Letters

Origin of Life

The recent review by Miller and Urey [*Science* **130**, 245 (1959)] discounts the pioneering contribution of Calvin *et al.* to our understanding of the origin of organic compounds on the primitive earth. Miller and Urey object to the low yields recorded in 1951 for the conversion of carbon dioxide and water to formaldehyde and formic acid. Perusal of the details published by Calvin reveals, however, one conversion of carbon dioxide to formic acid of 25 percent, which is in excess of Miller's typical total yield of amino acids, natural and unnatural. More relevant, however, is the fact that while highest possible yields may be an appropriate objective in some situations, this goal does not necessarily have meaning in the context under discussion. For life to begin, no more is required conceptually than an infinitesimal pinch of organic stuff of the proper sort and organization; this pinch would need the ability to replicate itself from carbon compounds in the environment and to adapt. By the same reasoning, small proportions of carbon dioxide are adequate as Calvin's inorganic intermediates.

The objections raised to the thermal theory in this same review have already been raised and answered by me (except for some discussion about malic acid which I prefer to reserve until relevant experiments have been completed). With the exception of an incomplete allusion to thermal algae and bacteria, these answers do not appear in the review by Miller and Urey.

Other papers which answer the objections even more fully and have not been cited are Fox, Harada, and Vegotsky, *Experientia* **15**, 81 (1959) and Fox, *Bull. Am. Inst. Biol. Sci.* **9**, 20 (1959). To repeat here briefly an answer to a principal criticism, it is well known that proteins are not readily coagulated if relatively *dry*, and that they are also protected in hot aqueous solution by other substances, notably acidic polymers such as nucleic acids. Temperature and hydration must be specified in such studies. It is moreover possible, by changing these conditions properly, to demonstrate the inevitable formation from synthetic protein-like polymers of microscopic entities in the bacterial range of size and with other properties of bacterial cell membranes [S. W. Fox, K. Harada, J. Kendrick, *Science* **129**, 1221 (1959)].

Once the proper intermediates existed, the first formation of life need not have required as much time as is supposed. Although some organic intermediates may have evolved slowly, there is no basis for excluding the possibility that many biochemical sequences occurred too rapidly for complete thermal decomposition of organic substances to constitute a barrier. Neither is there a basis for decreeing that reactions must have occurred at the surface of the earth rather than in warmer subterranean passages, or for implying that reactions which are demonstrated at 170°C in the laboratory cannot occur more slowly at lower temperatures, or for ignoring the effect of phosphoric acid, which we have shown increases rates of many thermal polymerizations of amino acids. [A. Vegotsky and S. W. Fox, *Federation Proc.* **18**, 343 (1959).] There is also no basis for invoking Abelson's experiments with alanine in water as a direct guide for the behavior of amino acids heated while dry in the absence of oxygen. We, and also Meggy, have shown in this case too that the presence or absence of water greatly alters results; a difference was, furthermore, anticipated on the basis of thermodynamic theory, as indicated in papers from our laboratory and from Meggy's laboratory.

Polyglycine and polyaspartic acid, the latter actually a polyimide, have been produced by dry heat and may be considered well known, as claimed by Miller and Urey. The thermal synthesis of peptides containing all of the 18 common amino acids is the significant advance in this context, however, and was not accomplished before our discovery of the necessary conditions. These conditions, notably excess dicarboxylic amino acids, largely protect 16 otherwise thermolabile amino acids from decomposition and yield relatively colorless protein-like polymers. These reactions have been repeated in other laboratories. Miller and Urey seem to have missed in particular this critical point about the protective effect of the hypohydrous acidic milieu.

As Miller and Urey have acknowledged, amino acids may be produced with each of many forms of energy, including electrical, thermal, and solar energy, from plausible prebiological intermediates. Incidentally, yields of aspartic acid by thermal conversion of ammonium hydrogen malate exceed 40 percent, but the case for thermal pathways can rest alone on relationships to biochemical and evolutionary principles. It seems to me that our present state of ignorance does not permit anyone to maintain that any one or any several syntheses were applicable to the primordial situation. Perhaps the best that one can do at present is to collate experiments in this context and determine which modes are intraconsistent and extraconsistent with other knowledge.

Miller and Urey recognize that a working premise of similarity between prebiological chemistry and biological chemistry provides the precious attribute of testability [S. W. Fox, *J. Chem. Educ.* **34**, 472 (1957)]. They nevertheless seem to prefer, as intermediates for amino acids, aminonitriles, which have no known biological counterpart, to Krebs-cycle acids which are both biological and thermal precursors.

Seemingly logical preconceptions about the difficulties of a thermal mode are outlooks I once shared [*Am. Scientist* **44**, 347 (1956)]. It is nevertheless true that if the conditions are studied closely enough, and if hydration is controlled in a continuum as indicated, there result not only polymers with properties markedly like those of natural proteins but a relatively comprehensive outline suggestive of the origin of biochemical and cellular systems. Although such details may at first glance seem trivial, they might well be critical in the chain of events that have led to our all being here.

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We are very glad to see that Sidney Fox is presenting his own ideas in regard to the problem of the origin of life. However, he misunderstands our attitude in regard to the article which we presented to *Science*. We were not writing a general review article of a summary kind but were definitely expressing our own conclusions in regard to the problem. In this sense it is a biased article since it does express our views, which may not accord with those of other people.

Thus, we do not believe that particles accelerated by cyclotrons or other analogous particles which exist in nature as cosmic rays were important in the origin of life. The amount of energy available, as shown by our Table 1, is very small indeed. It is ineffectively used for chemical processes and has a negligible effect at the present time on the properties of the atmosphere of the earth. We think it also had a negligible effect on the primitive earth, and we intended to say this and believe that our statement is correct.

In the second place, we intended to say that we do not believe that high-temperature processes in the neighborhood of 150°C were important in the origin of life. We also conclude this because of the data given in Table 1. The total heat from volcanoes is very small indeed; it is most ineffectively used for chemical processes, is very sporadic, and is localized on the surface of the earth.

What is needed in the prephotosynthetic time on the earth is a steady source of free energy that permits a primitive type of metabolic process during which organized life could evolve before photosynthesis occurred. We disagree with Fox's statement that only a small amount of material is sufficient. We maintain that a steady source of production of compounds is required, which then go through spontaneous chemical reactions to produce more stable compounds again. A small amount of high temperature produced at one spot on the earth, with many years going by before any additional source of energy is available at that location, can make little contribution to an evolutionary process. Only continuous processes enable metabolic experimentation to go on. Of course, a very small amount of "organic stuff of the proper sort and organization" would suffice, provided it were a living cell, but it is the origin of this which is being discussed, and it should not be assumed.

Aside from these general remarks, we wish to criticize certain points in the arguments of Fox.

Fox has not answered our objections to the thermal theory of the origin of life. The question of the source of the malic acid and urea in his experiments has still not been answered, and much of the theory stands or falls on this point. The stability of proteins with respect to coagulation when dry or in the presence of acidic polymers is not an answer to our criticism. We were discussing the stability of the amino acids contained in the protein, and there is no reason to assume that they would be more stable as dry peptides than as amino acids in solution. In fact, serine and threonine would be less stable. Evidence for instability of amino acids in proteins is given by Abelson's experiments with ancient fossils. Only six out of the 18 amino acids present in the original proteins of the sea shell remained, the others having decomposed.

We are surprised that Fox does not accept the fact that most organic compounds are decomposed by long heating. His doubts on this point can, of course, be settled by his conducting experiments on the thermal decomposition of amino acids and other compounds under various "protective" conditions. We do not understand how regions of high temperature ($\sim$150°C) can be maintained for appropriate periods of time to produce his polymerization, with the material being expelled after reaction into appropriate lower temperatures. Where does this occur on the earth now? Why should such circumstances have occurred in the past?

We think that the use of such terms as *proteinoid* and *protein-like* is unfortunate. The polypeptides synthesized by Fox are essentially random, except for the end groups. Fox has not shown that these polypeptides have *any* biological activity and has certainly not shown that they have enzymatic activity, which is the activity that is pertinent to the origin of life. The use of the terms *cell-like* and *cell-like membrane* [S. W. Fox *et al., Science* **129**, 1221 (1959)] is also unfortunate. The formation of round particles in the micron range by heating and then cooling a solution of polypeptide and sodium chloride does not justify calling them "cell-like." Naturally there is a boundary between the particle and the solution, but is this a membrane? It is well known that biological membranes are lipid in character. Fox added no lipids to his polypeptide solution, so the particles can hardly have a "cell-like membrane." Also, biological membranes are not inert casings, but they actively transport ions and organic compounds and allow the entry of only a limited number of specific organic compounds.

If, as Fox states, the case for thermal pathways can "rest alone on relationships to biochemical and evolutionary principles," we think that this case will collapse. A scientific theory rests on experiment, and not on crude analogies to accepted theories dealing with other types of processes.

When we spoke of similarity between prebiological and biological chemistry, we meant the similarity of the gross aspects and not of the detailed processes. Were the first organisms made up of proteins, nucleic acids, sugars, and lipids, or were other types of compounds used in place of these? It would be convenient for the investigator if the primitive pathways followed the present ones, but surely this is not necessary. If there are different pathways for the synthesis of a certain compound in different organisms, how do we pick the more primitive pathway? If we choose the pathway of the more primitive organism, then why should not even more primitive organisms have used pathways different from these? And certainly one would expect that the chemical reactions which occurred before enzymes were present might have been different. In any case, Fox's pathways do not follow present biochemical pathways particularly closely, in spite of his claims.

Finally, we do not agree that Fox has synthesized polymers "markedly like those of natural proteins." His "relatively comprehensive outline suggestive of the origin of biochemical and cellular systems" is a "theory" that is not testable in its present form. It says little more than the statement that life arose from a rare event by chance.

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Discomfort Index

The letter by Kenneth H. Jehn [*Science* **130**, 826 (1959)] presents two arguments against the use of a "discomfort index." The first argument is that the index does not include all the factors that affect comfort. The second is that there are individual differences in personal reaction to the environment.

These two difficulties are true of many indexes now in use. You can't declare an index useless merely by stating the existence of these problems. The usefulness of an index is determined by how much information it yields in spite of these difficulties, the value of this information, and the convenience with which the index can be computed.

As a most elementary example, the spoken word is a useful index to our thoughts and emotions in spite of the fact that words cannot express all the factors involved and the meaning of words varies from person to person. The existence of difficulties does not render speech useless. In a more formal manner, the science of statistics has developed quite a body of techniques, some of them quite elementary, for reducing the number of factors in representing a complex process and for expressing information about processes that are so complex as to appear to be random.

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