, and a large majority of the research has been funded by the agency, which has been consistent in its support. No other funding body, whether governmental, academic, or private comes anywhere near its influence. The nearest competitor may be Craig Venter's private ventures, but, as noted, they have as of yet contributed little to knowledge in the origin question.

What might the effects of this symbiotic relationship be? Specifically, what effect, if any, do NASA's objectives and character have on the field, and what, if anything, does the agency receive in return for its money (assuming that government officials do not act solely out of sheer benevolence and thirst for knowledge)?

Since research field and institution emerged nearly simultaneously (and independently of each other), it is difficult to assess the situation. There is no alternative to look to for comparison; before NASA came along, experiments in the Origin-of-Life were few, far between, and poorly funded.

As Steven Dick, formerly NASA's Chief Historian, relates, NASA's exobiology activity from virtually its beginnings was directed at searching Mars for signs of life (Impey, 2010). Post-Viking, and

with the realisation that a project approaching Viking-type magnitude is not in the offing, NASA's life

sciences activities became less mission-oriented and less focussed on prebiotic chemistry. NASA

funding was now being allocated to many quite different avenues of research: although the by-now

'traditional' aspects of Origin-of-Life research, such as the Orgel lab's RNA studies and Oró's prebiotic

chemistry research, were still on the payroll, other aspects of early life on earth were beginning to

receive attention – Woese, Margulis, Lovelock. 'Top-down' as well as 'bottom-up' approaches,

'metabolic' as well as 'genetic', 'broth' and 'ventist', membrane research, and protocell and 'minimal

cell' research were all done under the NASA mantle. It is a telling fact that a large majority of the

studies mentioned in this chapter, and virtually all notable workers, have enjoyed NASA support.

This is not to say that pre-Viking NASA was not supportive of varied ideas in Origin-of-Life

studies; we have seen, for example, NASA support for Harold Morowitz's efforts that were

concentrated around membranes and minimal cells from the early 1960s. Indeed, it is very difficult to

say that NASA's support is particularly directed towards any theoretical 'camp' or practical approach. It

does, however, share with the Origin-of-Life research community two of its basic tenets – a

commitment to abiogenesis, and a working optimism regarding the possibility of reaching the goal of

an explanation of Origin-of-Life.

My examination of the aggregated history of NASA support indicates that NASA, perhaps

surprisingly, has been indiscriminately supportive of research in abiogenesis. It funds chemists,

biochemists, microbiologists, biophysicists, mathematicians, and geochemists; research programs in

the genetic as well as metabolic traditions; lipid people, bioenergetics people, hydrothermal ventists,

and even researchers whose interests lay somewhat to the side of the core question of abiogenesis or

exobiology (such as Carl Woese and Lynn Margulis) – all received funding. In the case of Woese, Leslie

Orgel, David Deamer and others, it is clear that NASA funding was elemental in enabling their research.

Given its focus on space research, one might reasonably expect NASA to be more favourably

inclined towards projects and researchers whose fundamental stance leans towards the idea of the

emergence of life as a highly probable (if not inevitable) event. Indeed, as we have seen in chapter 1,

in its early days this was explicitly stated by NASA officials. However, though the 'necessity' stance is a

popular one amongst Origin-of-Life researchers, we have seen that researchers who express more

sceptical views are by no means excluded from support or from the community. Norman Horowitz,

Leslie Orgel, Gerald Joyce and Stanley Miller, all affiliated with NASA for significant portions of their

careers, have all expressed (often repeatedly) their scepticism of the necessity or high probability of

the appearance of life, and seemed to suffer not at all from their attitudes or pronouncements

thereof.

In Frankenstein's Footsteps, Jon Turney (1998) writes of attempts to synthesise life in the lab:

The assertion that certain experiments represented steps toward the creation of life was no

longer made to justify a philosophical stance…Now it was used to gain publicity for a university

department worried about cuts in research funds.

The character of NASA's involvement in, and influence on, the origin question, appears to agree

with Turney's assessment.

That said, one criterion that does appear to be common to all the funded researchers is a core

commitment to the idea of abiogenesis. Current prevailing opinion in the scientific community is that

this is the only viable scientific option on the table (with a begrudging inclusion of the less extreme

panspermia version of abiogenesis); dissenters are viewed as unreasonable if not worse. It would

therefore be as commonsensical for a modern Origin-of-Life researcher to be committed to

abiogenesis, as it would for a modern clinical microbiologist to be committed to the germ theory of

disease.

Nevertheless, we could yet speculate whether it is possible that in the future, an alternative, non-

abiogenetic scenario for life's beginnings might present itself. Since abiogenesis is the most logical

consequence of the Darwinian theory of common descent, it is difficult to see how this could happen

without a rather radical reformulation of the principles of Darwinism, if not their complete overthrow.

As is usual, to us, creatures of our time that we are, this seems unlikely[113]; the question remains

whether, or, rather, to what extent, NASA's dominance over the Origin-of-Life debate over this long

period has distorted scientists' consideration of the origins question.

5.2.b. Utility

The current highly competitive scientific climate encourages results-driven programs. Basic

research, especially of the more abstract questions, often suffers. From NASA's point of view (and that

of the American taxpayer), a space program is a costly endeavour whose benefits are never

immediately apparent. Therefore, a space agency is expected to encounter sustained criticism, leading

to the advocates of the program having to face a more or less constant state of justifying its existence.

What utility does Astrobiology and Origin-of-Life research serve?

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[113] The one aspect in which the core idea of abiogenesis could seem to be unravelling a little at its edges is that of the LUCA; Carl Woese's speculations, based on recent findings regarding Horizontal Gene transfer, suggest that our view of the LUCA as a single entity may be subject to revision in the none-too-distant future, and that the concept of 'the first living cell' might also someday be replaced by a more nuanced understanding.

5.2.b.1. Providing knowledge and justification

NASA needs to receive input from the life sciences in order for the agency to construct planetary missions. In its earlier days the contamination question formed a large part of this, but later on the focus shifted to life detection. For the researchers, in addition to the intellectual curiosity and the availability of funds, there is the motivation of working on a cutting-edge, collaborative project. In addition, the relation to exobiology makes basic research more justifiable, as questions regarding the universality of biology turns from an abstract issue into a practical consideration (Dick, 1996). Suddenly the question 'what is life?' becomes an engineering concern.

5.2.b.2. Practical utility

One of the more interesting of the justifications offered for space programs in general is that the technical and conceptual challenges posed by the extreme goals that the space program pursues leads to a significant number of unforeseen results and beneficial side effects. Advocates of this line of argumentation (sometimes referred to as the 'Teflon argument', though Teflon preceded NASA) can point to a surprising number of novel materials and commercial products emanating from the challenges of the space program; examples range from the 'Space-pen' to the mathematical algorithm lying at the heart of modern wireless communication networks.

This is a work in the history and philosophy of science rather than an economic analysis or a congressional enquiry, but if Origin-of-Life studies are to be considered a part of the American space program, then one might reasonably extend the question of beneficial side effects, and ask whether the sustained funding of Origin-of-Life projects through the Exobiology program and its successor, the Astrobiology Institute, have had any effects on science in general, or, for that matter, on any other

sector of human affairs, other than the advancement of the Origin-of-Life question itself. Has the research into these challenging and interdisciplinary questions borne any unexpected fruit?

In the simple sense of useful products and technologies, Origin-of-Life research is not very productive. Gerald Joyce mentions some therapeutic ENA aptamers (Joyce, 2007), and Leslie Orgel and colleagues have patents relating to nucleic acid probe tagging and related methods.

5.2.b.3. Advancing theory formulation in the life sciences

The picture improves when we consider more intellectual contributions.

I believe that the most significant contributions that have come out of the Origin-of-Life field are three of the evolutionary insights that emerged from projects supported in part or in whole by the NASA life sciences office, all of them during the 1970s: Carl Woese's realignment of the taxonomic tree of life (see section 4.3.a.), Lynn Margulis's development of the concept of endosymbiosis in its modern form, and James Lovelock's Gaia model (see section 3.1.d.). The ideas would undoubtedly have emerged eventually even without NASA backing – all three scientists were active in their respective avenues of inquiry before being associated with NASA and can in retrospect be shown to be heading in the 'right' direction at the time – but the fact remains that NASA supported arguably three of the most influential theoretical models in the life sciences of the last five decades –i.e. since its inception.

It is, I believe, no accident that these advances came at a period when NASA Exobiology was suffering from an institutional 'identity crisis' – as we have seen, following the first two decades of relatively generous funding and a general sense of purpose up to the Viking mission, the mid-1970s saw NASA facing an uncertain future. The prospect of life on Mars was as distant as it had ever been, a straightforward model of the emergence of life was likewise not forthcoming (despite Sidney Fox's

vocal pronouncements to the contrary), and so the NASA Life Science administrators needed to find new places to look. To their credit we can see that they did not limit their sights to the narrow confines of space-related research and prebiotic chemistry, but took in the broader significance of their subject matter and supported promising leads therein.

A final output from the exobiology field is the hope of satisfying human curiosity: The search for life outside the earth is supported by few overt claims of applicability. There is little promise of new and exciting processes or products of the discovery of alien life (although these are quite possible in principle). The scientist hopes to achieve perspective on the character of life. To the non-scientist, the issue of extra-terrestrial life *per se* rarely holds more than a modicum of interest. The truly interesting issue is that of extra-terrestrial intelligence; those who dream of it wish for the same sort of perspective, but covering a much wider field – a perspective on intelligence itself, on morality, philosophy, science and all aspects of the human condition.

The theme of the (intelligent) alien in fiction has a long history of highlighting these aspects of humanity. The imagined alien perspective has been called to use in countless works of fiction. In form, thought and behaviour, the alien in fiction can be found at any point of the spectrum ranging from those nearly indistinguishable from human to beings so remote and ineffable as to render even their very identification difficult. The one characteristic that all fictional aliens share is that their origin is the human imagination, and the human need for perspective: the alien in fiction is a vehicle for asking questions (whether trivial or profound) about human life. The nature of the fictional alien is determined according to the nature of the issues that are relevant to its creator, and to the society within which the creator operates.

I would suggest that the search for extra-terrestrial life – and of the origins of life in general –
provides scientists with a similar opportunity for asking fundamental questions about life itself – and
that the history of the search can be used to discuss perspectives on life.

5.2.c. A note on NASA public relations

NASA's largely optimistic attitude is also reflected in its public relations, and here it is, in my
opinion at least, going a little too far. NASA has been 'burnt' by premature announcements of exciting
findings.

Even disregarding NASA scientist Richard B. Hoover's extraordinary claims for evidence of life
on Mars, which the organisation has decisively distanced itself from without disowning Hoover
himself, we can see NASA being repeatedly criticised by the scientific community due to its
overambitious claims. The Viking results, the ALH84001 and the 2011 Mono Lake bacteria are the high-
impact examples we have covered, and to them we can add the more subtle but more ubiquitous,
fairly constant, stream of press releases announcing new extra-terrestrial findings – quite legitimate in
themselves – which are then tenuously linked to the possibility of finding life beyond earth.

5.3. Delegate theories

It seems a recurring theme: a researcher has made a discovery in his specific field of inquiry – a property or function of a bio-material (protein, RNA, lipid, etc.) or organism, which they deem particularly significant. It then appears to imply to the researcher that perhaps this material or organism was also the first, and thus an Origin-of-Life theory is constructed on that basis.

Biochemist Leonard Troland proposed enzymes as the original primordial replicating entities. Early virologists suggested viruses and bacteriophages (Podolsky, 1996). Protein chemist Sidney Fox saw proteins as the stuff of life and developed his 'microsphere' ideas regarding their origin, which were effectively marginalised as the primacy of the gene became apparent. Upon the advent of molecular biology, 'genes first' Origin-of-Life theories were suggested by Crick and Woese, who worked on genes. Later, Woese goes one better: by 1979 he is concerned with his revolutionary phylogenetics, and thus he proposes another Origin-of-Life theory – this one giving primacy to the methanogenic micro-organisms which he found were among the most ancient forms of life.

The replicator-first approach reigned supreme in the Origin-of-Life arena until the primacy of the gene in biology was contested, which is when metabolism-centred theories of the origin of life started coming into prominence. Peter Mitchell discovered the properties of lipid membranes, and an Origin-of-Life theory soon followed. Later, shortly after the discovery of the self-organising capabilities of membranes, lipid researcher Deamer and his co-workers put forth a lipid-centred Origin-of-Life

scenario. Recently, discoveries of hydrothermal vent ecosystems give rise to hydrothermal Origin-of-Life theories.

This recurring phenomenon can be rationally justified: if a scientist discovers a new phenomenon, it is only natural that he try and apply it to any unsolved problems and see whether the new information can help solve these problems. And so, lipid people are offering lipid-based solutions to the Origin-of-Life problem, while gene researchers offer the gene perspective, and chemists try and make sense of the origin by applying their knowledge of chemical reactions. Since the question of the origin of life is still very much an open one, I suggest a view of it as a sort of arena, a microcosm of ideas which can be a battlefield, a negotiations table or a shared workspace, to which the different schools of thought in science send their 'delegates' – their theories of origin – to interact with each other.

This dynamic has the effect of creating a sort of poll. Because the Origin-of-Life field attracts this kind of input, then an examination of the small field of Origin-of-Life research, consisting of a few hundred workers at most, and significantly less in earlier times, can offer us an interesting assessment of trends, a litmus test of the state of life science at any given period.

The various Origin-of-Life theories draw their power from the concurrent explanatory power of their respective schools. In that view, we can analyse the current emerging trend of collaborative, cross-disciplinary projects in the Origin-of-Life field as an expression of the development of Systems Biology as the new vogue within the realm of biological research.

Origin-of-Life research, while not coalescing into a homogenous, generally agreed-upon state, has been showing signs of the various opposing camps inching towards each other – though the

debate between the camps is as lively as it was throughout the past nine decades. Many 'replicator-first' supporters now acknowledge that the 'naked gene' scenario will be hard to demonstrate, and that the transition from an RNA World (whether or not RNA was the original replicating molecule) to the first primitive, metabolising cell, is a difficult explanatory barrier rather than a trivial detail. 'Metabolism-first' proponents have likewise not been able to propose a workable metabolic solution, nor adequately explain the origin of genes.

Both camps recognise the importance of compartmentalisation (exhibiting several important attributes) in which the prebiotic reactions can take place. The concept of autocatalytic networks is currently very persuasive, if still not demonstrated outside mathematical formulae (as we have discussed in chapter 4), and on reading recent papers, especially ones dealing with protocell research, one can sense that the Origin-of-Life community is willing to explore this new and exciting trend in science[114] – as it has for every previous trend that appeared.

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[114] The systems approach isn't restricted to biology: Can we speak of "Systems Chemistry"? Apparently the term exists: "prebiotic systems chemistry, though still in its infancy, is already suggesting new solutions to old problems" (Sutherland 2010),

5.4. Chance and Necessity

The contingency problem is the subject of long-running debate in the Origin-of-Life arena, and is not yet settled. However, it is not easy to find contemporary researchers in the field who address it. We have seen Jacques Monod in the 1970s arguing for one extreme – life as a completely 'chance' in occurrence. Meanwhile several theoreticians, such as Stewart Kauffman, are seeking an 'organising principle', a demonstration that life can arise as a robust, or even inevitable, result of adequate pre-biotic conditions.

For active laboratory-based Origin-of-Life researchers the picture is often not as decisive. There are several prominent Origin-of-Life researchers whose convictions appear to differ from the 'organising principle' view, and tend towards the 'stepwise' option. Stanley Miller is one (Strick 2004, p.41). A telling case study would be that of Leslie Orgel[115]. One of the most influential Origin-of-Life researchers, he was originally an inorganic chemist before becoming interested in biological questions. He was a colleague and collaborator of Francis Crick, and belonged firmly in the "genetic" camp of Origin-of-Life theories and a supporter of the 'RNA World' hypothesis. He was even a member of the loose fraternal network known as the 'RNA tie club'.

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[115] Miller: "RNA is an unlikely candidate". Quoted in (Hazen 2005).

Orgel published several criticisms of the more hypothetical metabolic approaches, such as Wächtershäuser's and Kauffman's (Orgel, 2000, Orgel, 2008). In their contribution to the 2006 book RNA World, Orgel and his student and collaborator Joyce write [bold mine]:

Scientists interested in the origin of life seem to divide neatly into two classes. The first, usually but not always molecular biologists, believes that RNA must have been the first replicating molecule and that chemists are exaggerating the difficulties of nucleotide synthesis. They believe that a few more striking chemical 'surprises' will establish that a pool of racemic mononucleotides could have formed on the primitive earth, and that further experiments with different active groups and minerals will solve the enantiomeric cross-inhibition problem. The second group of scientists is much more pessimistic. They believe that the de novo appearance of oligonucleotides on the abiotic earth would have been a near miracle. (The present authors subscribe to the latter view). (**Joyce** and **Orgel, 2006**).

Based on this alone (if we disregard the tone of the quote) Orgel and Joyce may be placed in the 'chance' category, but it should be noted that they then go on to discuss various scenarios in which the RNA world could have come to being not directly from prebiotic conditions but via a series of genetic or proto-genetic intermediates – the so-called "RNA-later" scenarios. Based on this and on their research output, I claim that Orgel and Joyce place themselves in a firmly critical position of the 'necessity' camp and of its members' quest for a self-organisation principle. Orgel and Joyce's own efforts are directed towards explaining the appearance of an RNA World not as a result of a near-miraculous chance event explained by an "appeal to vastness", but as a result of a stepwise process - not law-like or inevitable, but far more likely than a "near-miracle".

The 'argument from vastness' option also does not necessarily require any addition of organising principles (be they conscious entities or otherwise) to the scientific worldview; a careful

thinker should opt for the simpler option. The downside of this position is, of course, the extreme unlikelihood given for the spontaneous creation of life from non-life in a single step. Adherents of the 'chance' view therefore commonly follow their acknowledgement of the gap of understanding that lies between the inorganic and the first primitive cell in two complementary ways: The first is the argument that, given enough time and environments, even highly unlikely events will eventually take place:

"We are faced with the question of the origin of all this RNA. Could the appropriate sequences have arisen by chance? We do not feel this is totally impossible"(Crick, 1968)

Eigen's anti-chance position can serve as a good argument against the scenario advocated by another arch-selectionist, Richard Dawkins, both in his The Selfish Gene (1976) and in his The Blind Watchmaker (Dawkins, 1988). In the later book, Dawkins says that we have to assume "a single-step chance event in the origin of cumulative selection itself. Similarly to Monod, Dawkins considers this "chance event" as the only alternative to Design. Though considering Cairns-Smith's clay theory as an example of a mechanism capable of bringing about life, in the end Dawkins relies on the enormity of time and space in the universe to make even the most miraculous event possible.(Fry, 1995)

It should be noted that this view is generally less popular among dedicated Origin-of-Life researchers than it is among thinkers and workers in disciplines that touch on the question of Origin-of-Life (such as evolution and molecular biology). For modern Origin-of-Life research, taking the notion of abiogenesis as its guiding principle, the 'organising principle' is the holy grail of the field, and is searched for passionately.

Most committed Origin-of-Life researchers, both past and present, would seem to hold some form of the 'necessity' view. This traces its beginning, as we have seen, to Oparin, who, speaking at the 3rd International conference on the origin of life, said:

It has now become quite clear that the origin of life was not the result of some "happy chance" as was thought until quite recently, but a necessary stage in the evolution of matter. The origin of life is an inalienable part of the general process of development of the universe and, in particular the development of our earth. (Oparin, 1970)

Iris Fry has dubbed this intellectual commitment "the continuity thesis": "the assumption that there is no unbridgeable gap between inorganic matter and living systems, and that under suitable physical conditions the emergence of life is highly probable".(Fry, 1995) [italics in the original].

For scientists working in Origin-of-Life and yet unwilling to commit to hypothetical law-like principles, a way of avoiding the two extremes of both 'chance' and 'necessity' views is a pragmatic acknowledgement that the 'chance' explanation is not complete – it is a challenging scientific question that demands either further research for intermediate steps, or alternative explanations. The originators of the "Directed Panspermia" hypothesis show us a good example of this difference between Origin-of-Life researchers and the other scientific thinkers: Francis Crick and Leslie Orgel proposed the idea together in 1973. Crick wrote a book on it in 1981 and offered it in 1993 as a "heretical" option for bridging the large gap in understanding (Crick, 1993, foreword to the "RNA World" book); in essence, he was reasserting the intractability of the question. In contrast, Orgel had moved on from the theory, and by 1993 can be seen expounding on intermediate steps towards a working RNA genetic system.

This way of managing the problematic nature of the contingency question is understandable both on an intellectual level (on which the question is normally discussed), as well as for more mundane considerations: more "continuity" supporters would be found among Origin-of-Life researchers because people who would dedicate their working lives to a task of finding something would tend to be the ones who believe there is a fair chance that this thing does indeed exist, and this

positive belief would be far more likely to result in a productive research program. Conversely, a scientist who is highly sceptical regarding the existence of an organising principle is not likely to go and seek it anyway, and would find more worthwhile projects to work on instead; any researcher setting out to empirically disprove the possibility of an organising principle is in for a tedious intellectual exercise – hardly the makings of a rewarding scientific career.

Fry in 1995 argues that 'chance' views are essentially equivalent to creationist views. Perhaps we can describe Orgel, Joyce and others as endeavouring to reduce the apparent improbability of the appearance of the first replicators, an effort that, if successful, would reduce the element of chance to a reasonable level and dispense with both the necessity for an added natural principle, as well as with any suspicion of abiogenesis being merely a subtler manifestation of creationist views. This approach is a good way out for thinkers in the molecular biology tradition – it makes their ideas of the origin of life seem much less strained while maintaining a commitment to a replicator-first framework maintaining the primacy of the 'traditional' gene concept.

The events taking place since Fry's 1995 paper have borne out her contentions. The Origin-of-Life community has closed its ranks in relation to the contingency question, and a large number of researchers profess optimism for the prospect of arriving at a satisfactory conclusion of the question in the not-too-distant future.

Both camps of the contingency debate level claims of lack of scientific rigour at each other. The claim that life is an emergent process of the universe is described by its opponents as teleological, and therefore, unscientific. Conversely, the idea that the emergence of life was a near-impossibility brings up two philosophical objections: the first is that by acknowledging a 'near-miracle', science is approaching (and, in the case of Fred Hoyle, arriving at) a religious explanation of life on earth.

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The second objection calls upon a more historical view of the nature and goal of modern science: the acceptance of the uniqueness of life on earth in the universe goes against the long move of scientific thought away from the view of the special place of mankind and the earth in the universe. A 'chance' view of life brings back echoes of the long-discarded notion of the earth as the centre of the universe, (this time only in a figurative sense), and, by further acknowledging the uniqueness of human intelligence on the earth, reasserts the status of mankind as the apex of creation.

As we can see, to accept an abiogenetic explanation for the origin of life and hold to either a 'chance' or 'necessity' view places one at risk of being blamed for special pleading to either a 'higher force' or a 'yet-unknown principle', respectively. A common way of avoiding these accusations is to take the assumptions 'into the field' and try to collect empirical data to support them. The executive arm of the 'chance' camp is concerned with finding ways to make the probabilities smaller; the parallel research effort of the 'necessity' camp is to find and demonstrate the workings of the self-organisation of chemical systems to produce a protocell.

Although their origins are philosophically distinct, the empirical research programs have become complementary rather than mutually exclusive, and the recent trend in Origin-of Life research bears this out – it is becoming progressively harder to divide the researchers into distinct schools of thought.

5.5. The State of the Art

There may be no better testimonial to the current state of Origin-of-Life research than the special 2009 issue of *Origins of Life and Evolution of the Biospheres* which provided the abstracts of most of the presentation given at the 2008 International Society for the Study of the Origin of Life (ISSOL) Meeting, held in Florence (Italy) in August of 2008 (2009). The lengthy document contains several hundred contributions; contributors hail from varied scientific disciplines, institutions and countries. There can be no doubt that the field is an active one.

Reading through the different submissions, it is perhaps equally striking to note that there is little that is universally agreed upon. Papers are still coming forth with new 'theories of the origin of life', suggesting radically different means, locations, conditions and routes by which life came to be on the planet. Even discounting the more extreme suggestions, we can see that the experiments and discussions revolving around the more mainstream theories of Origin-of-Life – RNA World, lipid micelles, autocatalytic cycles, clay – are not set around any well-established, generally accepted model. The situation is reminiscent of Kuhn's description of a science in its 'pre-paradigmatic' stage (Kuhn, 1962). The Origin-of-Life field is, however, markedly different in several important respects: First, it is not a well-defined scientific field, but a historical question that can be seen as relevant to several research fields. Second, excluding the extreme fringes of the field (such as the more radical Panspermia advocates) a general consensus reigns within the Origin-of-Life researchers regarding several key points:

First among these, and in a historical perspective quite a recent development spanning only a few decades at most, is the shared opinion, both within the Origin-of-Life community and in wider scientific circles, that the origin of life is in principle an explicable phenomenon. In addition, there exists a consensual opinion on the metaphysical constraints (such as the need for any explanation to fit recognised chemical and physical reaction laws) and on the timeframe under discussion, a broad agreement on the general sequence of events that transpired therein and on the problems requiring explanation at present, and several other important parameters.

Origin-of-Life researchers from different disciplines can communicate their ideas without any particular fear of misunderstanding. However, there is as yet nothing to prevent several independent and conflicting narratives to coexist, sharing varying degrees of similarity with each other.

In the 'replicator-first' versus 'metabolism-first' front, recent years have seen a discernible trend of a gradual movement drawing these two major schools of thought in Origin-of-Life studies closer together, each camp admitting to the strengths of the opponents and to weak points in its own favoured theory. Here, for example, is how John Sutherland, who, as we have seen, is currently one of the prominent researchers championing the RNA World hypothesis, begins his 2010 review article of recent RNA-World-related developments:

If synergies are found between RNA assembly chemistry and that associated with the assembly of lipids and/or peptides, the purist RNA world concept...might have to be loosened to allow other such molecules a role in the origin of life. Metabolism, or the roots of metabolism, could also potentially have coevolved with RNA if organic chemistry happened to work in a particular way on a set of

plausible prebiotic feedstock molecules in a dynamic geochemical setting. Such considerations point to the need for an open mind when considering the chemical derivation of RNA.(Sutherland, 2010)[116]

It is a dangerous move to attempt to construct an analogy of the world of human ideas using a concept coined for explaining the natural world; doubly dangerous when the concept being used is actually one of the ideas that are being modelled. Nevertheless, I am reminded of Manfred Eigen's quasi-species concept, wherein the determining genetic sequence of a viral population may not be an existing physical entity inside any one individual viral particle, but rather a consensus sequence, a weighted 'average' of the sequences of the viral particles composing that population. The current theories of Origin-of-Life are related to each other, sometimes strongly so, and they form a cloud around a hypothetical consensual Origin-of-Life scenario – one which is yet to take shape.

All this is not to say that a consensual account of the Origin-of-Life will indeed ultimately emerge; or that if it were to emerge it would be correct and that the 'problem' of the origin of life would be 'solved'. Indeed, as we have seen, time and time again a more-or-less satisfactory answer to the question of the origin of life is merely the precursor to a reformulation of the question itself, often with additional problems requiring additional work. For Origin-of-Life researchers, the goalposts never stop moving.

In addition, the history of science repeatedly shows that there is no guarantee that what Origin-of-Life researchers presently consider to be advances might not in the future be considered steps in a fundamentally misinformed endeavour. That said, I would suggest that it is precisely this loose

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[116] To be fair, it should be noted that following those words, Sutherland then continues: "notwithstanding these caveats…" and goes on to review recent RNA-World-related developments.

configuration of ideas and lack of any hard-and-fast principles that affords the field its most substantial

advantage; at present, no Origin-of-Life researcher can be so confident of the validity of his or her

ideas and methods that they can disregard alternatives and intellectual cross-fertilisation.

Timeline

1668: Francisco Redi's experiments casts doubt over the spontaneous generation theory.

1675: van Leeuwenhoek develops microscopy, discovers microorganisms.

Mid-eighteenth century: The Needham-Spallanzani spontaneous generation debate.

1779: Buffon estimates the age of the earth to be 75,000 years.

1786: Galvani experiments discover electric current from frog muscles – linking the concepts of 'electricity' and 'life' in contemporary thinking.

19th century: Lamarckism suggests his theory of evolution – a gradual change of organisms.

1827: Brown discovers Brownian motion – in both living and nonliving matter. Motion is now not limited to living systems.

1828: Synthesis of urea from inorganic compounds by Wöhler – the first crack in the wall separating 'living' from 'nonliving' matter.

1830: Lyell publishes Principles of Geology, his 'uniformitarianism' theory of geology.

1833: Berzelius reports indications of organic matter in the Alais meteorite.

1835: Berzelius postulates that catalytic activities occur in living organisms.

1839: Schwann postulates cell theory.

1848: Pasteur discovers chirality (complicating question of Origin-of-Life).

1850 Adolph Strecker achieves the laboratory synthesis of alanine from a mixture of acetaldehyde, ammonia and hydrogen cyanide. (Bada and Lazcano 2003)

1859: Darwin publishes "On the Origin of Species"

1861-4: Pasteur-Pouchon debates; Pasteur's "swan-neck bottle" experiment popularly disproves spontaneous generation theory. Pasteur maintains that 'life comes from life' (in contrast to biogenesis).

1866: Richter advances extraterrestrial model for Origin-of-Life.

1866: Haeckel, following Darwin, suggests the three-kingdom classification, separate kingdom "protista" for microorganisms.

1868: Huxley dicovers Bathybius haeckelii

1869: Miechner discovers nucleotides. Their role in heredity waits until Avery in 1943.

1870: Huxley coins the term 'Abiogenesis'.

1871: Lord Kelvin suggests extraterrestrial origin of life – and all existing species thereof. Religiously-oriented theory suggests "seeds of all species of the present day" arriving on earth by meteorite or similar. Lord Kelvin also deems age of Earth too short for evolution (based on known astrophysics);

1871: Darwin's writes his famous "warm little pond" passage.

1874: Discovery of DNA (in trout sperm).

1875: Pflüger publishes first chemically defined theory of abiogenesis.

1876-7: Cohn, Koch and Tyndall independently discover heat-resistant bacterial spores.

1877: Engels publishes Anti-Dühring.

Late 1870s: Hahn claims to find fossils of organisms in meteorite samples.

1890s: Kossel describes the composition of nucleic acids (A,T,C,G,U).

1896: Becquerel discovers radioactivity – the age of the Earth is recalculated to be 20-400 million years.

1897: Eduard Buchner demonstrates sugar to alcohol fermentation by yeast extracts – nonliving omponents (enzymes) functioning outside living cell.

Late 19th century: cytological techniques reveal sub-cellular mechanisms; 'protoplasm' as a homogenous material becomes an indefensible view.

1905: Burke's 'radiobe' synthetic life theory is published.

1907: Emil Fischer achieves first chemical synthesis of a protein-like fragment

1908: Svante Arrhenius publishes his Panspermia theory.

1911: Bastian publishes arguments against Pasteur's conclusions on the origins of life.

1912: E.A, Minchin first proposes a nucleocentric view of the origin of life, favouring the primordial emergence of the substance of chromatin. H.E. Armstrong later that year takes the cytoplasmic side.

1912: Herrera produces 'sulphobes'. Though subsequently determined not to be living entities, they demonstrated a proof of concept.

1912: The Braggs invent x-ray crystallography.

1913: Walther Löb produces amino acids by exposing wet formamide to electrical discharge, UV light.

1914: Troland proposes a (nucleo-centric) autocatalytic model of Origin-of-Life.

1920s: Hevesy introduces isotopes into biological studies (also see 1934 below).

1924: Oparin publishes his first booklet on Origin-of-Life (in Russian).

1925: Gorter and Grendel propose, after a series of experiments, that lipids in the erythrocyte membrane are arranged in the form of a bimolecular leaflet – a lipid bilayer. This is correct, although their experiments were flawed, and the errors fortuitously offset by other errors.

1927: Muller publishes first paper on experimental mutation (in Drosophila).

1929: J.B.S. Haldane publishes an article in Nature outlining a possible scenario for abiogenesis.

1931: Electron microscope invented. Provides researchers insight into complex nature of subcellular composition and interactions.

Early 1930s: Lipman claims to find bacteria in meteorite samples.

1934: Urey develops a practical method for preparing D_2O -"heavy water", immediately used by many experimenters, particularly Schoenheimer, for biological studies. Urey also pioneered labelled nitrogen, oxygen, and carbon. Experiments also rely on Geiger counters, first developed in 1908 and successively improved thereon.

1934: Curie and Joliot artificially induce radioactivity in phosphorus by bombardment of alpha rays (requires cyclotron – a rare piece of equipment even today).

1935: Davson-Danielli "paucimolecular" model of proteins coating surfaces of lipid bilayer. Since supported by X-ray diffraction and electron microscopy, and also modified by later discoveries.

1936: Oparin publishes his influential "The Origin of life on the earth", translated into English in 1938.

1942: Alfonso L. Herrera publishes an article in Science detailing his work (performed mostly around the 1910s – as noted in the 1912 entry above) and suggesting a new theory of Origin-of-Life, titled "Plasmogeny".

1943: Avery experiments establish the role of nucleic acids in genetics.

1944: Schrödinger publishes his influential book What is Life?

1944: Paper chromatography developed. Used in Miller-Urey experiment. (1947: Gas chromatography developed.)

1944: Avery shows strong indications that DNA has a role in heredity.

1945: A paper by Horowitz elaborates on Oparin's ideas.

Post-1945: ultraviolet spectrophotometry, developed initially in early 20th century, becomes generally available.

Late 1940s: Chargaff discovers equal concentrations of C and G, A and T, in DNA.

1949: Bernal first suggests clay minerals (primarily aluminosilicates) necessary for organic synthesis, since they would adsorb organic molecules, thus increasing their concentration and enabling effective reactions. Also suggests catalytic activity of minerals.

1950: Calvin performs Abiogenesis experiments (in oxidising environments).

1953: Watson and Crick elucidation of double helical structure of DNA.

1953: Miller-Urey experiment; Watson and Crick discover DNA double helix structure

1953: Sanger determines amino acid sequence of insulin. Insulin is also the first natural protein to be chemically synthesised in solution, the traditional way, in the early 1960s.

1954: George Wald proclaims Oparin-Haldane process a natural, inevitable event, not merely on Earth but on a cosmic scale.

1955: Nier develops mass spectrometry – quantitative detection of radioactive isotopes.

1955: Ycas proposes simple 'metabolic' model of Origin-of-Life.

1956: The analytical technique of mass spectrometry is developed.

1957: The first Origin-of-Life conference is held in Moscow.

1958: Arthur Kornberg isolates DNA polymerase I.

1958: NASA is established.

1959: Sidney Fox creates first "proteinoid microspheres".

1960: Joshua Lederberg coins the term 'exobiology'.

1960s: Negative staining methods for electron microscopy are developed, making electron microscopy much more useful.

1960: Oró experiments show synthesis of nucleic acid purine base Adenine.

1961: Oró and Kimball synthesise other purines; Fox and Harada synthesise pyrimidine uracil

1960-1961: DNA:RNA hybridization techniques developed by Sol Spiegelman.

1961: Oró suggests role of comets in carrying organic compounds to earth.

1961: Mitchell publishes his chemiosmotic theory of cellular membranes.

1961: Bangham discovers that amphiphilic molecules in solution can self-organise into lipid vesicles (liposomes).

1961: Nagy reports finding microscopic "organized elements" in samples of Orgueil meteorite (landed 1854).

1962: Rich first suggests an 'RNA World' hypothesis.

1962: Spiegelman develops nucleic acid hybridization, a technique that allows the detection of specific RNA and DNA molecules in cells. In 1965 he becomes the first to synthesize biologically competent and infective virus RNA in test tubes.

1962: Morowitz publishes paper suggesting mycoplasmas as model 'minimal cells'.

1963 Second Origin-of-Life conference organised by Sidney W. Fox, the Institute for Space Biosciences and NASA at the University of Florida.

1965: Sanger introduces gene sequencing method.

1966: Cairns-Smith suggests clay-based Origin-of-Life, drawing parallels between living systems and crystal growth.

1965: Brock isolates the thermophilic bacterium Thermus aquaticus.

1966: Complete DNA code established.

1966-1968: Orgel and co-workers demonstrate pyrimidine synthesis under simulated prebiotic conditions. Begin work on non-enzymatic template-directed oligonucleotide synthesis.

1967: Morowitz establishes genome of mycoplasma mycoides.

1967: isolation of DNA Ligase - important tool in molecular research.

1967: Spiegelman produces self-replication of RNA in vitro. "Evolution in a test tube". Eigen later continues this line of research.

1967: Allen and Ponnamperuma synthesise long-chain fatty acids in a Miller-type spark discharge experiment, producing mainly short and branched fatty acids, not the longer, straight ones found in modern cells.

1968: Space Life Sciences, the first scientific journal dedicated to Origin-of-Life studies, is established by NASA in the year 1968 (later retitled Origins of Life and the Evolution of the Biospheres).

1968: Gilbert, Crick, Orgel, and Woese all suggest RNA world theories (none suggest finding catalytic activity in extant RNA molecules).

1968-1970s: Prigogine puts forth his theory of dissipative structures – important in self-organisation theories.

1968: NASA initiates Viking Mars project, originally planned to be launched in 1973.

1969: The Murchison meteorite falls and is discovered, analysed.

1970: Isolation of first restriction enzyme - another important tool in molecular research.

1970: Reverse transcriptase discovered independently by Howard Temin, and by David Baltimore.

1971: Eigen first publishes his "hypercycle" concept.

1971: Gánti first publishes his "chemoton" concept.

1971: Kauffman publishes ideas of autocatalytic peptide networks.

1971: Monod publishes 'Chance and Necessity'.

1970s: Woese identifies Archaean extremophiles.

1972: Boyer, Cohen et al develop recombinant DNA technique using restriction enzymes, ligases.

1973: Foreign DNA fragments inserted into plasmids, found to be functional in E.coli. Paves way for bacterial cloning, protein manufacturing.

1973: NASA budget shrinks due to economic slump.

1973: Orgel and Crick publish their 'directed panspermia' theory.

1973-6: Public and scientific concern over recombinant gene technology. The Asilomar conference is held in 1975. US Government (NIH) guidelines for recombinant DNA research (relaxed in 1979 enabling recombinant work with viruses).

1974: Maturana and Varela publish first account of their autopoesis model of the origin of life.

1975: Southern describes method for transfer of DNA to nitrocellulose filters, hybridization to radioactive probes and detection of fragments by autoradiography – the notable "Southern Blot" technique.

1976: Viking expeditions to Mars.

1977: Barghoorn and Knoll establish that life on earth was present 3.5 billion years ago.

1977: Deamer demonstrates that lipids can form under simulated prebiotic conditions.

Jan. 1977: discovery of hydrothermal ecosystems. Hydrothermal vent origin theories begin to appear.

Nov. 1977: Woese publishes evidence of 'third domain of life – Archaea.

1979: Woese suggests 'cloud model' of Origin-of-Life.

1979: Jack Corliss detects "black smokers" in ocean bottom (paving way for Wächtershäuser's theory).

1980s: PCR developed, eventually making molecular work far easier.

1981: Deamer discovers amphiphilic (lipid-like) molecules, capable of self-organisation, in Murchison meteorite samples.

1982: Cech and Altman discover ribozymes. Prions discovered.

1982: Dyson proposes a "double origin" theory of Origin-of-Life (nucleic acid polymers and proteins developing concurrently).

1984: the ALH84001 meteorite is found in Antarctica.

1986: Gilbert coins the term "RNA World".

1986: Kauffman proposes theoretical model of catalytic peptide system.

1988: Deamer and Morowitz propose a 'metabolism-first' minimal cell model.

1988: de Duve proposes his 'Thioester World' theory of Origin-of-Life.

1988: Wächtershäuser first proposes his theory of an autotrophic 'iron-sulphur world' origin of life.

1988: Russel and Hall propose their 'hydrothermal vent' theory of Origin-of-Life based on 1981 findings by Russel.

1992: Noller demonstrates that rRNA is elemental to the action of the ribosome.

1992-1993: Initial report by Folk of 'nannobacteria' microfossils in rocks.

1993: Kajander and Çiftçioglu report nanobacteria in bovine blood.

1994: Deamer and Joyce produce polymerase enzymes encapsulated within lipid vesicles.

1996: McCay claims to find 'microfossils' in ALH84001 meteorite.

1996: Ghadiri begins experiments with self-replicating peptide model.

1998: NASA announces the founding of its Astrobiology institute.

2001: Lancet proposes 'Lipid world' model of Origin-of-Life.

2001-2004: Szostak lab suggests mechanisms for RNA incorporation into lipid membrane vesicles.

2003: Rasmussen and Chen propose theoretical 'minimal protocell' model.

2004: PAH theory.

2008: Venter and Smith insert synthesised minimal genome into 'empty' bacterium.

2010: Wolfe-Simon team announces "silicon-based" life discovered.

2011: Hoover claims to find bacteria microfossils in Orgueil meteorite samples.

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