The Teachers' File

THE ORIGINS OF LIFE: WHAT ONE NEEDS TO KNOW

by Ronald F. Fox

Abstract. Many solar systems in the universe may be expected to contain rocky planets that have accreted organic compounds. These compounds are likely to be universally found. In addition, the chemistry of sulfur, phosphorus, and iron is likely to dominate energy transductions and monomer activation, leading to the eventual emergence of polymers. Proteins and polynucleotides provide living matter with function, structure, and information. The conceptual puzzle regarding their emergence is discussed. The fitness of various elements to serve various roles is analyzed from the viewpoint of electron orbitals. Elements with *d* orbitals are of central importance.

Keywords: *d* orbitals; energy metabolism; evolution; fitness; periodic table of the elements; phosphates; phosphorus; polymers; polynucleotides; proteins; silicon; stellar nucleosynthesis; thioesters; uroboros.

CONSTRUCTIONISTIC APPROACH TO THE ORIGINS OF LIFE

The study of the origin of life is a multidisciplinary undertaking involving both experimental and conceptual components. For example, physics, mathematics, chemistry, cell biology, geophysics, and cosmology each contribute essential features of a complete picture. Consequently, most research papers or books on these subjects involve isolated particulars, and the student must work assiduously to provide a general synthesis within which to place this information. The following material is intended to aid the student in building a sufficiently rich context for such a synthesis.

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At its most fundamental level, an understanding of the origin of life must have an experimental foundation. When truly understood, humankind will be able to reconstruct in the laboratory the chemical processes leading to the formation of a cell. Such an approach is called a constructionistic approach by its principal contemporary proponent, Sidney Fox (S. W. Fox 1988; Fox and Dose 1972). In addition, such understanding will require conceptual constructs that enable widespread communicability. This presentation will focus on the conceptual side of the story.

ABSTRACTIONS

Conceptualization is the process of creating abstract ideas. Mathematics and the physical sciences are replete with this process. Several abstract ideas that are crucial for a study of the origin of life come to us from the disciplines of biochemistry and molecular biology (de Duve 1984; Stryer 1988; Watson 1975). They include (1) catalysis (autocatalysis), (2) allostery (flexibility of multiple weak bonds), and (3) self-assembly.

Catalysis. Many proteins in the cell are enzymes, specific catalysts of specific reactions with the ability to recognize specific substrates. Their functionality follows from their structure, in particular from their conformations, which are the result of a combination of covalent bonds, ionic bonds, hydrogen bonds, hydrophobic/hydrophilic interactions, van der Waals forces, disulfide bridges, and so on. A central phenomenon is the complementarity of interaction afforded by multiple weak bonds. This provides recognition and specificity. James Watson's *Molecular Biology of the Gene* (1975) did much to make an appreciation of these ideas widespread. Watson and Francis Crick showed how multiple weak bonds, specifically hydrogen bonds, permit the transfer of genetic information during replication of deoxyribonucleic acid, or DNA, transcription of DNA into ribonucleic acid, or RNA, and translation of RNA into protein amino acid sequences.

Allostery. Binding of an effector or chemical modification (often phosphorylation—the introduction of a phosphate group—or dephosphorylation) can trigger a conformation change. Often, the change occurs in a part of the protein spatially removed from the site of the binding or modification. This is the essence of allostery. Many regulatory interactions involving proteins are allosteric. Sometimes a modified protein in turn modifies another, and so on, in a cascade of activations or inactivations that may endow the initial effector with a highly amplified effect.

Self-Assembly. Enzyme complexes, subcellular organelles, and membranes self-assemble from their constituents (de Duve 1984). This

means that once the proteins have been translated and perhaps have also been post-translationally altered, they recognize and combine with other proteins to form specific complexes. Lipids self-assemble into vesicle membranes. These processes are often driven by the increased entropy of water molecules (R. F. Fox 1982) initially associated with the proteins or the lipids, and for this reason the term *self-assembly* is a bit of a misnomer. Nevertheless, sophisticated visualization techniques see decreased entropy of the proteins, the lipids, and the assembled structures while the water molecules remain invisible, and so the observer really does think he or she is seeing self-assembly.

EVOLUTION

Evolution is a dynamical process, the interplay of amplification, variation, and selection (de Duve 1991). In this context, amplification refers to the population size of a particular type of living unit. In its simplest form, this amplification is achieved by replication of the units by division; in its most complex form, by bisexual reproduction. Replication isn't perfect, and some variations may confer felicitous functionalities. These are selected for by the dynamics of the interaction of the individual with the environment. The central concept here is fitness. Fitness means that the interaction with the environment promotes amplification of numbers of units within the niche. Fitness may well change, even reverse, over geophysical time scales (tens of millions of years).

THE PERIODIC TABLE OF THE ELEMENTS

As a starting point, we will choose to make all the matter needed for life from electrons, protons, and neutrons. All atomic nuclei are made up of protons and neutrons (nucleons), and the number of protons determines the atomic number. The production of the atomic elements, called stellar nucleosynthesis (Fowler 1967), involves a number of nuclear reaction cycles. Protons combine and some decay to form alpha particles that contain two protons and two neutrons. An alpha particle is the atomic nucleus of helium, ^{4}He. Alphas are especially stable combinations of nucleons. Subsequent synthesis, at great pressures and temperatures, tends to produce nuclei that are simple multiples of alphas, such as ^{12}C (carbon), ^{16}O (oxygen), ^{20}Ne (neon), ^{24}Mg (magnesium), ^{28}Si (silicon), ^{32}S (sulfur), and ^{40}Ca (calcium). Note the absence of ^{8}Be (beryllium), which happens to be especially unstable. Reactions of these nuclei with protons, such as in the carbon-nitrogen-oxygen (CNO) cycle, produce the intermediate elemental nuclei (it should be noted that in first-generation stars, ^{1}H (hydrogen) and ^{4}He nuclei overwhelmingly dominate, whereas in second-generation stars, ^{12}C acts catalytically to generate much greater amounts of

heavier elemental nuclei). These processes explain the relative abundance of the elements and especially the periodic dominance of alpha multiples. In a first-generation star, this progression is dominated by elements up to ^{56}Fe (iron), the most stable nucleus. Thus, life might be expected to be based most naturally on H, C, O, Mg, Si, S, Ca, and Fe. Indeed, it is (except for Si), although one must not overlook the central importance of N and P (phosphorus) and of Na (sodium) and K (potassium) as ions as well. Given their positions near the beginning of the second and third periods of the periodic table, Mg and Ca are usually the ions Mg^{2+} and Ca^{2+} in aqueous, living matter.

Our own solar system is second generation, having accreted from the products of first-generation supernovas. The inner planets (Mercury, Venus, Earth, and Mars), Earth's moon, and the asteroids make up 0.0006 percent of the mass of our solar system and only 0.44 percent of the mass of the planets. Volatile compounds, such as H_2O (water), CH_4 (methane) and NH_3 (ammonia), were deposited on planet Earth by bombardments of planetesimals that formed in the outer reaches of the planetary disk (Faure 1991) early in the solar system's evolution. These volatile compounds were blown to the cold outer reaches of our nascent solar system by a strong solar wind where they coalesced into billions of planetesimals. The less volatile matter, primarily silicate rocks, remained closer in and became the foci of accretion for the planetesimals. A reminder of this early period is the extensive cratering throughout the solar system, both on rocky planets and on the moons of the gaseous planets.

While abundance is important, fitness is just as important (Needham 1965). By weight, three quarters of the Earth's crust is made of O (50 percent) and Si (25 percent), primarily as silicates. The oceans are mostly O (85 percent) and H (11 percent). George Wald (1962) has explained why Si, although the second-most-abundant terrestrial element, is highly unfit for living matter and indeed readily combines with O_2 to make silicates, for which it is much more fit. By examining the electronic structures of the elements it is also possible to understand why C, N, and O, along with S and P to a lesser degree, are suited to making complex molecules with both single and double covalent bonds. The relative smallness of the atoms C, N, and O enables them to make strong bonds with short bond lengths. As the atomic number increases, size increases with each period of the periodic table, and internal electron repulsion of greater numbers of electrons per atom also increases. Once the third period is finished, with the possible exceptions of selenium (Se) and bromine (Br) in the fourth period, all heavier atoms are typically incapable of overcoming these inhibitions to making multiple bonds. An interesting wrinkle to this view is that within a given period, the atomic size decreases as electrons fill up the electronic orbitals. Thus Si is bigger than P, which is big-

ger than S. The bonds are correspondingly shorter and stronger in P and S than in Si. Thus, it is to be expected as natural that many solar systems throughout the universe will contain some interior, rocky planets, primarily made of silicates, containing lesser amounts of a huge variety of molecules, primarily made of H, C, N, O, P, and S (Calvin 1969).

S and P are especially interesting in that P is usually most fit in an aqueous milieu as phosphoric acid, H_3PO_4, and its ionization products, and S is most fit as either combined with O, such as in sulphuric acid, H_2SO_4, or as sulfhydryl, -SH. P, as phosphate, is virtually the sole form of P in living matter. P and S, as well as Si, are in the third period of the periodic table, and this means that they possess unfilled *d* orbitals for their electrons. This feature confers on P and S especially felicitous properties for group transfer and rapid reactivity as compared to C, N, and O, whereas it simultaneously explains the lack of fitness seen in Si to serve the role served instead by C, even though both have the same valence, or degree of combining power, of 4. While about 135 times more abundant in Earth's lithosphere than is C (Needham 1965), Si makes weaker bonds that are longer than those of C. Unfilled 3*d* orbitals enable nucleophilic molecules with lone pairs of electrons to easily attack Si-Si bonds. In the presence of O_2, NH_3, and H_2O, such bonds are especially labile. The corresponding C-C bonds are not. It is hard to imagine any sort of life without O_2, NH_3, and H_2O.

The ability to form double bonds depends in part on being small enough. This is why C, N, and O are frequently found with double bonds. P and S also are found with double bonds, whereas Si is not. This is because within a period of the periodic table of the elements, the size of the atoms decreases with increasing atomic number. Si is just too big, while P is the largest atom with this capability and S is the heaviest.

The presence of unfilled 3*d* orbitals in P and S, and not in second-period elements such as C, N, and O, is what creates the versatile reactivity seen in them. Because they are bigger than second-period elements, their bond strengths are weaker and bond lengths are longer but not as weak or as long as with Si. Their unfilled 3*d* orbitals provide opportunities for intermediate states of reaction for many chemical species. Together, these special properties make them more susceptible to attack or cleavage and more able to engage in exchange reactions than C, N, and O. When studying biochemistry, the student should make note of the frequent and central occurrence of P (as phosphate) and S (often as -SH) in reactions and in structures (Stryer 1988). It is hard to miss the P in polynucleotides, in adenosine triphosphate (ATP), and in allosteric protein modifications (phosphokinases). It is also hard to miss the S in acetyl-CoA, in proteins, especially in crucial structural disulfide bridges and in iron-sulfur proteins central to energy metabolism.

C is about 10^4 times more abundant in the universe than is P. Compared to Si and O, this means that C and P, as well as other elements, must be concentrated by organisms in order to provide them with the amounts they require. (While some writers on the subject emphasize the low levels of natural abundance reported above [Monod 1971], it is much more realistic to recall the size of Avogadro's number, 6.023×10^{23} [the number of molecules in a mole of material], which means that for every mole of Si in the universe, there are 6×10^{17} atoms of P. Planet Earth contains at least 10^{25} moles of Si!)[1]

By studying the many particular properties of the different elements, we can begin to see the naturalness of many of life's molecular features, and because of this we also see why life should be similar throughout the universe, at least at its fundamental chemical level.We see myriad organic compounds and a central importance for P, S, and Fe.

Free Energies of Formation

Free energies of formation of small molecules give us some idea about which molecules should be expected in any rocky planetary setting. Many have free energies of formation more negative than the elements from which they are formed. This includes H_2O, NH_3, CO_2 (carbon dioxide), CH_2O (formaldehyde), H_2SO_4 (sulfuric acid) H_3PO_4 (phosphoric acid), amino acids, simple sugars, and a host of other biologically relevant small molecules (Calvin 1969; Fox and Dose 1972). Mineral combinations such as $Ca^{2+}HPO^{2-}$ (apatite), FeO/Fe_2O_3 (magnetite), and SFe (pyrite) are additional examples. Bone contains apatite in an organic matrix; banded iron formations dating back more than 3 billion years may represent deposits created by ultraviolet excitation of Fe electrons and subsequent precipitation of iron oxides in early prebiotic chemistry (de Duve 1991), and nano-scale pyrite (troilite) crystals (common in iron meteorites) make up the active centers of several essential iron-sulfur proteins. These are examples of naturally occurring atomic combinations with low free energies of formation and no special kinetic barriers to formation.

Biopolymers

Deoxyribonucleic acid, DNA, has been called the quintessential molecule of life because its self-replicability makes it a macromolecular substrate for evolution. However, study of the detailed mechanism of replication reveals a host of large protein complexes, most notably the DNA polymerases. Without these, DNA has no chance to replicate and clearly does not self-replicate in experiments in which DNA is simply incubated with its precursor trinucleotides. Instead, hydrolysis of the

nucleotides dominates. Moreover, without an even greater number of other proteins to support metabolism, there would be neither the precursor monomers nor the necessary energy for the replica's construction. Francois Jacob (1973) has proposed that the first level of integrated molecular behavior deserving to be called a living organism occurs with the cell. Only at the level of the cell do we find a system truly reproducing itself from small molecular precursors, from which all precursor multimers and polymers are made and from which the necessary chemical energy is generated. Ribonucleic acid (RNA) and DNA cannot do this without proteins.

The Polymer Phase Transition

What really sets life processes apart from other chemical processes is the transition from monomeric molecules to polymeric macromolecules (R. F. Fox 1982, 1988). The principal polymers are proteins (made from amino acid monomers), polynucleotides such as DNA and RNA (made from mononucleotides), and polysaccharides (made from simple sugars). In each case the condensation of the monomers into polymers is chemically a dehydration condensation, that is, it involves the elimination of a molecule of water between two combining molecules (Calvin 1969). This is thermodynamically inhibited by the large concentration of water in all living systems and requires the input of chemical energy to be achieved by a living cell. This energy is directly or indirectly provided by the universal currency of chemical energy adenosine triphosphate, ATP (Lipmann 1941). The monomers must be activated with phosphate groups before they can spontaneously condense into polymers. Thus, antecedent to any model of polymer evolution must be an account of the emergence of phosphate energy and monomer activation. Most probably, simple pyrophosphate sufficed very early on, and it was probably formed in prebiotic oxidation-reduction reactions involving S (as thioesters) and Fe (de Duve 1991; R. F. Fox 1982, 1988). With Fe as the absorber, ultraviolet light may well have been the primary source of the energy through photo-oxidation.

Coenzymes (Multimers)

Before full-scale polymers emerged, it seems probable that a period of chemical evolution developed in which mixed oligomers ("multimers" [de Duve 1991]) were formed that contained some amino acids, some sugars, some nucleosides, and some sulfhydryl compounds (e.g., acetyl-CoA, NAD, NADP, FAD (pyridine and flavin nucleotides), and pantetheine). Today, we identify these substances as coenzymes, of which there are roughly a couple dozen kinds, pieces of which we call vitamins.

These catalytic multimers are central to all of modern metabolism. The core of this metabolism comprises the energy-yielding pathways: glycolysis, the citric acid cycle, the pentose phosphate cycle, and the electron transport chains. The coenzymes structurally recall the early evolutionary dependence on S and P (pyrophosphate). Many enzymes are a complex of a coenzyme and a protein. The coenzyme is the true catalytic center, whereas the protein portion of the complex confers specificity for substrates and allosteric regulation. The protein may also enhance the overall catalytic rate for the coenzyme-mediated reaction, perhaps by several orders of magnitude.

The Uroboros Puzzle

A sequence of stages ("worlds") of molecular evolution can be envisaged. The small molecules that have negative free energies of formations form naturally in appropriate geophysical niches and can be expected throughout the universe wherever there are solar systems with some rocky planets that have accreted planetesimals containing volatile organic compounds. Therefore, the finding of amino acids on the moon and in some meteorites is not a surprise. They will surely be found on Mars as well. Electron current generated by ultraviolet light impinging on Fe, or by inorganic oxidation-reduction reactions involving S, provides the primary source of energy, ultimately yielding thioesters and then pyrophosphate energy, the "thioester-pyrophosphate world." This last form of chemical energy is extremely fit for promotion of dehydration condensation reactions, leading at first to multimers that would otherwise be thermodynamically prohibited and therefore very improbable constituents of the geophysical world (Monod 1971). But with the thioesters and pyrophosphate energy, their occurrence becomes very likely. These multimers catalyze a variety of chemical reactions that lead to a rudimentary chemical metabolism, perhaps still prior to actual living cells (i.e., encapsulation by a membrane). Modern metabolism contains many apparent vestiges of a prior thioester- and pyrophosphate-dominated world. In this energy-driven milieu, the emergence of true polymers changes from virtually impossible to highly probable. Moreover, the particular catalogue of molecular species that evolves in this way should be universal.

Two classes of polymers have evolved that capture the functionality of life at the molecular level: proteins and polynucleotides. The proteins are both catalytic (with specific recognition capabilities and allosteric conformation mutability) and structural. The polynucleotides are informational, providing the coding for the amino acid sequences in the proteins as well as providing part of the apparatus for the informationally directed synthesis of the proteins. Curiously, the replication of the informational

polynucleotides and the transcription of DNA into RNA, as well as the translation of the messenger RNA (mRNA) into protein, requires numerous specific proteins and special RNAs (as transfer-RNAs [tRNA] and as ribosomal-RNAs [rRNA]) to catalyze the reactions. The proteins also are needed to catalyze the metabolic pathways that provide the essential ATP energy and to provide the essential monomers from which the polymers are made. Thus, contemporary life needs proteins to make polynucleotides and needs polynucleotides to make proteins.

This sort of "chicken and egg" interdependence is referred to as the "uroboros puzzle"(R. F. Fox 1982, 1988). It poses the conceptual problem of constructing a plausible, "prebiotic," chemical scenario in which some very simple processes emerge that are capable of further evolution that could lead to the contemporary complexity of the genetic apparatus and its protein biosynthesis machinery. Such a uroboros model has been proposed by the author (R. F. Fox 1982, 1988).

The uroboros model is based on the scenario given earlier for the emergence of chemical energy and multimeric catalysts. In this system, polypeptides (i.e., very small proteins) can be expected to emerge. Their emergence should not be viewed as the creation of merely random chains of amino acids, as is so often suggested in the literature (de Duve 1991; Eigen 1971). Rather, their condensation is greatly constrained by the chemical identities of the various amino acid residues,[2] and the polypeptides produced possess relatively ordered sequences (Fox and Dose 1972; S. W. Fox 1988). This is an experimentally observed fact. A highly limited number of sequences occurs when compared to the combinatorially possible random sequences. (There are $20^{60} = 10^{78}$ possible random sequences of 20 amino acids in a protein of 60 residues in length. This number is as large as the total number of nucleons in the universe. Some simple organisms have a mere 6,000 enzymes and structural proteins, many of which are longer than 60 residues. Clearly, life depends on an incredibly small fraction of the combinatorial possibilities. This does not mean life is impossible as a natural process [Monod 1971]; it means that the limited sequences that do naturally arise possess enough diversity of function for the evolutionary process to unfold.) These small peptides would further promote the diversification of early metabolism.

It is also possible to produce rather larger polypeptides (proteinoids) from amino acids by dry heating (Fox and Dose 1972). If one envisages the early Earth and considers its great variety of geophysical niches, it is not hard to picture many types of zones in which there is daily or seasonal variation in heat and water content. Tidal zones, volcanic shorelines, hot springs, and areas experiencing periodic rains are examples. In such zones, during the dry periods, which can be quite hot if volcanism or even simple baking in the hot sun is considered, the spontaneous condensation of

monomers into multimers and polymers takes place without input of chemical energy. The byproduct and inhibitor of condensation, water, is driven off by the heat. In the laboratory, all sorts of biologically relevant molecules have been synthesized in this way (Calvin 1969; Fox and Dose 1972). When the water returns, the polypeptide constituents created by the dry heating spontaneously self-assemble into spherical cells of micron dimension. This is a very robust process, and it produces many billions of cellular units from milligrams of material (S. W. Fox 1988). This is the "proteinoid-microsphere world." The stage is now set for the emergence of energy-driven vesicular micro-environments in which conditions are ripe for the emergence of small polynucleotides.

In the uroboros model, these small polynucleotides, in the presence of pyrophosphate energy, are imagined to be able to condense activated amino acids into polypeptides with sequences determined by the polynucleotide sequence. The proposed mechanism postulates amino acyl RNA ester intermediates. This model potentially explains the origin of both coding and protein biosynthesis. The RNAs serve simultaneously as genes, messenger RNAs, and transfer RNAs. This model solves the conceptual uroboros problem by providing a simple, primitive mechanism that has the capacity to evolve into the complex contemporary mechanism. This is the "RNA-polypeptide world." Nevertheless, none of the model's key features has been demonstrated experimentally to date.

During the last fifteen years, another perspective has gained temporary popularity following Thomas Cech's discovery of ribozymes (Cech 1986a), RNA molecules capable of catalyzing self-excision. In laboratory settings, additional catalytic capabilities have been identified for RNA, including self-replication (Cech 1986b). This has led some researchers to the notion of an "RNA-world" for the origin of life, in which a primitive RNA molecule served both as information carrier and as catalyst. However, there are many shortcomings to this model that are becoming increasingly realized by its proponents (de Duve 1991). First of all, RNA molecules are thermodynamically contraindicated because of their dehydration condensate structure. Even their monomeric precursors, the ribonucleosides, are small multimers also subject to the thermodynamic dehydration barrier. Second, being a catalyst for a very special process, or for perhaps a few processes, doesn't confer general catalytic ability on the RNA species. There is absolutely no evidence for the diverse catalytic repertoire required both for energy metabolism and for monomer synthesis. Clearly, the RNA-world emerged well along the way in the evolution of living matter, after the thioester-pyrophosphate and RNA-polypeptide worlds, and did not play any role at the start.

I described my uroboros model as a colloquium presentation at Rockefeller University on 28 March 1973. The following year, on 8 February, at

Larry Gold's invitation I presented the model at the Charles Yegian memorial symposium at the University of Colorado in Boulder. At the first talk, when I described how an RNA molecule could serve both as an information carrier and as the template for direct synthesis of polypeptides, I was asked by a member of the audience if I was suggesting that RNA was acting as a catalyst. I answered yes. I believe someone in the audience already used the word *ribozyme* at that time. The catalytic activity for RNA I was postulating was not the self-excision activity found by Cech, but it is not excluded chemically that the postulated activity is possible and will one day be demonstrated in the laboratory.

The Mystery of the Second Code

One of the details of the uroboros puzzle involves the mystery of the second code (Eigen 1971; R. F. Fox 1982, 1988). The protein translation apparatus requires that a messenger RNA, (mRNA) be read and translated into an amino acid sequence. This is achieved by a complex process that is coordinated by ribosomes and that necessitates the intermediacy of transfer RNAs, tRNAs. The tRNA's anticodon reads the codon on the mRNA, and the tRNA carries the cognate amino acid. The attachment of the cognate amino acid to the tRNA with the corresponding anticodon is achieved by the action of a group of pure protein enzymes called amino-acyl-tRNA synthetases. While the transcription of the DNA genes into mRNA and the reading of the mRNA codons by the tRNA anticodons is achieved by Watson-Crick base pairing, the mechanism of attachment of the correct amino acid to the correct tRNA by the synthetases is not by base pairing and involves an as yet unknown recognition mechanism. Hence, the mystery of the second code.

Many students of the subject believe that Manfred Eigen's hypercycle model (Eigen 1971) somehow solves this problem, but Eigen's own account clearly states otherwise and leaves the problem open. My uroboros model addresses this problem and poses a conceptual solution that includes the suggestion that amino-acyl-tRNA synthetases have had a long evolution that now obscures their origins and also makes their contemporary mechanism obscure. The mystery of the second code remains the outstanding unexplained chapter in the protein translation story for all contemporary organisms.

Inferring Dinosaurs

Max Delbruck (1978) observed that it is difficult to reconstruct the "tree of life from paleontology and comparative anatomy" because fossils provide a spotty record. Although comparative anatomy, physiology,

and biochemistry are much more useful than fossils for such a reconstruction, he concludes that "no amount of study of present forms would permit us to infer dinosaurs." Nevertheless, the context presented here for the emergence of life and all of its molecular constituents has the quality of an inextricable progression. Contrary to Stephen Gould's metaphorical assertion about replaying the "tape of life"—"any replay of the tape would lead evolution down a pathway radically different from the road actually taken" (Gould 1989)—nearly all of the molecular features would be reproduced. What about the organismic level?

Especially central is phosphate as the universal carrier of chemical energy in the pyrophosphate linkage. Although we haven't emphasized it so far, Ca^{2+} (as well as Mg^{2+}) is very frequently associated with phosphate compounds, where it plays a regulatory role. This is especially true in muscle function, in which the cycle of actin and myosin cross-bridge attachment and detachment is closely controlled by Ca^{2+} fluxes into and out of muscle tissue fibrils (de Duve 1984; Stryer 1988). The extremely favorable free energy of formation of the mineral apatite makes it clear that bone will surely be a concomitant of muscle as more and more energetic muscular organisms evolve, that is, as more and more phosphate and calcium are required. So it is not so hard to "infer" vertebrates somewhere along the way during evolution (following worms with, first, calcium carbonate and, later, calcium phosphate shells, i.e., mollusks). Remembering that teeth are largely made of apatite as well, we easily infer an emphasis on teeth. Perhaps it is not so hard "to infer dinosaurs" after all at the end of an evolutionary sequence emphasizing muscle, bone, and teeth and including predatory fish, amphibians, and reptiles.

The "Ferocity of Ca and P"

If we take seriously the suggestion in the previous section that the inextricable progression of life will naturally lead to something like dinosaurs, what we are doing is saying that these organisms are merely an evolutionary manifestation of the way certain particular elements manifest themselves in living tissue, for example, phosphorus and calcium. One might go further and argue that this manifestation as dinosaurs reflects the potential "ferocity of Ca and P." It is presaged by predatory fish, amphibians, and reptiles. This view is not lessened by contemplation of the more recent mammalian predators instead. Watching a videotape of a lion making a kill we clearly see the ferocity of muscle and bone and tooth.

In this regard, it is sobering to consider the evolving role of silicon. As mentioned earlier, Si is not fit for an essential biological role. While Si is more abundant than C, C is nevertheless far more suited as a constituent of living molecular matter. We do find Si in the very sharp

spines of some cacti and in several other plants where it serves to strengthen stems and leaves and perhaps to inhibit herbivores by wearing down their teeth as they eat these gritty plants. With the advent of humans, evolution has taken a new direction because of the enormous human impact on the environment. Recently, Si (along with Cu [copper], which has had several earlier impacts, e.g., the bronze age and the electrified twentieth century) has entered this evolutionary process in a dramatic new way through micro-electronics, computers, and the Internet. While we cannot neglect the multifarious benefits of glass (silicates) and the wonderous contributions of computers, it is not obvious that this new role for Si (and Cu) will not, instead, add to the ferocity of Ca and P.

NOTES

1. Mole: That amount of a given substance or species having a mass in grams numerically the same as its molecular or atomic weight; now defined equivalently in the International System of Units as the quantity of specified elementary entities (molecules, ions, electrons, or the like) that in number equals the number of atoms in 0.012 kilograms of carbon 12 (*A Supplement to the Oxford English Dictionary*, ed. R. W. Burchfield, [Oxford: Oxford University Press, 1976], s.v. Mole).
2. All proteins are made up of twenty different building blocks known as amino acids, combined linearly in various ways. Each amino acid contains a residue, or group, that gives it its identity.

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