THE EVOLUTIONARY SIGNIFICANCE OF PHASE-SEPARATED MICROSYSTEMS*

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Abstract. The source, preparation, and properties of phase-separated systems such as lipid layers, coacervate droplets, sulphobes, and proteinoid microspheres are reviewed. These microsystems are of interest as partial models for the cell and as partial or total models for the protocell. Conceptual benefits from study of such models are: clues to experiments on origins, insights into principles of action and, in some instances, presumable models of the origin of the protocell. The benefits to evolution of organized chemical units are many, and can in part be analyzed. Ease of formation suggests that such units would have arisen early in primordial organic evolution. Integration of these various concepts and the results of consequent experiments have contributed to the developing theory of the origins of primordial and of contemporary life.

1. Introduction

The unit of life as we know it is the cell. Major interest in the formation of phase-separated multimolecular open systems stems from the desire to understand the cell (Bungenberg de Jong, 1949) and its origin (Oparin, 1924). That understanding may arise through (a) finding clues for the processes involved in the origin of the cell, (b) identifying principles underlying such self-association or aggregation, or (c) constructing a laboratory model of the original cell (Table I). In the usual analytical study of the cell, the first act of the research worker typically is to destroy the organization in order to isolate the components. It does not logically follow that the final step in the formation of the cell is the reverse of that process, to wit, the appearance of a unified organization as a final step. Indeed, a principal difference between the analytic and the synthetic approaches is the intermediacy of evolution in the latter sequence (Figure 1). Recognition and acceptance of the need for evolution from an original cell demands a scheme involving an original cell, i.e. a protocell, as an evolutionary precursor to a contemporary cell.**

TABLE I

Objectives in modelling protocells

Identification of clues for understanding or constructing a protocell.
Determination of principles of formation of true protocells.
Artificial production of a true protocell.

* Invited paper. Presented at the International Seminar 'Origin of Life', 2–7 August 1974, Moscow, U.S.S.R.

** Oparin (1957) was perhaps the first to analyze the related controversy of nucleic acids-first (Muller, 1961; Crick, 1968) *vs.* proteins-first. Oparin's inference was that of cells-first. My own view, based on experiments, rephrases the chicken-egg question to read: proteinoids-first (not proteins-first), and protocells-second (Fox, 1974a). In considering the arguments against nucleic acids-first one should especially note the papers of Lederberg (1959) and Eigen (1971).

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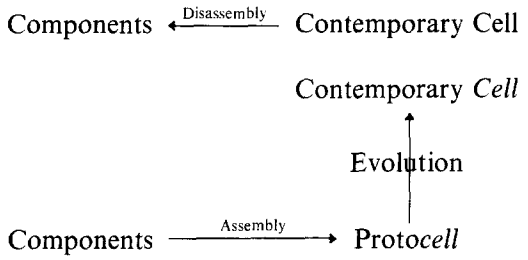

Fig. 1. Current reductionistic research requires disassembly. Constructionistic research is in the direction of assembly and evolution.

My observations of presentations in this area indicate that usually neither the analytic nor the synthetic premise (Figure 1) is explicit. As an example, a perhaps most obvious assumption of the cells-*last* premise in an evolutionary context was a 1964 symposium in Evolving Genes and Proteins (Bryson and Vogel, 1965), a title which omitted the word 'cell'. Cursory mention of the need for cells in the evolution of genes and proteins did occur at that meeting (Fox, 1965), and more recently Lehninger (1970) has expanded the concept. The view that a cell of some sort was early on the geological scene is however not new; early proponents of the view have, for example, been van Niel (1956), Ehrensvärd (1962), and the man whose contributions we honor here (Oparin, 1924, 1957).

A number of the benefits that were conferred by an evolvable organic micropackage (Table II) may turn out to have been crucial; this judgment is reenforced by the way in which some of the individual functions of Table II support each other.

TABLE II

Benefits of a cell

Physical protection of organic material	
Organization of chemical reactions	(Oparin, 1957)
Compartmentalization of functions	(Oparin, 1957; Brooke 1975)
Thermodynamically favorable hydrophobic zones	(Fox, 1968)
Maintenance of kinetically favorable concentrations	(Oparin, 1966)
Reproduction at microsystemic level	(Fox, 1973d)
Adaptive selection (Darwinian) of individual variants at microsystemic level	(cf. Kenyon, 1974; Hsu, 1974)
Screening of macromolecules from diffusible molecules	(Fox *et al.*, 1969)
Promotion of dynamic interactions with the environment	(Oparin, 1966)
Juxtaposition of enzymes, organelles, etc.	(Fox and Dose, 1972)
Systemic support and development of photosynthesis	
Enlargement of metabolic pathways through (re)combination	(Hsu, 1974)
Favorable spatial relations for coding interactions	(Lacey and Mullins, 1974)

The special significance of the fact that phase-separated systems are phase-separated systems is the avoidance of dilute aqueous solution. The production of anhydropolymers: proteins, nucleic acids, and polysaccharides has not been modelled in dilute aqueous solution except through the agency of dicyandiamide, ATP, or other energy-rich compounds, *compounds that themselves were produced under conditions other than dilute aqueous solution.* The first cell and its descendants seem to have known what they were doing thermodynamically (Fox, 1974c).

At the least, the benefits listed in Table II strongly suggest that, whenever an evolvable protocell arose, the consequent cellular line of development would have had much evolutionary advantage over any noncellular line. When we recognize these advantages, the basic question becomes one of how easily any given kind of protocell could have arisen. Some of the models that will be discussed here form with extreme ease.

We may next turn to, accordingly, models of the protocell, their sources, the evidence for their ease of formation, and their properties or functions. These types of model are now somewhat numerous. I shall focus on a selection from Goldacre's films (1958), lipid layers (Shah, 1972), coacervate droplets as described by Oparin (1966), Liebl and Lieblova (1966) and others, Herrera's sulphobes (1942), proteinoid microspheres (Fox and Dose, 1972), and other models.

2. Lipid and Lipoprotein Models

Goldacre has conceptualized the interaction of lipids and proteins on the primitive Earth at air-water interfaces in the context of origins (Figure 2). Experimentally, lipid layers have been extensively studied, both as monolayers (Deborin and Sorokina, 1974) and bilayers (Shah, 1972). These have been especially useful for generation of insights on the absence of proteins or proteinlike molecules, although

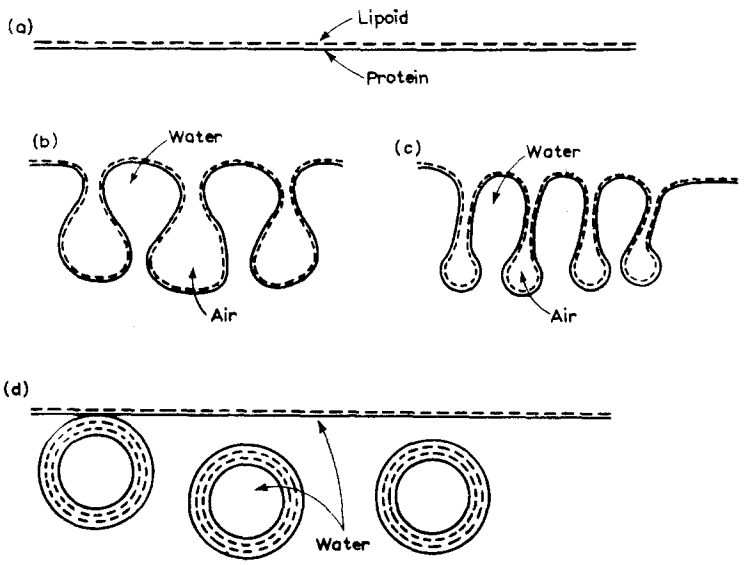

Fig. 2. Goldacre's concept of protocellular lipoprotein vesicles (Goldacre, 1958).

the systems lack biochemical function and structural stability. The liposomes, black films, etc. form easily under a wide range of conditions, they are stable to steep chemical and electrical gradients, and they permit efficient separation of two aqueous compartments by a hydrophobic partition. They are easily amenable to experiments permitting controlled comparison of properties when proteins and other compounds are added to them. One can hear statements by many experts in this field that the most meaningful kind of model for a protocell must include both lipid and protein or proteinlike macromolecule (cf. Stoeckenius and Engelman, 1969).

Lipids, proteins, or proteinoids each contribute, however, to the quality of hydrophobicity. Undoubtedly, the subtleties and function-related aspects of lipids are ramified by association with proteins or proteinoids. This unity in avoidance of dilute aqueous solution is related to the proposed need for hydrophobic, or hypohydrous, conditions throughout all stages of precellular and cellular evolution (Fox and Dose, 1972).

3. Coacervate Droplets

The coacervate droplet itself is represented by a wide variety of open-system phase-separated entities. One typical coacervate droplet preparation, however, is seen in Figure 3. The droplets are often produced in aqueous solution by the neutralization of oppositely charged colloids.

Experiments of the Oparin school on coacervate droplets containing contemporary enzymes indicated in earlier years what many biochemists have belatedly recognized – that the course of action is more rapid and more directed in a boundaried colloidal structure than in dilute aqueous solution. Oparin's early awareness of this important fact is reflected in the title of his 1938 book, *Enzyme Action in the Living Cell.*

A number of reactions have been studied with enzymes and substrates in coacervate droplets (Oparin, 1965, 1971); their behavior is, again, more like that in a cell than that in a solution in a flask. Most striking has been the coupling of reactions in coacervate droplets, as in Figure 4. Phosphorylase, in a manner of speaking, was microencapsulated in a coacervate droplet and suspended in a solution of glucose-1-phosphate. Starch was formed in the interior, as indicated by the starch-iodine test. When β-amylase was included in such coacervate droplets, starch was degraded to maltose, which then diffused out of the droplet into the medium.

Another kind of activity studied in coacervate droplets concerns the synthesis of polyribonucleotides (Figure 5). In this experiment and in the production of starch, it is especially significant that monomers can diffuse freely through the boundary, while macromolecules are retained. Both hydrophobicity of the membrane and the screening of macromolecules appear to promote the synthesis of macromolecules. Related to this property is the oft-demonstrated ability of the coacervate to concentrate large molecules (Table III).

As another example (Oparin, 1971), the first step in the pentose cycle has been modelled with reduced NADP entering the coacervate droplet (Figure 6).

The coacervate droplet has also been used to model photosynthetic processes when chlorophyll and ascorbic acid are included (Oparin, 1966).

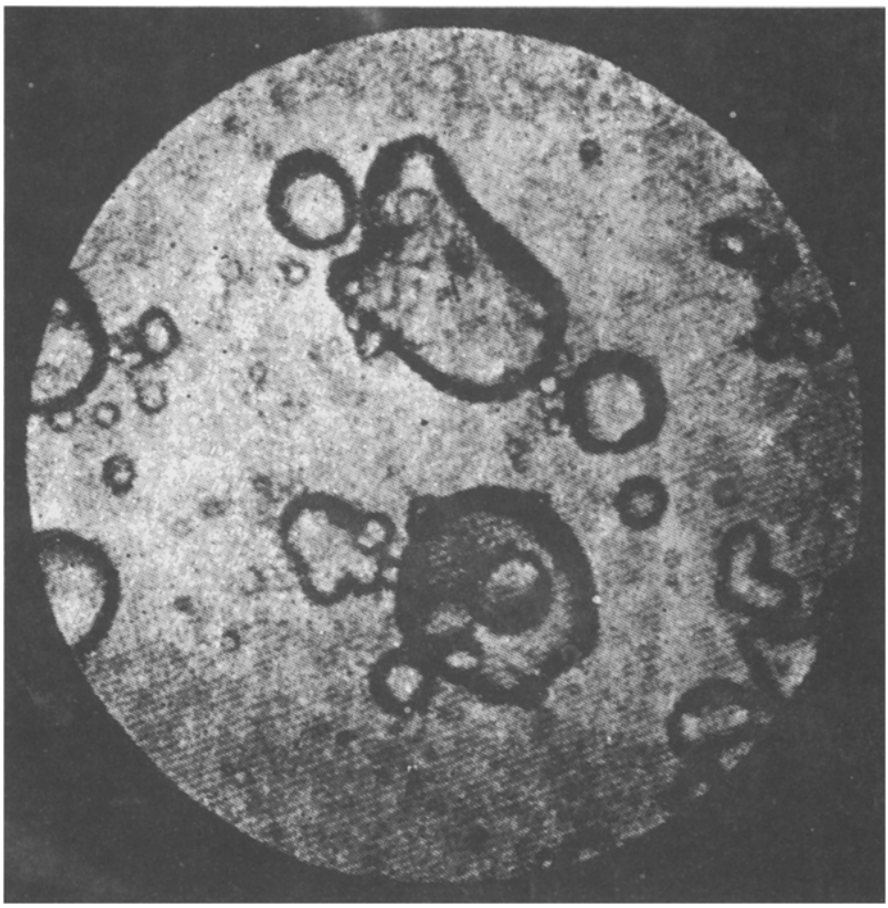

Fig. 3. Coacervate droplets.

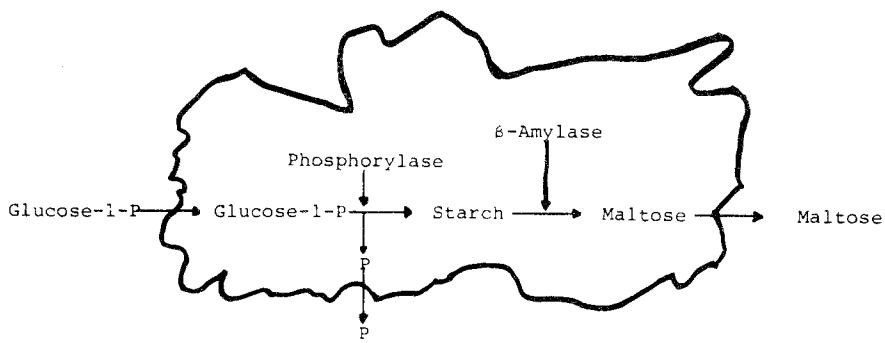

Fig. 4. Enclosure is histone: gum arabic coacervate droplet. Synthesis of starch by phosphorylase acting on glucose-1-phosphate, and hydrolysis by β-amylase. Both reactions occur in a coacervate droplet.

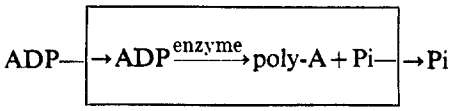

Fig. 5. Polyadenine synthesis in a coacervate droplet from RNA and histone.

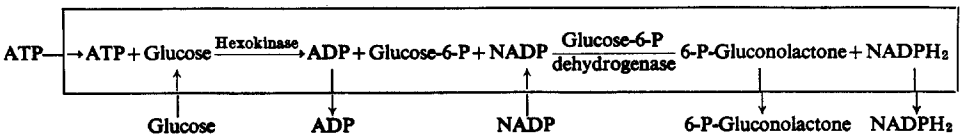

Fig. 6. Modelling of first steps of the pentose cycle in coacervate droplets.

As Oparin has pointed out (1966), the inclusion of enzymes in such coacervate droplets serves to "establish phenomena" in cellular structures. In 1966, he proposed subsequently to replace contemporary enzymes by "less advanced . . . catalysts," and such concepts were subsequently extended by inorganic catalysts (Oparin, 1968).

The origin, development, and deployment of enzymes within a cell evidently must have been a central part of organic evolution. Oparin's studies have done much to suggest principles and possibilities through which such phenomena could have emerged.

TABLE III

Relative concentration of solids in coacervate droplets and surrounding fluid

Expt. no.	Weight of droplet (10^{-12} g)	Volume of droplet (10^{-12} ml)	Conc'n (%)	Conc'n/droplet / Conc'n/Solution
1	3.7	7.4	50	75
2	14.2	38.2	37	55
3	24.1	86.9	28	41

Coacervate droplet of phosphorylase, histone, starch, gum, pH 6.0–6.2
Adapted from Evreinova *et al.* (1961, 1963), in Oparin (1966).

4. Sulphobes

As these statements and my introduction indicate, a true model for a protocell would require at least structural and catalytic polymers derived from simpler components under geophysically relevant conditions, rather than from contemporary organisms. It is appropriate, therefore, to turn to the sulphobes of the Mexican cosmologist, A. L. Herrera. Herrera studied many ways to imitate many types of cell morphologically. Most of the compositions were inorganic and were thus capable of yielding little more than phenomenological analogy. The exceptions were ones that he made by evaporating aqueous solutions of formaldehyde and ammonium thiocyanate (Figure 7). These have been criticized by Oparin, I believe justifiably, for the fact that they lacked vital properties. Herrera did claim in 1942, also without

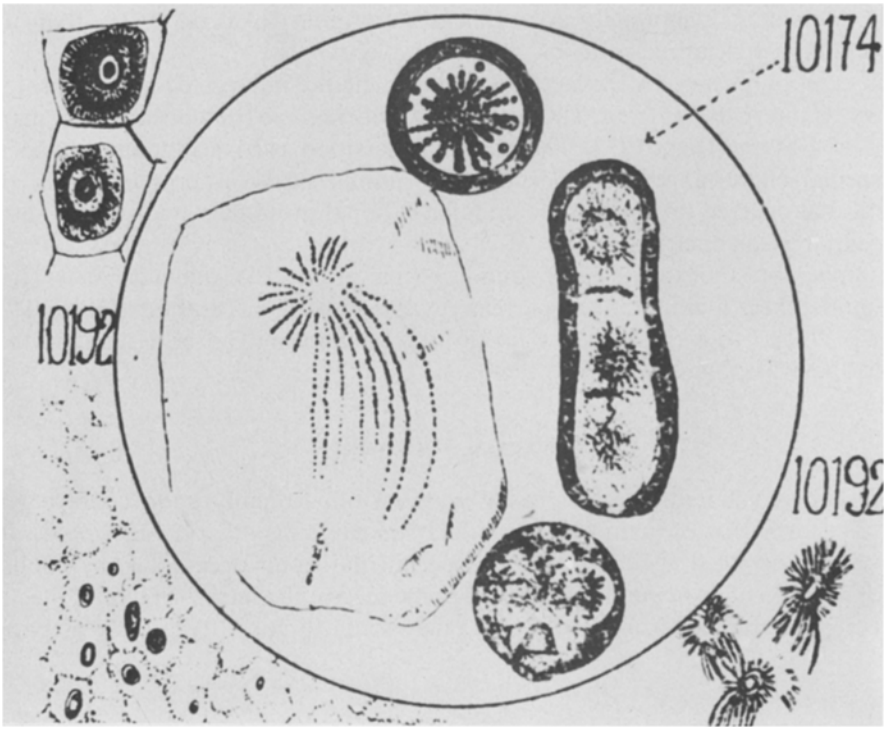

Fig. 7. Herrera's sulphobes.

adequate documentation, that he had produced amino acids from formaldehyde and ammonium thiocyanate.

The remarkable feature of Herrera's experiments with these sulphobes is that, in 1941, he used compounds that, since 1968, have been recognized as organic raw materials present in abundance in our Galaxy (Oró, 1973). It is unfortunate that Herrera's presumed polymers were essentially not characterized, and that the functions of his sulphobes were not catalogued in addition to the suggestive morphology.

5. Proteinoid

In contrast to the components of coacervate droplets and of sulphobes, proteinoid microspheres, which we will now take up, are composed of polymer which has both (a) been rather extensively characterized and which (b) is produced from monomers under geophysically relevant conditions. The proteinoid polymer is mostly composed of true polypeptides. Indeed, the characterization of proteinoid has retraced much of the history of Emil Fischer's establishment of the Peptide Theory (Fox and Foster, 1957). The proteinoid closely resembles contemporary protein both structurally and functionally. Proteinoid is, however, not identical to contemporary protein. Moreover, it has a few structures and functions that are not found in contemporary protein; in other words, it appears to be more complex structurally and more

widely competent functionally as a general 'urprotein' (Alcock, 1936) than are contemporary, specialized proteins.

Of special significance is the fact that such proteinoid, interpreted as a preprotein polymer, is internally ordered. The supporting evidence has been presented in many papers (cf. Fox and Dose, 1972). The effect is understood as basically stereochemical. The special significance of self-ordering of amino acids in proteinoids is the concept that ordered processes yield an informational protomacromolecule without the need for prior nucleic acid.

A number of laboratories have found specific enzymelike activities in various proteinoids; these findings have also been reviewed by various authors (Dose, 1971; Oshima, 1971). From these, the origin of protometabolism can be visualized on a material basis (Rohlfing and Fox, 1969).

6. Proteinoid Microspheres

The self-ordered macromolecules easily undergo self-assembly upon contact with water. The formation of vast numbers of microspheres by contact of proteinoid with cold water is depicted in Figure 8. The experimental result occurs also by cooling of a hot solution of proteinoid (Figure 9).* Some idea of the intrastructure of the cell model may be obtained from an electron micrograph (Figure 10) recently prepared

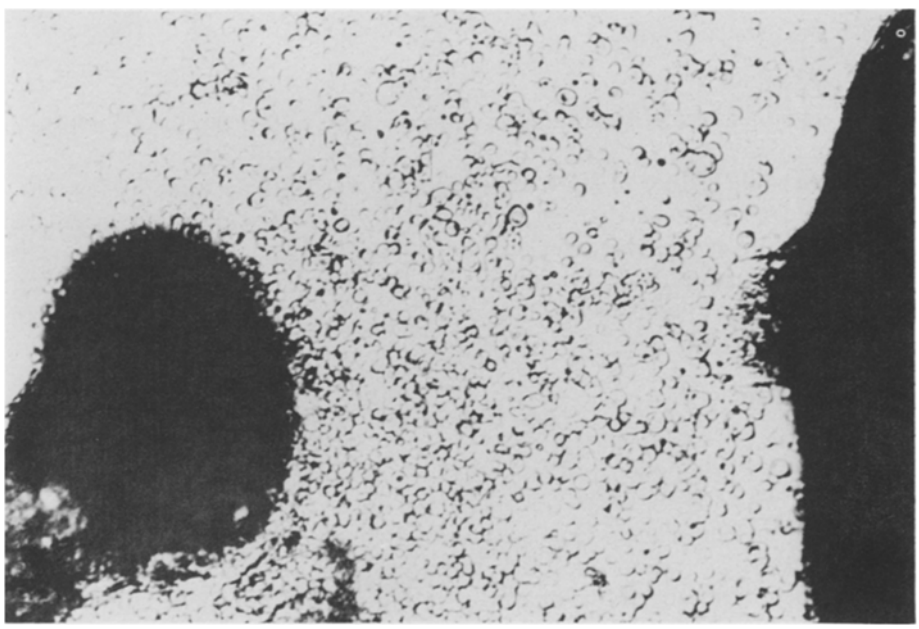

Fig. 8. Proteinoid microspheres by contact of cold water with amorphous proteinoid. (By Dr Shuhei Yuyama.)

* I am informed that thousands of high school students have performed this simple experiment in various ways.

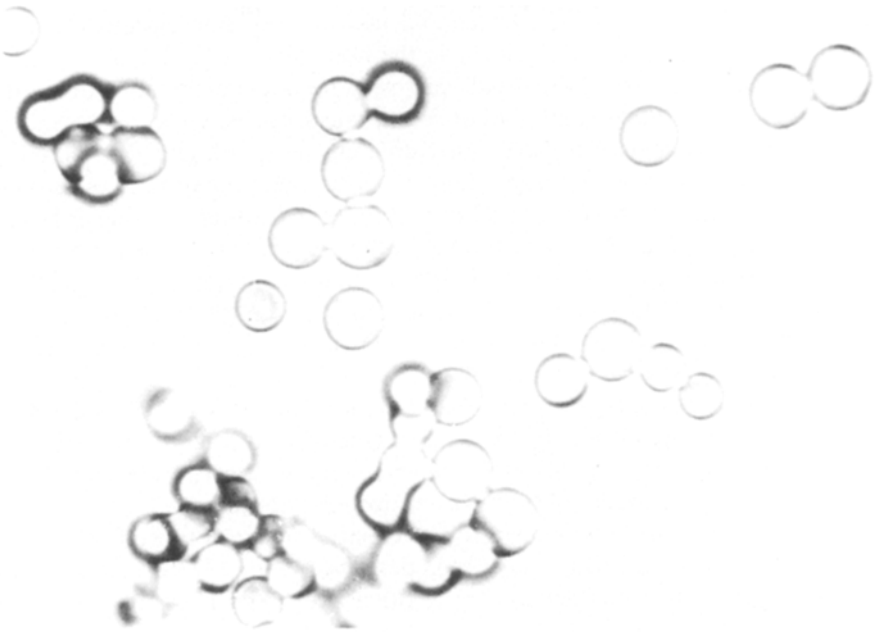

Fig. 9. Proteinoid microspheres from a hot aqueous solution of proteinoid. (By Mr Steven Brooke.)

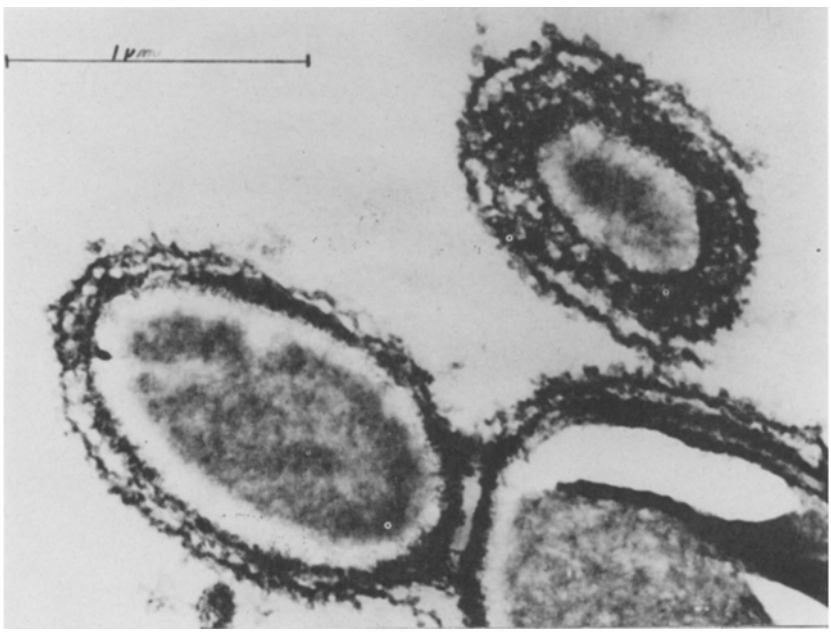

Fig. 10. Electron micrograph of microspheres from crude proteinoid.
(Courtesy of Dr Walther Stoeckenius.)

by Dr Walther Stoeckenius. The proteinoid used for this micrograph was a crude acidic polymer; multilayers are evident in the boundary.

As Figure 9 shows, the proteinoid microspheres are much more ordered, i.e., uniform, than, for example, sulphobes or coacervate droplets. We know that different thermal polyamino acids yield somewhat different morphologies (Fox, 1960). The finding of close-to-the-same morphology for any one preparation of proteinoid microspheres appears to be a manifestation of molecular order at a higher level than that of the macromolecule, i.e. at the level of the aggregate. This near-uniformity is also seen in a scanning electron micrograph of microspheres made from proline-rich proteinoid (Figure 11). One may also see junctions in this micrograph; these junctions have special meaning for communication (Hsu *et al.*, 1971) and as neurophysiological models (Fox *et al.*, 1972).

The microspheres contain enzymelike activities such as are included when the active proteinoid is aggregated. In some cases, synergism in catalytic activities occurs in the microspheres (Hsu, 1974). It is not necessary to incorporate contemporary enzymes to produce a model of boundaried protometabolism.

The microspheres possess intrinsically the capacity for protoreproduction by four cytophysical mechanisms, which have been described (Fox, 1973d), and all of which are heterotrophic. The units possess many other properties (Fox and Dose, 1972),

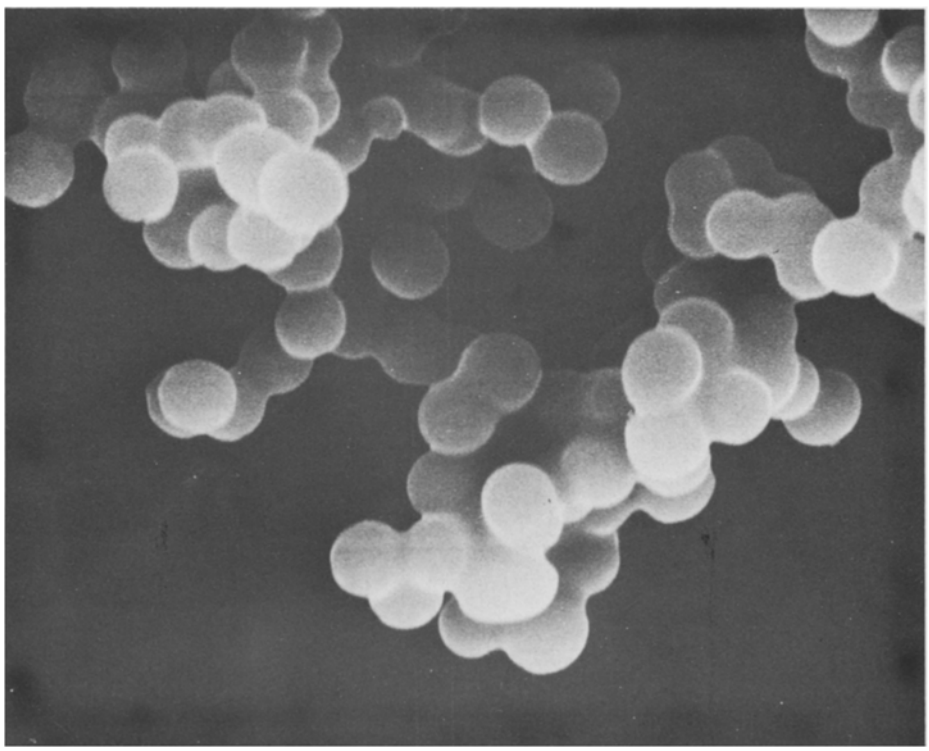

Fig. 11. Scanning electron micrographs of microspheres from proline-rich proteinoid. Junctions between microspheres may be noted. (By Mr Steven Brooke.)

including the ability to screen macromolecules (Fox *et al.*, 1969), as is true of coacervate droplets.

Of special interest are microspheres prepared by Snyder and Fox (1975) from proteinoid that was in turn produced by heating amino acids in the presence of seawater salts. These seawater proteinoid microspheres have many of the properties of the other microspheres, plus stability at pH 8 and above (Figure 12). This finding enlarges the possibilities for survival of protocells in an early alkaline ocean.

The essence of proteinoid microspheres is the proteinoid, with its internal order, its catalytic and other activities and, in addition, its salient tendency to aggregate in the presence of water, all occurring through processes of high efficiency.

When we summarize the functions of the proteinoid microsphere and subtract those from the functions of the contemporary cell, we are able to identify salient properties necessary for evolution of the model for a primordial cell to a contemporary cell. These are listed in Table IV. Conceptually, these are functions that the first phase-separated multimolecular open systems would have needed in order to make their own offspring multimolecular phase-separated open systems, still with *some* help from the environment, i.e. provision of elementary intermediates. Dependency upon the environment continues to this day.

TABLE IV

Functions needed for evolution from proteinoid microsphere to contemporary cell

Synthesis of cellular nucleic acid
Synthesis of cellular protein
A genetic code relationship between cellular nucleic acids and cellular proteins
Mechanism for conversion of solar to chemical energy, directly or indirectly

7. Copolyamino Acid-Polynucleotide Complexes

Basic proteinoid and phase-separated proteinoid particles can make internucleotide bonds (Figure 13) from ATP in the presence of water. Although it is possible to produce pentamers or hexamers in nonaqueous solvents (Jungck, 1973), nothing larger than trinucleotide has yet been produced by these phase-separated systems in the presence of water (Jungck and Fox, 1973).

A special phase-separated system is that obtained from polynucleotides and basic copolyamino acid. Oparin and coworkers (1966) have described polynucleotide-protein complexes, as referred to earlier. In our work, we have used proteinoids instead of proteins, occasionally we have used thermally prepared oligocytidylic acid (Waehneldt and Fox, 1968) to give a totally chemically synthetic particle, and usually we have employed enzymically synthesized polynucleotides. This system thus in part provides an understanding of principles; in part it yields a direct model for origins. As Waehneldt showed in our laboratory, the proteinoid-polynucleotide complexes are pH-sensitive and salt-sensitive, comparable to nucleoprotein organelles

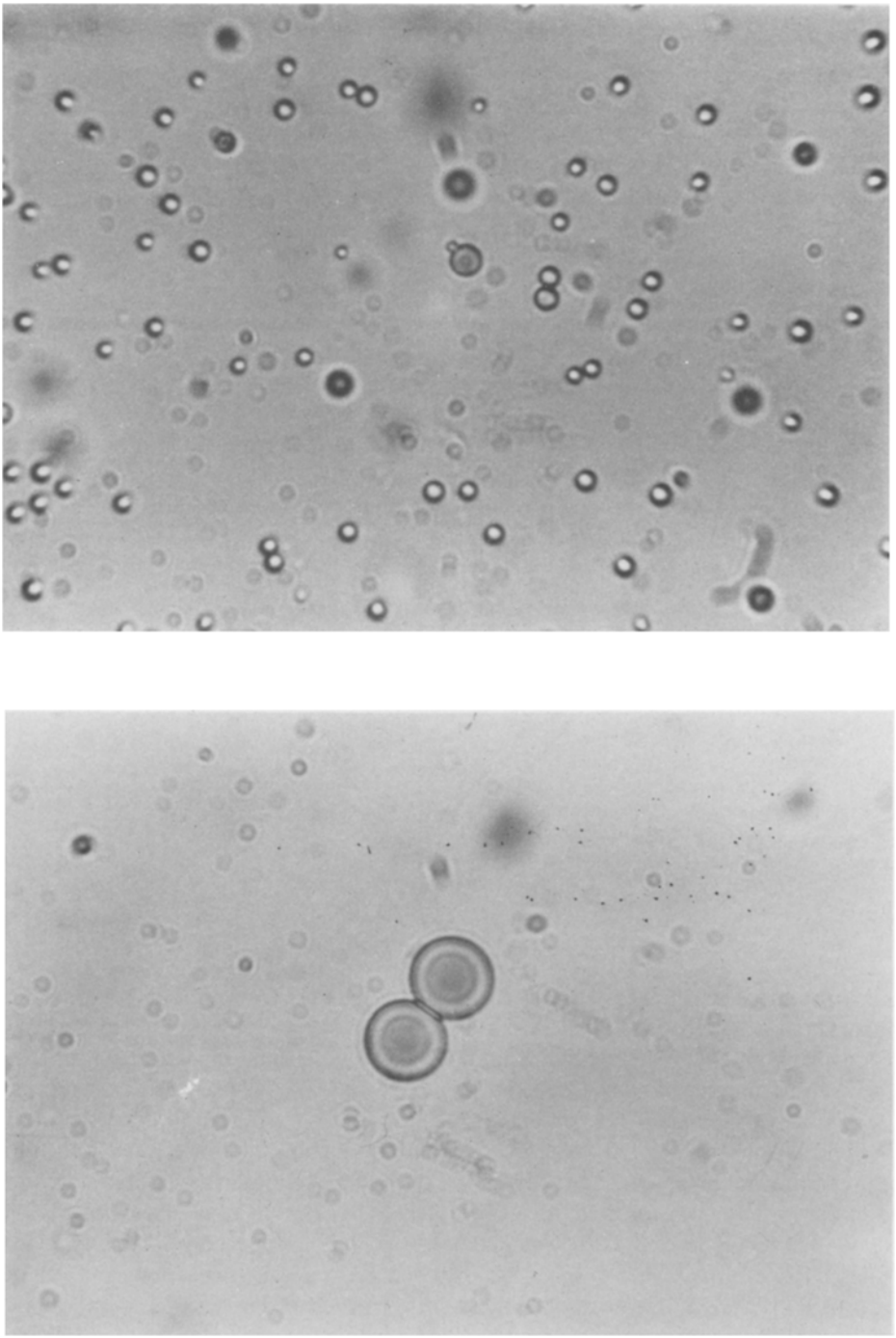

Fig. 12. Budded, unbudded, and joined microspheres from "seawater proteinoid" (Snyder and Fox, 1973).

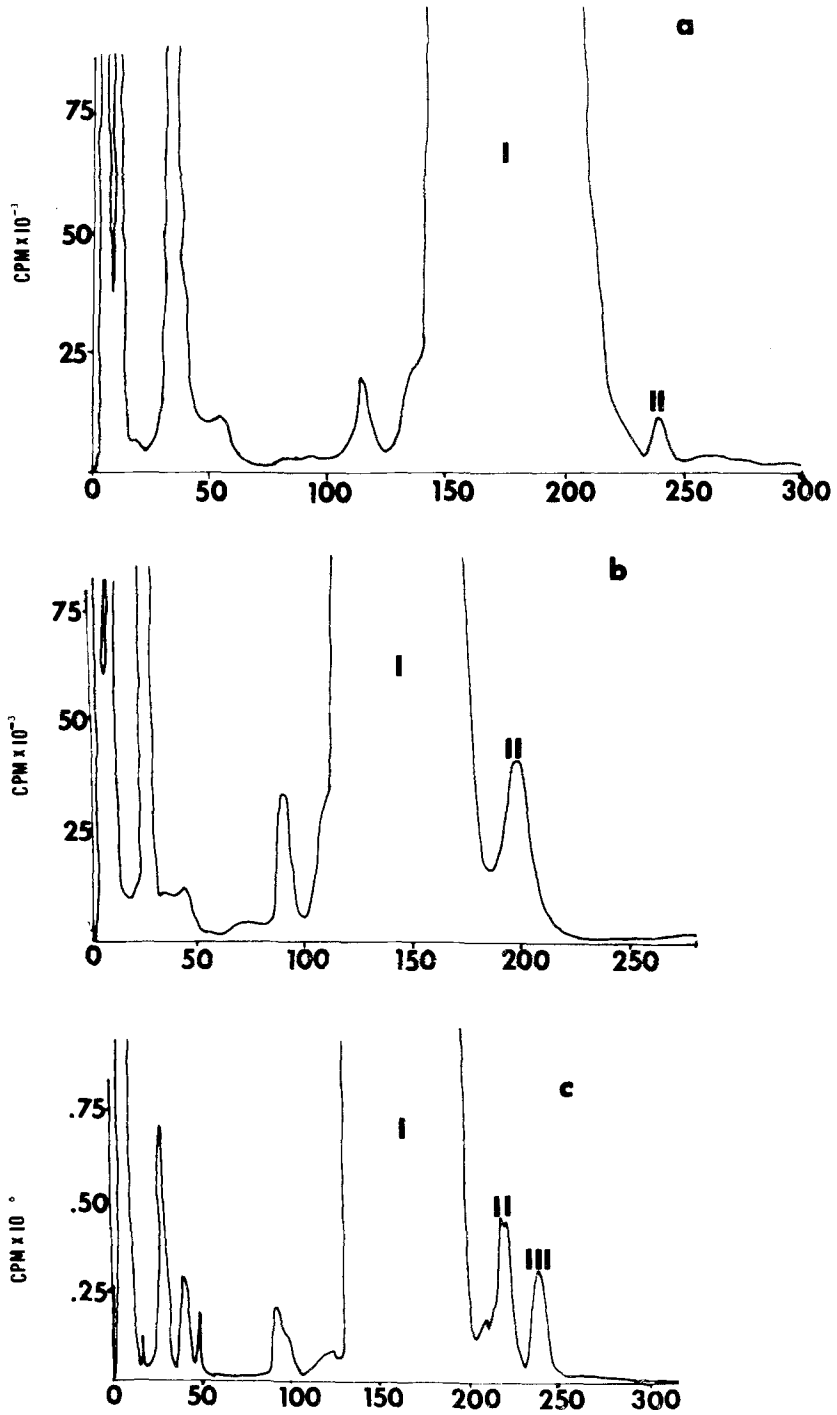

Fig. 13. Formation of internucleotide bonds by proteinoid acting on ATP (Jungck and Fox, 1973).

TABLE V

Interactions of individual homopolyribonucleotides of a complementary pair with a lysine-rich proteinoid (turbidity at 600 nm)

Proteinoid	*Poly G*	*Poly C*
Proline-rich	0.108	0.007

(From Fox, Lacey, and Mejido, unpublished)
These interactions are selected from a much larger number of results.

(Waehneldt and Fox, 1968) in chemical behavior. Yuki and Fox (1969) first demonstrated that such interactions to yield phase-separated particles can be selective.

This last result was of interest because attempts to demonstrate any selective interaction between polynucleotide and amino acids had previously been unfruitful. Interaction between polyamino acids and polynucleotides can, however, be demonstrated liberally. Polynucleotide-polyamino acid interactions are undoubtedly demonstrable because of molecular cooperativity in the polymer-polymer system although polynucleotide-amino acid interactions are essentially not demonstrable.*

Among other results, Lacey *et al.* (Fox *et al.*, 1971) have shown that selective interactions related to codonicity or anticodonicity depend upon lysine content in the polyamino acid. Other factors influence the identity of the selectivity. An illustrative effect from some unpublished studies is shown in Table V.

The data so far collected suggest that the stereochemical forces operating at various stages of molecular and protocellular evolution are quite similar, since the products at various stages have much in common compositionally (Table VI).

In a more dynamic model, Nakashima has reacted various aminoacyl adenylates with the protoribosome model containing poly U, poly A, poly G, or poly C. Nakashima demonstrated that incorporation of amino acids *into the particles* is most favored by the codonically related homopolynucleotide in the particle composed of appropriate lysine-rich proteinoid and polynucleotide (Nakashima and Fox, 1972). More recently, Nakashima has demonstrated that phenylalanine and ATP are converted to phenylalanine peptides in the supernatant in the presence of poly A-basic proteinoid microsystems (Fox *et al.*, 1974). Despite numerous attempts at variation of amino acid in this synthesis, and despite relatively unlimited incorporation into particles, the applicability to amino acids other than phenylalanine and to other polynucleotides has not yet been demonstrated in synthesis of peptides.

The significance of photosynthesis and protophosphorylation in the evolving cell (Baltscheffsky, 1974; Evstigneev, 1974; Groth, 1974; Hall *et al.*, 1974; Halmann, 1974; Hodgson and Ponnamperuma, 1968; Krasnovsky, 1974; Kritsky, 1974; Rubin, 1974; and Schwartz, 1974) need only be mentioned here to place this important evolutionary development in a precellular and cellular perspective. This subject will be discussed intensively in this meeting (Krasnovsky, 1976).

* The laboratory model of Saxinger and Ponnamperuma (1971) can also be understood as consistent with polymer-polymer interactions.

TABLE VI

Compositions of average protein, equimolar adenylate proteinoid, and thermal proteinoid from equimolar mixture
(mole %, ammonia not included)

Amino acid	Average protein (Vegotsky and Fox, 1962)	Adenylate proteinoid (Krampitz and Fox, 1969)	Thermal proteinoid (soluble fraction) (Fox and Waehneldt, 1968)
Lysine	5.9	6.5	7.1
Histidine	1.8	2.4	2.8
Arginine	4.9	4.2	3.3
Aspartic acid	9.7	10.3	3.9
Threonine	4.8	4.9	0.3[b]
Serine	6.0	4.2	0.2[b]
Glutamic acid	12.7	9.7	8.7
Proline	6.2	5.1	2.3
Glycine	12.6	11.1	7.1
Alanine	9.6	14.3	10.3
Valine	5.9	7.3	8.2
Methionine	1.8	0.7	5.8
Isoleucine	6.0	4.5	5.1
Leucine	6.0	9.6	5.1
Tyrosine	2.3	0.1[a]	4.3
Phenylalanine	3.7	4.5	3.9

[a] Abnormal reaction [b] largely destroyed
Irrespective of mode of synthesis, such amino acids as glutamic acid, alanine, glycine, and aspartic acid (one exception) tend to exceed 6% and dominate composition, while histidine, phenylalanine, arginine, and methionine are each <6% by all methods.

8. Coacervated Proteinoid Microspheres

As a last set of experiments which have allowed significance to be imputed to the experimental study of phase-separated microsystems, I turn to those which hybridize coacervate droplets and proteinoid microspheres. These two kinds of microsystem are individually often discussed in tandem (Fox, 1974a). Occasionally inferences are drawn from both models.

As *models* for *proto*cells, the proteinoid microspheres are the only entities which possess structure, and enzymelike activity, both derived from the same polymer, which in turn arose as partially ordered macromolecules from precursor monomers (Fox and Dose, 1972). In other words, the source is unique, and crucial for a true protocell (Young, 1965). The proteinoid model in its fullest expression and the evidence for it have been reported a number of times, often in quite different contexts (Fox, 1973a,b,c,d, 1974a,b,c). The proteinoid microsphere has also contributed especially to the total developing *theory*.

The knowledge that has been derived originally from coacervate droplets includes: the overall contribution of organization, the ability to concentrate organic molecules, the demonstration of the possibilities in aiding metabolic reactions by bringing them into proximity, the consequent multiplication of rates of reaction over the rates in aqueous solution, and the facilitation of the production of polymers within boundaries.

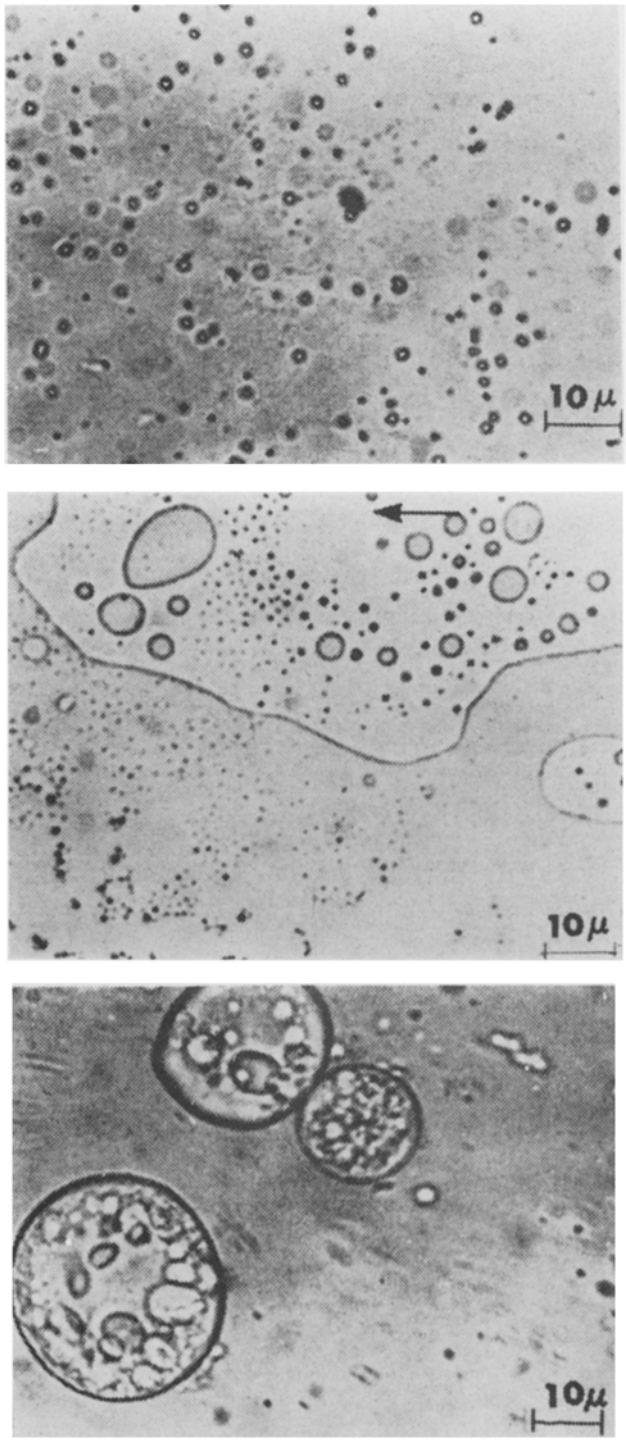

Fig. 14. Coacervate-like proteinoid microspheres by dehydration and rehydration (Smith and Bellware, 1966).

A number of workers have reported altering proteinoid microspheres to render them physically more like coacervate droplets.

Young (1965) first incisively pointed out the advantages of nonbiological source, structural stability, and versatility in proteinoid microspheres. He also described their ability to divide despite that structural stability, to form buds, and to coalesce. The roster of versatility was extended later by Miquel *et al.* (1971), who incorporated either histone or basic proteinoid in the presence of calcium. In 1966, Smith and Bellware converted proteinoid microspheres to units having "several properties in common with coacervates" by dehydration and rehydration of suspensions. These common properties mentioned by Smith and Bellware (Figure 14) included complex morphology, selective adsorption as evidenced by concentration of methylene blue, and ability to coalesce. Rohlfing reported (1974) that lysine-rich proteinoids have many properties in common with coacervate droplets, including stabilization by quinone.

The confluence of concepts from both kinds of model is such as easily to explain the fact that coacervate droplets and proteinoid microspheres are often described side-by-side in recent textbooks.

9. Conclusion

For this presentation, I have made a necessarily incomplete selection from phenomenological clues, revealed principles, and suggestive models (Table I) and from that material a selection that is especially amenable to a unified overview (Figure 15). This experimentally and analytically based overview extends from cosmic reactants (Fox, 1973a) to a linkup of protocells with the first cells as analyzed from the contemporary perspective (Margulis, 1971). The steps to the first polymer, preprotein, are necessarily illuminated only by the studies of formation and properties of proteinoid.

This unified view is one governed basically by stereochemical influences. Amino acids have been found to be self-ordering when they condense, the resultant polymers are self-aggregating, the resultant protocell models are "self"-reproducing, and some of such systems possess limited ability to synthesize internucleotide and peptide bonds.

The model protoribosomes arising from the polymers make peptide bonds in the presence of water, and they serve as a missing link in the evolution of informational flow (Fox, 1974b).

When we review all that is made possible by various phase-separated systems, and recognize what has already been shown by activities in phase-separated systems arising from abiotically generated polyamino acids, and when furthermore we recognize the great ease of formation of the polymers under geophysically relevant conditions and the ease of formation of the cell models, we are led by the evidence to conclude that a protocell was easily, early, and often on the evolutionary scene. The thermodynamic, kinetic, metabolic, reproductive, hereditary, and other benefits of even a protocell were such as to give it a huge advantage over any other type of evolution that did not proceed through any kind of cell, at least in the first steps of the prelude to contemporary life. The route through an early (proto)cell

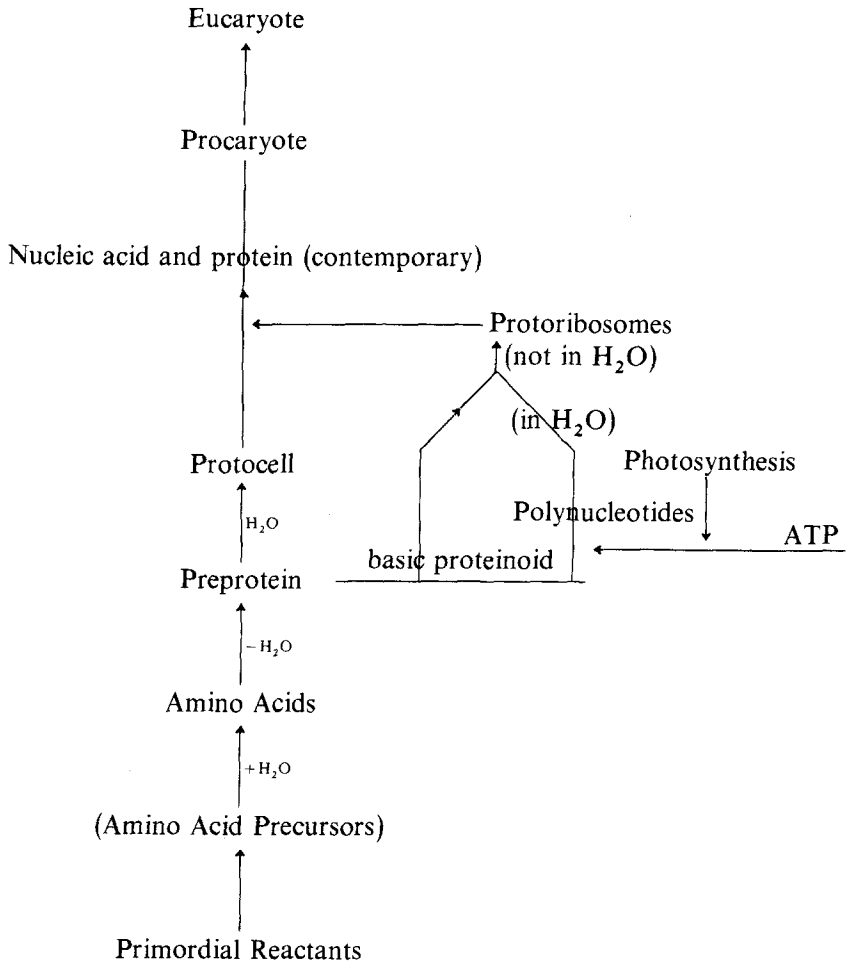

Fig. 15. Overview of molecular and cellular evolution, derived from experiments and analyses. Size of procaryote (1–10 μ) is consistent with that of proteinoid microsphere. Properties of models for preprotein and protocell are given in Fox and Dose (1972).

permits us to visualize, in accord with experiments, the origin of a contemporary macromolecule-synthesizing cell. Serious consideration needs to be given to the view that, as the textbooks in biology state: "the unit of life is the cell," so was the unit of protolife the protocell.

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