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SOME ASSUMPTIONS UNDERLYING DISCUSSION ON THE ORIGINS OF LIFE

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A few discussions can reasonably be expected to end with a definite conclusion. They are organized to consider where or how something happened, or what something was made of, and we can see at the start that there is a general line of research that should produce the answers. Discussions about the origins of life are not like this nowadays. It may be that before the seventeenth century the argument seemed reasonable that, if frogs and other animals could arise from mud now, they must have arisen in that way in the beginning. However, the issue was not considered very important. We now have little expectation of being able to conclude a discussion with the statement "this is how life did arise"; the best we can hope for is "this is one of the ways in which life could have arisen." All that we can do is to compare probabilities and, if we are to do that usefully, it is essential to keep all of the possibilities in mind. It is clearly impossible to state all the possibilities in one brief paper. Many of these need not be mentioned here because they figure in discussion so often that no one could overlook them; others are mentioned to show that they have been borne in mind, and the remainder have been selected, not because I regard them as being intrinsically highly probable, but because they are in danger of being overlooked entirely.

First among the possibilities to be mentioned, but to be discussed only briefly, is that life had no origin. This is one of the ways in which what is sometimes called the "perfect cosmological principle" could operate. According to that principle the universe has had, apart from local fluctuations, the same appearance at every epoch. If so, there must have been life in it always. This could arise constantly of necessity by one of the processes that we shall discuss, or it could drift around the universe as what Haldane (1954b) calls *astroplankton*; vital units ready to start the cycle of evolution when conditions are favorable.

If the universe had a beginning, so clearly had life. Our decision about how far back in the history of the universe this beginning occurred depends on the wholly arbitrary criteria that we decide to use to distinguish the living from the nonliving state. If nothing can be called alive unless liquid water is a prominent component of it, then life can start only on a cool planet, and so on. However, if we try to define life operationally, there is no need for this restriction. I argued twenty years ago (Pirie, 1937) that a rigid operational definition is not possible. This seems now generally to be accepted. Nevertheless, those who work with viruses are still asked whether their experimental material is alive or not or, more often, are told dogmatically that it is or is not. At most, all we can say is that we prefer not to call a system alive unless it has a certain proportion of the qualities in a given list. It is possible, in theory, for these qualities to be manifested in systems that consist predominantly of gas or fused

rock, as in the systems proposed by Preyer (1880) and by Pflüger (1875). Esthetically we tend to reject so wide an extension of the living domain. A gaseous system would not even satisfy Hopkins' (1913) minimum requirement that for life there should be a "dynamic equilibrium in a polyphasic system."* Still, the possibility remains that such systems were the ancestors of the systems we now know, even if such an origin is not very probable.

The only justification for paying any attention at all to ideas about interstellar or incandescent life lies in the assumed improbability of its spontaneous appearance under present conditions. The ancients did not make this assumption. It was forced on us, first by the success that Redi and Spallanzani had in defining experimental conditions that excluded the grosser forms of life, then by the commercial success of Appert and Bryan Donkin, who excluded the smaller forms and, finally, by Pasteur and Tyndall, who put the matter on a scientific basis. We all now agree that the appearance of life in any vessel under observation is so improbable that when it is claimed, as by Bastian and Pouchet, we put it down dogmatically to the result of faulty technique. In this we are probably correct, but our attitude tends to impede further experimentation. In the absence of experiment, can we invoke theory to put a value on this improbability?

This has been attempted in several different ways. Guye (1942) assumed that the problem was tantamount to considering the probability of the spontaneous appearance of a protein molecule. He made a series of dubious assumptions, wove his fabric together with some physicochemical fallacies, and concluded that the universe had not existed long enough to allow one protein molecule to appear spontaneously. Other similar attempts have been made. There are two basic fallacies in this type of approach: (1) it assumes that there is only one way in which a certain state of affairs, such as life, can exist; and (2) it assumes that the probability of a process can be calculated although its mechanism is unknown.

Let us consider the latter objection first. No one would try to calculate the probability of catching a fish of known weight in a pond of known volume without knowing something of the habits of the fish and the size of the holes in the net; nor would we calculate the accident rate from the number of vehicles on a given area of road without considering traffic conventions and the extent to which they are obeyed. Chemical reactions at catalytic surfaces are similar. The rate at which a certain polymer will be formed depends on the rate of adsorption, the rate of the reaction after adsorption, the stability of the first links before polymerization is complete, and so on. As a rule, these are not known, and the rate must be determined experimentally. It is also very relevant to this aspect of the discussion that the type of polymer built up in a given reaction mixture depends on the catalyst used. This has long been known in gas reactions; now Natta *et al.* (1955) find that, by suitable choice of catalysts, a series of nonrandom polymers can be made with properties that are sharply

* Hopkins did not claim to be the first to emphasize the importance of phase boundaries for living organisms. It is interesting to note that he had a forerunner in Jean Rey (1630) who, considering why lead got heavier when calcined, concluded that life had nothing to do with the matter because lead, as "a homogeneous body without distinction of parts," could not be alive.

distinguished from those of the products of ordinary polymerization. If specificity and regular arrangement among the component parts of a macromolecule can be introduced in this way, there is no reason to assume that all was random under probiotic conditions.

By studying present-day living organisms we see some of the ways in which they can function. This does not tell us that these are all the ways in which they have ever operated; many types of metabolism may have died out. Still less does it tell us that these are all the ways in which they could have worked. Given the chemical components of some present-day organisms (proteins, fats, polysaccharides, nucleic acids, and so on) we cannot construct a viable organism. The fact that no one has made (or, so far as I know, has even tried to make) a para-organism by the use of colloids such as silicates, polyphosphates, and cyanides, chelating agents such as ethylenediamine tetraacetate and the metaphosphates, and oxygen carriers such as rubrene, does not therefore rule out the possibility that there could be such an organism. When we predict a probability, it is the probability of something foreseen; it is obviously possible to predict that certain arrangements could not work, but it is not possible to assert that we have foreseen all of the arrangements and chemical patterns that could work. Science is only retrospectively logical. Thus, when a hand of cards is dealt, it may be certain that there will be five cards in it; the 1:1,000,000 odds are against any predetermined set of five. Unless we know how many of the possible hands could be "effective" for our purpose, there is no basis for calculating the odds on receiving an "effective" hand. Similarly, we cannot calculate how often a molecule that could have been the vehicle for life could have arisen in any given time or conditions.

Haldane (1952), as so often before, has introduced some clarity of thinking into the subject. He gives reasons for believing that a simple organism such as a bacterial virus contains about 100 bits of negative entropy or information, and that this is about the amount that would arise spontaneously in 10^9 years in the volume of the primitive ocean. Viruses are probably not a step in the route to genuine, free-living organisms, but probably are either degenerate organisms or the consequence of metabolic blunders in an organism (Pirie, 1952 and 1955). Their relevance here is that they probably contain as many bits as does an eobiont, with too few of some sorts and too many of others. Haldane's argument suggests that many quite complicated systems could have appeared complete in the time available. There is therefore no necessity to look for some extra terrestrial source or evocative agency for life. Even if life does pervade space, there is no need to assume that our forms came from space. This is not a question that will be settled immediately by astronautics, because only a very rudimentary form of astrophlankton would be expected to survive in space. Its subsequent development, in the different environments of different planets, probably would be so different that it will be difficult if not impossible to decide whether such similarities as may be found are the results of adaptive convergence or common ancestry. No one has suggested a valid means for telling whether the organisms we already know had one origin or many. Whatever their relative importance in human affairs, nurture probably has dominated nature in a contest that has lasted 2,000,000,000 years.

If, therefore, as seems probable, polymers and other substrates for life had accumulated in certain regions of probiotic Earth, waiting for chance to organize them, do we know to what kind of substance this chance happened, or to what kind of substance it could have happened? I maintain that we do not, and that the obsession with proteins and phosphoric esters, which is such a feature of the literature of this subject, may be based on an illusion. Admittedly, nothing that anyone wishes to call alive has been shown to be free from protein; but the search has been neither complete nor deliberate. The demonstration that all present-day forms of life depend on proteins would prove no more than that proteins are the most efficient way of living, and that they have superseded any others that may at one time have existed. Similarly, paper has superseded more primitive materials for writing, and money the more primitive means of exchange.

There is at present no reason to believe that proteins have any merit in living systems other than their colloidal properties and the possibilities for specificity that they offer. This potentiality, if we assume that every difference is biologically significant, is vastly in excess of anything that organisms can use. A peptide chain that contains 120 amino acids of 20 types could have more than 10^{130} arrangements, and the possibilities of configurational difference would be increased still more by folding and cross-connection. An organism weighing 70 kg. could contain only about 10^{23} molecules of such a protein. Most of the 2,000,000 species that may now exist are smaller than this, and it is unlikely that they have been preceded by 10^{100} more primitive species. There is, therefore, a fantastic superfluity of specificity available; every protein molecule that has ever existed on the earth could have been different. It is not, therefore, surprising that Fox and Homeyer (1955) find that even in their compositions, to say nothing of their configurations, proteins are not as variable as they could be. This is compatible with, though clearly not evidence for, the idea that protein complexity is a domain that organisms are only beginning to exploit. Haldane (1954a) makes a similar point. He accepts the common opinion that there is a trend toward biochemical simplification among the higher organisms, but he shows that this trend is obvious only when attention is confined to small molecules. The distribution of large molecules shows the reverse trend for the number of proteins and other antigens produced by each member of a species appear to increase as evolution proceeds. Haldane argues that this could broaden the range of action of enzymes and other active proteins usefully, and thus could open up possibilities of adaptation that are valuable enough to compensate for the difficulties that incompatibility introduces when a species reproduces sexually.

Consequently, if the full potentialities of proteins as biological agents are still used so inadequately, there seems to be no reason to think that life could not have originated among colloids with fewer potentialities if the smaller number were used more fully. Recently the idea that proteins have a fundamental role has gained strong support from the demonstration (Miller, 1953) that amino acids are among the products made when electrical discharges pass through certain gas mixtures. This is an observation of great importance because it adds another group of substances to those that it is reasonable to postu-

late as components of a probiotic environment. However, it is equally important to combat the assumption that the observation demonstrates either that the primitive atmosphere was a gas mixture similar to that used or that amino acids were components of the original organisms. These remain possibilities and nothing more. Even if the experiments are extended so that proteinlike materials are synthesized *in vitro* by similar processes, there will still be no proof—only a stronger probability.

Proof or disproof of the original significance of proteins will be very difficult to obtain. The anatomy of many early fossils makes it reasonable to assume that in many ways these organisms functioned in the same manner as those of the present day and, consequently, used protein. That carries us back 500,000,000 years at most—only one third of the way to the time when living processes may have started. There are two justifications for remaining skeptical in face of the general assumption that proteins must have been involved at the beginning. One of these is that for as long as this is assumed, insufficient effort will be put into the attempt to find ways to obtain genuine evidence. The other is summed up with pleasant irony by Hilaire Belloc:

“But Scientists, who ought to know,
Assure us that (it) must be so. . .
Oh! let us never, never doubt
What nobody is sure about.”

The conclusion to be drawn from this is that even if such substances as proteins were essential at the beginning, the spontaneous appearance of organisms is reasonably probable and, if a more extensive group of substances could have been the vehicle for the operation, it becomes still more probable. This was the opinion of Darwin, Huxley, Tyndall, and others. They looked on the process as so improbable as to be unlikely in any vessel under observation, but they thought that, if enough space and time were available, it could happen and even happen frequently.

This type of argument could be pursued through the various types of substance now most intimately associated with living (sugars, purines, and so on) to see whether we must postulate an essential role for any of them at the beginning. That would be tedious and we may move to the other extreme and consider the elements. To the group of generally accepted bioelements—C, Ca, Cl, Cu, Fe, H, I, K, Mg, N, Na, O, P, S, Si, and Zn—we must now add B, Co, Mo, Mn, and V, while Al, As, Ba, Br, Cr, F, Ni, Se, and Sr, appear as possibles that we may soon be forced to accept. This composes one third of the naturally occurring elements, and it would be foolhardy to contend that the list would then be complete. The properties and sites of occurrence of Ga, Ge, Th, and Ti suggest that these also may have, or may have had, biological roles. If organisms now have this catholic approach to chemistry, by what canon would we decide which reactions were significant for the original organisms?

It is often argued that the most common environment is the one in which life most probably originated. There are two objections to this. First, it

amounts to the assumption that any environment and material would be equally suitable; the probability would then depend simply on the scale of the environment. When put in this way, the argument is generally seen not to be attractive. Esthetically, people cling to the idea that biopoiesis was an activity of rather special regions and substances. Furthermore, it is commonly seen that evolutionary advances are now characteristic of atypical habitats. Second, the assumption cannot logically be made by one who believes in the primacy of proteins. Silica, carbonates, phosphates, and aluminates would be very much more probable vehicles if quantity were the important factor. Indeed, a case can be made for the original importance of these compounds because they play a prominent role in many ancient species.

If the origins of life took place in regions that were, for various reasons, distinctive, it is profitable to consider what the nature of the favorable peculiarity might have been. First, as nearly everyone has agreed, is the presence of an interface. Some have thought of air:water or of Oparin's (1938) liquid:liquid interfaces; these fit well into the ideas of traditional biochemistry. Goldschmidt (1952) made the valuable suggestion that the faces and edges of mineral crystals could have played an important part in the concentration and collection of uncommon molecules from the environment and their arrangement in ordered and reactive groups. In his paper he wrote of such crystals as quartz, mica, clay minerals, apatite, and snow; but in conversation he spoke of the more reactive crystals that contain elements such as Cu, Fe, Mn, and V. Working from this idea I suggested (Pirie, 1948) that at least an analogue for an organism would be made if the synthesis of a water-holding substance on a crystal depended on the leaching out of the active element and, by the retention of water, promoted that leaching. If such a suggestion is taken seriously, we can dismiss from consideration tables of the relative abundance of the chemical elements. It matters little how rare the regions are so long as they exist, for they serve only to initiate the process. Once begun, other activities, depending perhaps on other interfaces, would accrete to the system and, as Haldane (1954b) suggests, independent subvital units might cooperate.

In a quodlibet or parable such as that there is no necessity to limit consideration to carbon compounds. Carbon compounds of various sorts probably were present at the beginning, and they may well have been among the compounds that participated. Life, considered throughout its history, can be likened to a pair of cones placed apex to apex. The base is the group of eobionts, dependent on a very wide range of different chemical actions and energy sources that modify the original environment on the earth and, in the course of time, compete for sites, energy, substrates, and so on. The narrowing of the cone represents the elimination of many forms, partly by exhaustion of their substrates, partly by competition. In this way biochemical complexity and efficiency would build up until, at the common apices, there would be a few varieties comparable to present-day autotrophic bacteria. Half the present-day biomass is bacterial; this picture assumes that at that stage, well before the beginning of the fossil record, all of it was. Once this evolution and selection for biochemical efficiency has taken place, it is very difficult to see past it to the more diverse biochemical state by which it was preceded. Using the analogy

of the cones, it is hard to see through the constriction to the broadening cone below. The only clues, as I have argued elsewhere (Pirie, 1957), may come from some surviving oddities of metabolism in ancient species, and from some elementary associations in sedimentary deposits.

From this apex of biochemical capacity the upper cone broadens, representing the evolution of morphological complexity. It is of this that the fossil record gives evidence, and it is this that is accompanied by the biochemical degeneration that is such a common feature of evolution (Lwoff, 1943). Morphologic elaboration permits biochemical inadequacy; it may even encourage it. An organism, at the primitive stage at which it is a simple bag that contains enzymes, depends on metabolites diffusing to it and must make everything it needs from whatever materials may come to hand. This puts a premium on biochemical efficiency and adaptability. An organism such as that needs the unspecialized genius of a successful Robinson Crusoe. Along with morphologic and mechanical evolution goes a greater independence from the environment, because the organism can increasingly recognize favorable or noxious conditions and arrange to enjoy or avoid them. For a mechanically highly evolved organism, biochemical expertness loses some of its survival value. We see this in the great synthetic capacity of the sessile plants, as compared to the more generally motile animals and, to some extent, in the distribution of such things as vitamin requirement among the animals.

Many other assumptions could have been discussed usefully, but one more must suffice. It is commonly assumed that the occurrence of optical activity is peculiarly significant in biology, and that its initial appearance presents difficulties. However, the possibility of optical isomerism arises of necessity by simple geometry at a certain level of chemical complexity, and the probability that in a synthesis there will be a preponderance of one isomer increases as the amount of material that is synthesized diminishes, as Karl Pearson pointed out long ago. Once there is a bias, selection would favor any organism that used only one isomer. Although there is nothing surprising in optical activity in organisms, it might still be peculiar to them. There have been, however, several recent papers on spontaneous resolutions (Powell, 1952), and naturally occurring mineral crystals will supply regions of selective absorption. The argument that the appearance of optical activity in oil, after it has percolated through great thicknesses of assymetric rock crystals, is evidence for its biological origin is therefore suspect, however valid the conclusion may be.

All discussion depends on assumptions. My thesis here is not that assumptions should not be made, but that we should be aware that they are being made, and that we should consider whether they are needed for the real purpose of the discussion. Even when they are not needed in theory, they still may be useful; some people, whether engaged in observation or argument, need the extra stability that seems to come from a body of assumption. So long as the observations are sound, the status of the assumptions is secondary. It is better to have a productive scientist with a questionable philosophy than one who observes little, but whose philosophy is impeccable.

A critical examination of some commonly made assumptions, however, shows how difficult it is to formulate the problem of spontaneous generation in a

manner that poses questions that can be answered in the laboratory. We do not know what we are trying to generate, or from what. It is certain that further research will demonstrate the existence of a vast range of types of molecules that might be formed from different elements in the different possible environments and that could then interact. From among these reactions it will be possible to map routes along which analogues for life could have proceeded. This route mapping will be slow and intricate and, by the time we are well embarked on it, there may seem to have been some loss in the spontaneity of spontaneous generation.

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