THE BACTERIA: THEIR ORIGIN, STRUCTURE, FUNCTION AND ANTIBIOSIS

The Bacteria: Their Origin, Structure, Function and Antibiosis

by

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Table of Contents

Preface

This book may seem like three or four books even though the main focus is on a specialized topic—the bacterial cell wall. Its job is to formulate the innovations that caused life to initiate on earth, those that caused cell physiology to develop without diversity developing, those that allowed the murein walls of the cells to arise, those that led to the separation of the domain of Bacteria from other organisms, those that allowed the Archaea and the Eukarya to develop independently, and those that then led to the development of a very diverse biosphere. It must have taken a long time after the origin of the first cell; evolution had to proceed to produce very effective organisms. At some point a collection of very similar organisms arose that were first called collectively the Last Universal Ancestor (LUA), and stable divergence developed from there. The first bacterium had a protective cell wall and its descendants developed in many diverse evolutionary directions, gave rise to many species of bacteria with various life strategies, and expanded to fill the many niches in the collection.

As the kingdoms or domains of Archaea and Eukarya evolved, many of these organisms (and even some bacteria) acted against bacteria. The development of antibiotics acting on the wall of bacteria and lytic enzymes, called lysozymes, produced by protozoa, plants and animals, led to destruction of many bacteria. These antagonistic challenges to bacteria resulted from its own cell wall structure. This structure was both bacteria's most prominent advantage and its greatest liability. It led to growth success of bacteria and to development of a widespread domain—and to their destruction by other organisms. Man subsequently extended and elaborated these destructive tricks against bacteria, which led to the antibiotic era of medicine. Sometimes however, medical progress has turned out to be retrograde to long term medical advances. The attempt here is present the physics, chemistry and the evolution of life forms that created targets for antibiotics and the bacterial response to antibiotics. Logically all aspects must be considered together in order that new treatments for infection will not only work but will be effective for a long time.

Most of today's bacteria maintain a peptidoglycan or murein wall (called a sacculus or exoskeleton) that surrounds them completely. This strong wall protects them against osmotic differences between the inside and the outside

that otherwise might lead to the influx of water and the resultant rupture of the cell, but it also has many roles in the biology of bacteria. This book focuses first on the chemistry and mechanics of the cell's wall formation and function and how evolutionary forces probably led to its development. The makeup and structure of the wall permit bacteria to occupy diverse habitats and niches. It allows bacteria to do the same things that larger, multicellular organisms do, but in different ways. The book questions and tries to answer: (1) How does the bacterial envelope enlarge safely with the maintenance of cell shape? (2) How does the wall function as a critical cell organelle for other vital bacterial needs? (3) How does division of the sacculus and the bacterial cell occur? (4) How do other living organisms (the Archaea, Eukarya, and particularly, *Homo sapiens*) combat bacteria? (5) How have bacteria evolved in the recent past to overcome human production and distribution of wall-directed antibiotics? The ideas presented are logical conclusions from what we do know, but only tentative answers can be given because ideas about early evolution and more recent evolution have been deduced largely from properties of modern organisms and the current knowledge of molecular genomics.

Arguments throughout the book are mustered to illustrate that prokaryotic life is more directly and simply dependent on physical and chemical principles than are the life forms of multicellular organisms. Of course, either directly or indirectly, the exploitation of physical laws and chemical reactions is dependent on Darwin's three principles. In modern translation these are (1) replication of informational biomolecules must be accurate most of the time; (2) only occasionally do mutations take place, and (3) the translation into functional working forms takes place from the information propagated in molecular form. The role of antibiosis in evolution and man's attempt to use it is for his own advantage include the successes and the failures. In the future, the concepts presented in this book, I am certain, will be critical for medical advances in treatment of infectious diseases.

Legend to the Frontispiece:

The Structural Elements of the Bacterial Wall: Five Disaccharide Penta-muropeptides Forming a Glycan Chain and Two about to Form a Nona-muropeptide

Seven penta-muropeptides of *Escherichia coli* or *Bacillus subtilis* are shown in this frontispiece. The top portion shows a glycan chain formed from five NAG (N-Acetyl-Glucosamine) and five alternating NAM (N-Acetyl-Muramic acid) residues. The NAM residues are each linked with penta-muropeptides. The conformation of the glycan chain is a spiral with the top and bottom muropeptides in the same plane. The middle one is also in the same plane but points in the opposite direction. Two of these structures in mirror images are bound to each other by transpeptidation with the loss of the terminal D-Alanine (D-Ala) groups that are shown enclosed in blue ovals. This forms a tessera as shown more explicitly in Figs. 8.1 and 8.2. The bacterial sacculus is formed of many such tesserae and completely encloses the cell.

In the formation of a crossbridge the D-Alanine would be removed in the transpeptidation process and resulting disaccharide tetra-muropeptide coupled by endopeptide bonds (tail-to-tail bonds) with another disaccharide penta-muropeptide to form nine-membered nona-muropeptide. Other muropeptides are shown in the top part of the figure, two pointing above and two pointing below the plane of the cell; they either remain as such or are degraded. The remaining muropeptide is in the plane but points in the opposite direction.

In the bottom part of the figure, the terminal D-Ala groups are again shown in blue and the zwitter ionic groups of the diaminopimelic acid groups are indicated within yellow ellipses. They are placed correctly, but the bonding is not shown because they are part of the diaminopimelic acid group. This amino acid is abbreviated A_2pm (and also DAP in the literature) Diaminopimelic acid minus the dipeptide D-Ala-D-Ala and also minus the zwitter group is designated for clarity by ZZ. Two penta-muropeptides are shown positioned for the removal of the terminal D-Ala and formation of the tail-to-tail bond with a amino group of the zwitter ion. The two ways that this can be done are indicated. One precludes the other, but the remaining unbound D-Ala-D-Ala and the zwitter of

the diaminopimelic acid have ionic attraction to each other and this sterically precludes entry of additional muropeptides or the endo-transpeptidase enzyme as the nona-muropeptide molecule is originally formed. However, when the formed nona-muropeptide is stressed enough by growth to break the ionic attachment of these two groups, then entry becomes allowed and further growth is possible.

Part 1

Origin of Bacteria

Chapter 1
The Origin of Life Based on Physical Principles

All the life forms known to us are completely dependent on organic and physical chemistry. Life depends on the chemistry of carbon compounds and on the laws concerning chemical reactions. Life depends on a temperature low enough to allow covalent bonds to form, with enzyme assistance, but generally not at a high enough temperature to break chemical bonds. Life depends on having an aqueous environment within cells where vital reactions can take place. Living machines function as isothermal engines that require the abstraction of available energy from the environment into special forms that a cell can use. The energy is used to drive chemical reactions in non-favorable directions in order to form molecular and supramolecular structures necessary for cellular life to take place. In this chapter, the essential thermodynamics of life are stated and the real (anthropomorphic) meaning of "free energy" elucidated. Free energy is the basis of biochemistry but is not fully explained in modern courses in chemistry and biology nor, unfortunately, in microbiology.

THOUGHTS ABOUT THE ORIGIN OF LIFE

For a student of molecular biology, the first logical thought about the origin of life certainly would be that, since the system of specific enzymes and the ways to make them are so complicated and their number so extensive, life could not have arisen spontaneously in any imaginable physical and chemical environment no matter how long a time period was involved. There are two extreme rationalizations for the existence of life from this thought: either Divine Creation took place or repetitive random chemical reactions occurred until some combination worked to generate a growing and reproducing cell. Neither extreme seems reasonable to me. However, if many thousands of enzymes are needed to function to activate a reproducing cell, then nothing between the two is logical. On the Divine side, the universe obeys certain rules. Although the origin of these laws is unclear, the laws themselves are becoming clear, at least for our universe. Could they have been different than they are? If so, there is a role for God under any name. If by chance the Universal Laws had been different in

different universes, then maybe we are just lucky to have been in this particular one. At the other extreme, given whatever rules might apply to other universes, a very large number of trials might be needed in most in order to generate a "First Cell". In any case, it may have been necessary to once get a First Cell that lives, grows, and reproduces (Koch, 1985; Koch, 2001; Koch and Silver, 2005, and see the references in Koch and Silver, 2005) for life to have persisted on earth. It could subsequently grow, evolve, mutate, and differentiate. Life, of course, must initially have been started by chance with enough of the necessary paraphernalia to make a minimal, but working and reproducing cell.

Between these two extremes, and with the blessing of Darwin, we can imagine that life started very simply but was hobbled by the many things it could not do. The First Cell was probably very minimally endowed. However, long-term evolution, after the primeval First Cell arose, slowly generated the large number of capabilities possessed by all modern cells and subsequently many kinds of organisms. The evolutionary process that created cells with the essential cellular physiological capability possessed by modern cells must have taken a very long time (I guess almost a billion years). The generation of the diversity of organisms, their organization into multicellular organisms, and their interactions with each other occurred later. In the latter part of this book the interaction between bacteria and people and antibiotics will be stressed. However, this is simply another consequence of the development of a complex biology on earth.

First we need to consider how a chemical machine can work. The structure of any man-made machine allows an action on one part of it to cause a specific action on another of its parts. The machine's construction, or the repetitive construction to make many copies of a machine, requires an external entity: man. On the other hand, while an outside agent does construct each living machine similar to the way an assembly line constructs automobiles, the basis of life, at least in this universe, is that spontaneously the elements of chemistry, those of physical chemistry, the three laws of thermodynamics, available resources, and the subsequent occurrence of a lucky vesicle that was the ancestor of us all, caused growth and reproduction of living systems to occur.

ASTROBIOLOGY

This is not the place for discussion of the development of stars, planets, or the chemistry and environments conducive to life and energy transduction. These must have been involved in development of living systems. Recent reviews can be found in Brack (1988) and Koch and Silver (2005).

THREE LAWS OF THERMODYNAMICS

Various creationists make much of the fact that according to the Second Law of Thermodynamics, any system will gradually and eventually achieve its most stable equilibrium state. This state is, evidently, a non-living state. The creationist's thermodynamics is entirely correct. For example, if the earth were a closed system, it could not support life. When the sun grows cold, everything on earth will then become lifeless. There is no doubt that this will happen. The point is that our earth, for now, is not a closed but a dynamic system because radiant energy falls on it and infrared radiation leaves the earth; thus it has the hallmarks of an open system. However, the thermodynamic rules do permit some of the radiant energy to be trapped (at least temporarily), and it is this tidbit of energy that allows life to exist. The sun plus planets plus other intra-planetary materials out to some very large distance from the sun would approximate a closed system and one that slowly would be "winding down".

The laws of thermodynamics will never be proved, but, also, they will never be disproved. They are statements of "impotence"; they state only what cannot happen. At least, these laws have not yet been observed to have been violated. The First Law, "The conservation of energy", states that although you can convert energy from one form to another, the amount of energy will neither be increased nor decreased. The Second Law states that work cannot be converted totally from thermal energy to mechanical or electrical energy by any machine, except under a special condition stated by the Third Law. The Third Law is that, for a thermal machine, only if the reservoir to which the heat is delivered is maintained at absolute zero can the thermal energy be converted completely into other kinds of energy. Does this matter to a biological system? After all, life is isothermal; it should therefore function with zero efficiency as a heat engine. The answer is that it is not a heat engine. Except for photosynthesis, life is a chemical engine acting by converting covalent bonds.

The laws of thermodynamics are fundamental to life. A humorous paraphrase of the three laws of thermodynamics is (First Law) you can't get something for nothing, (Second Law) there is tax on it, and (Third Law) only at absolute zero is there no tax. When stated less frivolously, these laws are the basis of how all living cells function through chemistry and without physical connection between the parts, such as cogs, wheels, and drive shafts, although these things are necessary in an automobile's function or in any other mechanical machine. To state the laws in yet another way, the First Law states that (except for thermal energy) energy can be converted from one form to another without gain or loss. The Second Law states that a heat engine's mechanical efficiency depends on the temperatures of the source and sink. The Third Law states that thermal energy can be converted to another energy form with an efficiency of 100% only if the

sink is at absolute zero. This leads to the implication that a biological machine would have 0% efficiency because it is isothermal. This is wrong because it is not a heat engine, instead it is a chemical engine and quite different rules apply.

The way the cellular machine works is by having catalysts that favor only certain chemical reactions. This ability to catalyze certain specific reactions and not others is the major virtue of the living machine. Stated more strongly, the specificity of an enzyme is such that it does not catalyze other reactions than the one it was "designed" for. Add to this a little bit of structure and life could work. That structure was initially abiotic (in the first living generation, for example, life was a vesicle probably created by environmental wave action). In addition, there has been extensive evolution of cell structures after the First Cell. These include: chromosomes instead of unlinked genes, cell walls instead of no walls, protein aggregates like muscle fibrils to do mechanical work and form cytoskeletons to support the cellular structure. Add the existence of binding proteins and bound carbohydrates on the outsides of cells allowing them to interact and add other cells, and with little bit more development, here we are.

CHEMICAL REACTIONS

At too high a temperature, say in excess of 2000 °F, carbon, hydrogen, oxygen, nitrogen, sulfur, and phosphorus atoms will not form stable covalent bonds. Neither will they at very low temperatures. In the latter situation they may nearly come together but will not bind to each other because they do not have enough "energy of activation" and, subsequently will come apart and not be bound. In the former case the atoms may be bound temporarily to each other, but will have enough energy of activation to break these bonds and come apart. Life based on organic chemistry, as a result, is limited to a very narrow temperature range. The range is further limited because life depends on favoring only reactions useful to a cell. This dependency on catalysts (enzymes) to speed up some reactions is vital. Note that the key point is that they do not catalyze many other reactions. In the living world today, the cellular edifice has many thousands of vital enzymes to chart the course that it pursues. Nothing less would be sufficient in our competitive world.

THE MECHANICS OF COVALENT BONDING

At very high temperatures, as found in stars, there are nucleons but no atoms. At lower temperatures there will be the formation of stable atoms because the temperature does not dissociate the parts of atoms. At the lower temperature

the attraction of positive and negative charges overcomes the thermal repulsion. At still lower temperature the atoms will have equal numbers of positive and negative charges. At even lower temperatures a more stable state results when the positive charges of two atomic nuclei attract, because of associated negatively charged electrons, and they share electrons. This results in a force that holds the atoms together and effectively creates "the bond". This covalent bond is the glue that makes organic structures stable. This is not to say that weaker bonds are irrelevant. They are very relevant, and more will be said about them in later chapters.

The crucial fact is that very many organic molecules can be formed and they can be quite stable, and they can have many shapes while still retaining a covalent structure. Add to this that the series of weaker bonds can be part of a larger structure and contribute to its catalytic properties. For divine providence to have preordained, if that is the right word and concept, then these laws of chemistry together with its underlying physics are enough to generate life. No matter how the laws arose and even if they are the rules of only our universe, it is enough to make life form and evolve here.

REARRANGING COVALENT BONDS

The interatomic energies holding different covalent bonds together can vary. Consider the following reaction:

$$\text{A—B} + \text{C—D} \rightarrow \text{A—D} + \text{C—B}.$$

It involves an exchange of partners. The free energies of the four bonds will determine the equilibrium constant. The concentrations of the species in a reaction mixture, and the equilibrium constant determines which way and how far the reaction will go from its initial state in a given closed system. How fast it will go, however, is another question. Its speed depends on the energy of activation or the amount of additional energy, which will have to become temporarily associated with the bonds for the groups to dissociate and allow for the possibility to reform in a different combination. This additional energy is thermal energy. Such energy by chance either enters a bond as the result of bombardment of the molecule by other molecules or is reduced by bombardment of other objects by it. This chance exchange is the reason that temperature is so important for living systems. At high enough temperatures there is no function for an enzyme. A forward and back reaction will occur because a particular reaction can go in both directions, because the energy of activation is sufficiently small. Therefore, there is no cellular control. At low enough temperatures, the reaction will not advance at all or only go very slowly. The important condition for life is that some

reactions may not proceed because of lack of a catalyst, but certain catalyzed reactions can occur, in the same environment, if energy coupling and appropriate catalysts are present.

CATALYZED REACTIONS

A variety of substances can catalyze reactions: metals, organic chemicals, and enzymes. How do they do it? Basically, they bind the substances, affect the charge distribution, which lowers the energy of activation, and the reactants go over the "energy hill" to liberate products. A quite common case is that in which A—B reacts with an enzyme, say EH, and forms E—B; and A is bound to a group (usually a proton) abstracted from the enzyme, yielding AH. Then the C—D molecule reacts with the enzyme to form C—B. Finally, the enzyme recovers its H group by rebinding AH, and A is liberated from the enzyme by binding D to yield A—D. The enzyme is back in its original state, here designated as EH. While the involvement of a hydrogen atom is common, it is not obligatory. All of this business is much faster than the uncatalyzed reaction. Moreover, and very importantly, it can be much more selective and occur more rapidly.

DRIVING A CHEMICAL REACTION

If a cell "needs" to have a compound formed, but the spontaneous chemistry works the other way, then seemingly the needed compound would never be formed; and the molecule, if it were formed, would tend to fall apart. How can the cell accomplish its desired goal? The answer has to be that the cell must couple the "needed" reaction to another reaction so that the second one drives the needed one. Most typically, reactions are "driven" by another reaction that, if the driving reaction spontaneously occurred, would dissipate its free energy, thus wasting the energy from our anthropomorphic view. Only if the two reactions are mechanistically connected is there effective coupling. In other words, the driving reaction can only go if the reaction to be driven actually takes place. This coupling requires that the two processes are somehow linked. While enzymes are catalysts, they are more than just that because they can be constructed not to carry out either of two reactions independently, but to occur only if both enzymatic functions occur at the same time.

Chapter 2

Preamble to Life

The conditions that were necessary for life to begin on earth are reviewed; primarily these were the prerequisite chemicals and prerequisite processes for the origin of First Cell. Once arisen, it could grow, divide, and its descendants could evolve. Although the combination of events that actually started life is only dimly understood, it is evident that a simultaneous coalition of mechanisms had to function simultaneously and in the same place for life to be "kick-started". In an abiotic world these must have included the numerous and fruitless formation of "informational" macromolecues that could not carry out needed functional processes because of lack of support, but eventually there must have been a way to utilize these informational molecules to construct others. These would actually function as catalysts and probably were ribozymes, which are molecules that are almost enzymes. These could alter available small molecules and form macromolecules and do fruitful work. The third absolute requirement is the existence of a capability of transducing energy into a utilizable form that flexibly could enable (favor) the synthesis of small molecules and macromolecules and carry out other energy-requiring cellular processes. But useable energy alone would initially lead to nothing productive. The life-generating event had to do with the simultaneous existence of these three particular processes within a single lipid vesicle. Of course, it also required the availability of sufficient and appropriate chemicals from the environment. These essential processes and organic resources could spontaneously produce molecules that would catalyze the creation of more "cells" and then bigger and more sophisticated molecules. This continuing replication and continuing evolution eventually led to diversity and the massive world biomass on the assumption that new structures and mechanisms continued to evolve.

THE ABIOTIC WORLD

In the beginning there was a "big bang" resulting in an expanding and cooling universe. As the material became more spread out in the resulting cooler milieu, aggregates of various kinds formed. The spreading was not uniform, however, because of the effects of gravity. In many parts and regions of the

universe, concentrations of materials were higher. In these places high density developed as stars formed and went through their cycles. Nuclear reactions took place, and when the stars finally collapsed, some of the resultant materials were cool enough to become stable small atoms. Then the process repeated itself and the next star generation led to some still larger atoms. Finally, in the third generation of stars there was a sufficient quantity of large enough atoms so that the kind of life we currently experience on earth became possible. As a time line, our universe came into existence 13.7 billion years ago and our sun (Sol, a third generation star) appeared 4.5 billion years ago, as did everything in our solar system, including the earth. While the sun is too hot, the remainder of the solar system is cool enough to be able to coalesce into solids and molecules. The rest of the solar system includes interstellar space, planets, various comets, asteroids and planetoids. Organic molecules were made in various ways in various locations; they arose partly under the aegis of cosmic ray energy and ultraviolet light. These agents make and destroy organic molecules. However, some persisted, and some that fell to earth were probably important as resources for early life. These organic molecules were in addition to those produced on earth (see below).

Four and a half billion years ago, as the planet earth was formed, it was too hot for life. A barrage of meteorites bombarded it. If there had been any living thing to sterilize, these impacts would have killed them. There was no liquid water. It is thought that the intensity of meteorite bombardment decreased about 4.2 billion years ago. At this time surface water and oceans developed, and a variety of more stable organic chemical syntheses began to occur.

RESOURCES AVAILABLE FOR LIFE

The earth, as part of a third generation star, had adequate amounts of atoms of a reasonable size. Obviously, H, C, O, N were the key elements, but P, S are also vital. Then there are heavier elements such as Mg and especially Fe that also have a vital role. Getting all of them to form the appropriate compounds is not trivial and does require energy.

Light energy from the vacuum ultraviolet to the infrared would have been available in abundance, but other than for generating heat it would have been useless for a living creature with no ability for photosynthesis, and it would actually have been quite dangerous. When the earth cooled down sufficiently, there would have been liquid water, oceans, and rivers. There would have been organic compounds, vesicles, and reactants in the environment that had not yet reacted with each other, and there would have been atmospheric disturbances. The formation of vesicles would have depended on continual mixing by cosmic

events, volcanoes, deep-sea vents, and ocean currents. The reason for this discussion is that the First Cell would have needed everything "handed to it on a platter" from the environment.

THE STAGES OF DEVELOPMENT OF LIFE

Figure 2.1 shows the entire evolutionary process; however, for this chapter it is the abiotic chemical processes shown at the bottom and in an expanded way in Figure 2.2, which presumably supplied the chemical and physical basis

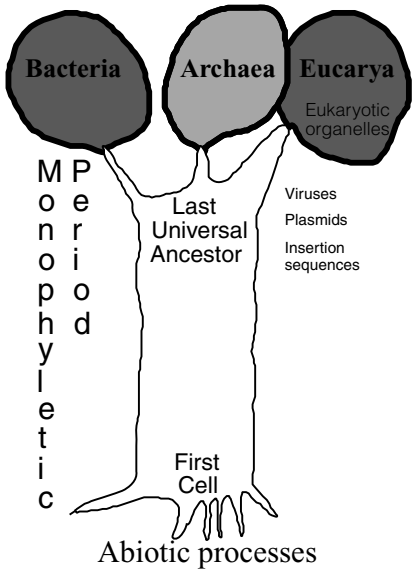

Figure 2.1 Abiotic, First Cell creation, Cellular processes, and Diversity.

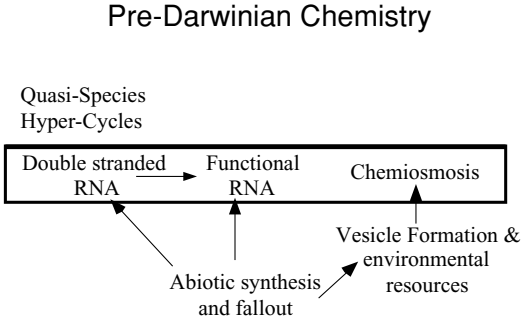

Figure 2.2 Abiotic processes in a lifeless world.

for life. For a non-photosynthetic organism, a chemical non-equilibrium situation in the environment could have been the only available source of useful energy.

THE GENERATION AND PRODUCTION OF THE ORGANIC MOLECULES NEEDED FOR LIFE

Miller and Urry (see Miller and Orgel, 1973; Chang, Mack, Miller, and Strathearn, 1983; Brack, 1998; Deamer and Bada, 1997; Deamer and Fleischaker, 1994) carried out a very important experiment. They prepared a gas mixture that

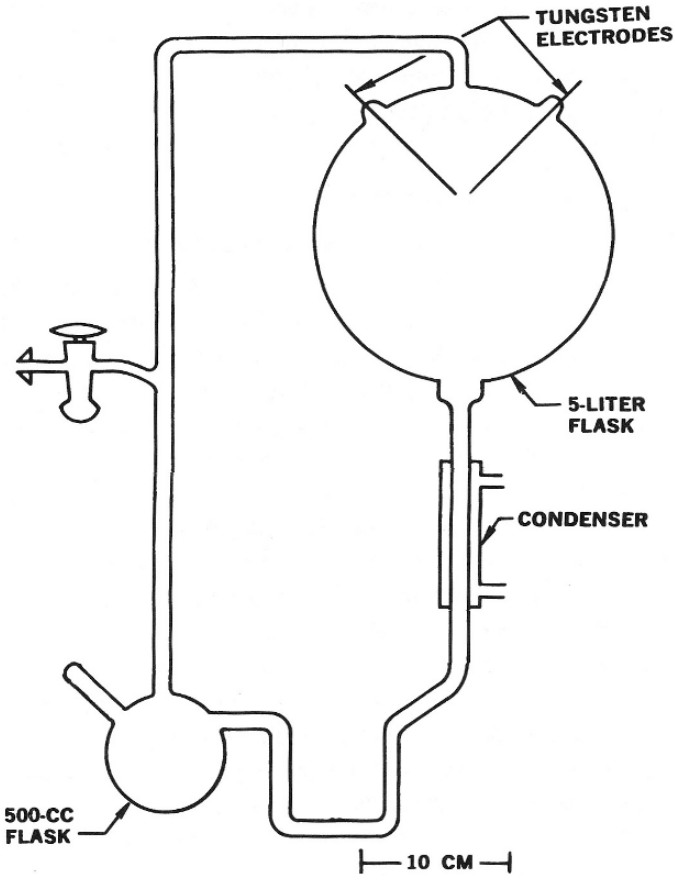

Figure 2.3 The essential aspects of the Miller and Urry experiment. Diagram taken from Miller and Orgel (1973) with permission.

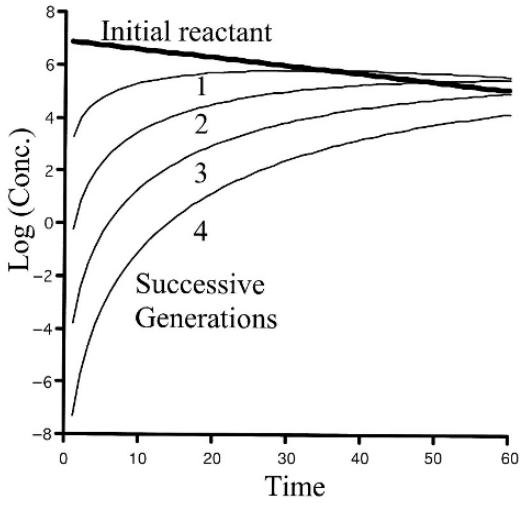

Figure 2.4 Kinetics (idealized) of successive stages of cycles of burying and unburying. Taken from Koch and Silver (2005).

they thought simulated the early atmosphere. Into this atmosphere they injected energy in the forms of electric arcs and ultraviolet rays. This energy led to combinations of very simple starting molecules and to larger ones that had more internal energy. As well however, the same sources of energy were able to break down these constructed molecules. The very clever part of their experiment was in the design of the apparatus (Figure 2.3). It was arranged so that the water-soluble compounds were condensed out of the gas phase and dissolved in the liquid aqueous phase by the condensation of the water vapor. Consequently, these molecules were no longer exposed to the destructive sources of energy. This meant that complicated molecules were made but then "buried" and not destroyed. Although the differential effect of the details of the condensation process should be important and we must assume that this part of the generic burying process is specific and selective, bigger more water-soluble molecules will accumulate over smaller ones. Molecules would be accumulated in a water phase or under ground and would have been preserved there. In the early world these accumulating resources would be around to serve for the formation of life. Figure 2.4 shows some idealized kinetics of such a process going through several burying and resuscitation stages. This would lead with time to larger and more complex structures. It is hard to imagine life arising and becoming more sophisticated without such cyclical processes. Such cycles of burial and upheaval of chemicals were needed and presumably occurred in a world experiencing many geological changes.

Chapter 3
The First Cell

The conditions necessary for life to begin on earth were reviewed in Chapter 2. The prerequisite chemicals arose abiotically on earth and in interplanetary space. We assume that abiotic processes allowed the First Cell to arise. It could then grow, divide, multiply, and evolve. The combination of abilities that actually started life is only speculation, but the mechanisms can be cataloged. In an abiotic world, they must have included the semi-conservative replication of informational macromolecules. Secondly, there must have been a way to utilize these informational molecules to construct molecules that actually functioned as catalysts (such as ribozymes, which are RNA molecules that are almost enzymes). These catalysts did alter available small molecules into molecules useful in living systems and in forming macromolecules with special shapes and chemical functions. The third requirement is a capability of transducing energy from the environment into usable forms in order to enable the synthesis in cells of thermodynamically useful but unstable, small molecules and macromolecules, as well as to carry out other cellular processes. The life-generating possibility had to depend on the availability of sufficient abiotic chemicals and at least these three essential abiotic processes that would have, by rare chance (once, for the first time, would be enough) have produced informational molecules, which grew and catalyzed the actions that created big and sophisticated molecules able to generate what was needed for further growth.

Consequently, we can tacitly assume that the current life on this planet started with a unique event empowering at least these three processes at a particular instant of time. This event was the concatenation and propinquity of several essential processes for life (at least the three mentioned: information transfer, chemical catalysis, and energy trapping). They had to be simultaneously functional at the same time and the same place, which no doubt was a single vesicle. All these essential processes had to be working in the same vesicle for it to become a living entity. Individually each one of these several systems, almost certainly, had been created many times by chance. However, once the important "protocell" had facilities for all of the absolutely essential component processes, it became alive because it could reproduce and grow. This unique vesicle had just become the First Cell.