

Origin of the first cell membrane?

Imaginative organic chemistry points the way both to the evolutionary sophistication of the mechanical elements of the cell membrane and to a model for the first synthesis of the archeobacterium membrane.

THE question of the origin of life can be broken into several parts. The most elementary requirement is for self-replicating molecules of some kind, but the most successful of them can ensure only that the whole of the available raw material is turned into material of the same kind when, at least in a closed system, synthesis will stop. That, in itself, is not life, but homogenized death.

That is not to diminish the importance of the search for self-replicating molecules of, say, RNA by people such as Orgel (at the Salk Institute), but merely to remark that living things as we know them are self-replicating entities, each embodying a distinctive blend of chemical components and separated from their surroundings (including other living things) by an external membrane. There have recently been some intriguing experiments showing that such systems can be fashioned from quite simple materials (see *Nature* **363**, 205; 1993).

The obvious difficulty is that there is no obvious connection between a demonstration that membranous vesicles can replicate under laboratory conditions and the course of events on the surface of the Earth more than 3 billion years ago. But those events may be more accessible than we suppose. So much is evident from the biomolecules whose structure is strongly conserved across species; if the nucleotide structure of ribosomal RNA molecules seems everywhere to be the same, it is a fair guess that it has been like that for a substantial part of 3 billion years.

Comparisons between the chemical constituents of different species may be even more revealing. Indeed, there is much in the view that a good deal could be learned about the origin of life by a sufficiently diligent hunt through the literature (*Nature* **367**, 409; 1994). That may not be the stuff of which mega-dollar grant applications are made, but there is now a neat illustration of the value of an appropriately archival approach to the subject.

Writing in the first issue of the new journal *Chemistry & Biology* (**1**, 11–23; 1994), Guy Ourisson and Yoichi Nakatani, from the CNRS laboratory for the organic chemistry of natural products at Strasbourg, reckon that they have been able to infer, from the constituents of the membranes of extant cells, that terpenoids were plentiful among the constituents of the first cell membranes. It is only proper to remark that this is not armchair science; the authors have been looking for pointers to experiments that may be carried out.

This is how the argument goes. We are
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now told at school (right?) that cell membranes are really double layers of phospholipid molecules, with polar phosphate groups on the external and internal surfaces and the lipid (hydrocarbon) parts of the molecules lying in the interior of the membrane. Experiments show that, in the right conditions of pH, phospholipid molecules will indeed assemble spontaneously into pieces of membrane.

But that is only part of the story. For mechanical reasons if no others, membranes must be reinforced by other polar molecules incorporated in their structure. In the membranes of eukaryotes, cholesterol is the most common reinforcing molecule. Ourisson and Nakatani start with the remark that this general rule applies neither to bacteria nor to archeobacteria. Instead, cholesterol is replaced in bacteria by hopanoids (substituted five-ring structures with four cyclohexanes and a furane welded together). And archeobacteria do not have simple phospholipids at all, but molecules on which phosphate groups are anchored to the two ends of a branched hydrocarbon structure through ether bonds and glycerol residues, so that (with the hydrophilic ends being pulled in two directions) they need no reinforcement.

Part of the interest of this tale is that traces of these molecules are common among the compounds of high molecular weight recovered from sediments and from petroleum. The hopanoids, for example, are closely related to the molecule called isoarborinol, another five-ring structure, which was first isolated (by Ourisson and a colleague) in 1969, and only afterwards (in 1989) recognized as a constituent of higher plants, but now inferred to be a constituent of an aerobic microorganism. Organic chemists with time on their hands (if there are such people) might do worse than mount a copy of Ourisson and Nakatani's table of "The terpenoid fossil record" on their office wall in the hope that it will suggest other connections.

Not that Ourisson and Nakatani are short of ideas. Among other things, they construct a tentative evolutionary hierarchy for the terpenoids in their fossil record. The starting point, they say, must have been some means of making isopentenol units, which are simple 5-carbon mono-alcohols which are then polymerized (perhaps by anchoring one end to a solid surface through a phosphate group). That is certainly one way of making long molecules with double bonds between adjacent carbon atoms in one position out of every four along the chain, with branching

connections at similar intervals.

Figuratively, at least, that provides the outline of a mechanism by which the first membranes might have arisen. There is a solid surface capable of binding isopentenol condensed with a phosphate group through the polar head, and some means by which further isopentenol units can be condensed at the growing ends of the molecules. Given a degree of uniformity in the speed of growth, the time will come when the molecules are just long enough to form a piece of membrane, whereupon the structure will simply peel off the surface in a kind of phase transition, enclosing whatever materials lie within reach in a primitive vesicle of a kind.

The captured contents would almost inevitably include the chemical components required to synthesize the isopentenol units themselves. In real life, so to speak, it would presumably have been a matter of chance whether a vesicle destined to be a kind of archeobacterium would contain genetic elements capable of directing its further replication.

This, it should be remembered, is not just armchair speculation. Ourisson and Nakatani make no secret of their goal, the design of further experiments. It will be interesting to see how soon they can design and demonstrate a catalytic solid surface from which pieces of primaevial bacterial membrane peel off at regular intervals.

But the manufacture of the ingredients of the membranes of archeobacteria is not the only goal. The polymerized isopentenol units provide just the kinds of structures needed to form (by cyclization) the polycyclic terpenes. So there is a prospect of being able to use the mechanical reinforcing molecules in the membranes of bacteria and eukaryotes as a means of telling when, in the course of evolution, the synthetic pathways required for making more complicated reinforcements were recruited to the biochemical repertoire. The outcome of that hierarchical exercise will be interesting and important in its own right.

The lesson to be learned from this is one familiar to historians of all kinds. It is rarely possible to recreate the environment in which a distant event occurred, but it is often possible to infer from scattered relics of the past what exactly happened. Ourisson and Nakatani have cleverly made meaningful relics out of apparently miscellaneous information about the organic content of sediments. What else can be recruited to the same good cause?

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