Letters

Biological Organization

Ehret's interesting article [*Science* **132**, 115 (1960)] deserves some comment regarding the evidence for the evolution of cell structure. The classification of cells on the basis of envelope systems lacks phylogenetic soundness for it is necessary to place some viruses, bacteria, and actinomycetes in all envelope groups; this can certainly not be an accurate classification on the basis of their evolutionary position. The primary difficulty, however, lies in the proposition that bacteria and actinomycetes form a class of inner or single envelope organisms, the plasma membrane of which would correspond to the nuclear membrane of two envelope systems or advanced cell types. This would imply a mechanism of cellular evolution in which the cytoplasm and cell organelles form outside the protobiote (nucleus). It is well to note that all nuclear membranes, unlike the bacterial protoplast membrane, are double, being formed of sacs of endoplasmic reticulum which are organized and flattened against the phase which they surround. The bacterial protoplast contains those enzymes that are found in the cytoplasm but are absent from the nucleus of higher cell types.

Endoplasmic reticulum in higher cell types is frequently seen to be continuous with the plasma membrane, and the outer component of the perinuclear cisternae, with the endoplasmic reticulum. Indeed, in some fungi the membranes appear to be a continuous system all associated with the plasma membrane [*Exptl. Cell Research* **16**, 689 (1958)]. These continuities in some cases occur by means of connections which resemble circumferential, centripetal infoldings of the plasma membrane, which, instead of cutting the cell in two as in bacterial cell division, spread over the nucleoid as in the early stages of bacterial spore formation. This appears to be the only evidence for the evolutionary origins of the nuclear envelope at the present time, and it seems therefore to be the best. The envelope theory makes little sense when one attempts to apply it to this schema.

The formation of the endomembranes of higher cell types does, indeed, appear to have involved two steps: (i) membrane invagination as a modification of the cytocinetic mechanism, and (ii) a progression from obligate to facultative membrane continuity. If the envelope theory is applied to bacteria, then it would be the inner envelope rather than the outer which is missing. I would suggest abandoning

the envelope idea, because it is unrealistic from the phylogenetic point of view and relies upon assumptions which are unsupported.

I would submit that at present the best defensible hypothesis regarding the relationships among membranes is the following: "All cellular membranes are phylogenetically derived from the plasma membrane and share with it the capacity to become structurally differentiated by the specific association of proteins thereon in genetically determined patterns" [J. H. McAlear, thesis, Harvard University (1958)]. I would further submit that attempting to apply mathematical rigor to morphology at any level, at this time, must only result in a pseudosophisticated over-simplification. The study of the evolution of morphology is an inductive process and requires the accumulation of information of a comparative nature.

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The article by C. F. Ehret entitled "Organelle systems and biological organization" expounds a view of the nature of living things that many of us thought had disappeared with the advent of evolutionary theory. It purports to be an account of certain entities obeying natural laws, termed "macromolecular aggregates" and "organelles." This is an inherently misleading approach to what are, in fact, biochemical and biophysical problems, because it deals with words from biological discourse as though they had the same kind of referents as similar words in physics.

There are, indeed, subatomic particles, atoms, and molecules which follow certain physical laws. A general class of larger things also exists—namely, the class of physical objects, obeying the laws of mechanics (relativistic or classical). The biological world does not contain classes of this variety, because its "components" have evolved according to their adaptive fitness to survive in various environments and not according to any internal "laws" of a paraphysical kind. Similarities between organelles, such as those mentioned by Ehret, demonstrate not a common law but a common origin. Likewise, the differences between bacteria and cellular organisms, about which Ehret makes such far-fetched topological play, demonstrate not two fundamentally opposed "patterns" derived from any natural law of cell construction but a more remote common origin.

One might also have thought that the "free-living nucleus" hypothesis—never a very likely one—would have

been scotched by recent work in bacterial biochemistry. But Ehret does not discuss biochemistry at all, because it does not fit into his formal framework. In his critique of the specification of organelles, by function, he claims (citing only a personal communication) that structurally typical but nonrespiratory mitochondria occur in a yeast mutant. He totally ignores all the most important work in this field since 1945, by such people as Chance, Lehninger, Green, Greville, Slater, Schneider, and many others, who show how close a relationship exists in the mitochondrion between structure and biochemical functioning. To say of such an organelle that its primary role is "niche-filling" or "space-filling" is either absurd or meaningless. In fact, the role of these structures seems to be to maintain the proper environments for certain reaction sequences, the structure being itself modified according to the reactions occurring within it [see, for example, L. Packer and A. L. Tappel, *J. Biol. Chem.* **234**, 525 (1960)]. Ehret's hypothesis of a role for such organelles concerned with "transmission, diffraction, oscillation [sic], and reception of electromagnetic energy" seems to be a deliberate attempt to confuse the issue as regards the well-founded chemical roles of such systems and also smacks of the aberrations of such pseudoscientific cults as "radionics."

In developing his peculiar *Weltanschauung*, Ehret makes various mistakes of fact and nomenclature. To refer to cilia from different organisms as "isotopes" is just wrong; a word exists to describe the relationship—namely, *homology*, which indicates a common evolutionary origin. To state that all cilia are homologous is to put forward an interesting theory about show. I find the meaning of his other statement on this issue, that "all particle sense. And what on earth are "non-atoms" (Fig. 7)?

His claim that "at the molecular level . . . the interacting particles . . . have relatively infinitesimal lifetimes" is untrue, as a glance at the half-lives for various types of cellular component, obtained by radioisotope labeling or other methods, would suffice to show. I find the meaning of his other statement on this issue, that "all particle concepts suffer from illusions of the reality of a static point," not entirely clear.

Ehret says that by his method, the "gap between the molecular and cellular levels is realistically bridged." It is difficult to see why the need for such a "bridge" was ever felt. The link between the physical and biological worlds is provided by the theory of evolution. "Nous n'avons pas besoin de ces autres hypothèses."

The editorial in the same issue of *Science* takes exception to a popular article about scientific things written in an anthropomorphic manner. In the circumstances, there is a temptation to cry "Tu quoque."

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McAlear's opening remarks regarding incongruity are based upon an erroneous notion about the relationships that are required between structural and phylogenetic categories. In taxonomy we frequently classify organisms with abbreviated life cycles on the basis of their larval stages, despite the absence of a terminal stage of development "normal" to their category; HeLa tissue cultures the world over remain generically *Homo* despite their structural simplicity and instability; each of us has arisen from a fertilized egg, structurally a microorganism but phylogenetically human; at the subcellular level, the transplanted frog nucleus remains phylogenetically an amphibian. But consider the interesting case of *Pneumococcus* transforming deoxyribonucleic acid, which retains only some of its host's phylogenetic

character; these structural units are smaller than the minimal phylogenetic unit, which is sensibly an approximation of the organism's entire genome.

The well-known relationships between endoplasmic reticulum and nuclear membrane are not only consistent with but a part of my central thesis. We must, of course, eventually account for the specific structural differences between nuclear membranes and bacterial envelopes, as well as for those between different nuclear membranes and between different bacterial envelopes. The envelope-system method of classification simply places central emphasis upon the interesting topological properties (especially the inside-outside relationships) associated with the various known and possible forms of cellular organization. Numerous alternative speculations, including McAlear's, are compatible with it (no test of their soundness). From the evolutionary viewpoint, gene mutation and selection have produced the diversity of outer wrappers seen in bacteria and could easily account for such specific differences as are known between nuclear membranes and bacterial envelopes. Basic to this must be both gene-product differences and environmental phase differences: the nuclear membrane is at a karyoplasm-cytoplasm interface; the bacterial envelope, at a "karyoplasm"-substrate interface. In this regard, it should be interesting to compare the "karyoplasm"-substrate interface (normal envelope) with a "karyoplasm"-host cytoplasm interface in the case of facultative intracellular symbionts or parasites.

Regarding the evolution of cell structure, there is, of course, no direct evidence. The fossil record offers little help at the subcellular level, and all extant "living fossils," from coelacanths to protozoa, are 1960 models, most of which appear to be in an evolutionary cul-de-sac. From this point of view a word like *protozoa* is etymologically acceptable; in this sense and within the context of the discussion of envelope systems I have lumped bacteria and actinomycetes as "protobiotes." Whether they represent primitive or degenerative forms of life has been argued brilliantly, but also fruitlessly and *ad nauseam*, in a voluminous literature.

Irrespective of how any particular system has actually evolved, the presence in multienvelope systems of a unique ensemble of organelles unquestionably permits the development of cytoplasmic structures of greater diversity than is possible without them. This follows of logical necessity, as should be obvious if one considers the physical basis of diversity: for example, generically more structural forms are possible in a 100-atom than in a ten-atom system. The first appearance, then, of such a supramolecular unit as a cilium is surely to be regarded as a major innovation within the bios, and the subsequent capitalizations upon such units are indeed remarkable achievements in the evolution of metazoa.

In the history of science, logical rigor, though always difficult in virgin territory, has been indispensable for progress; it has invariably led to oversimplification, and as mortals the best we can hope for is an orderly progression from good oversimplifications to better ones.

It is commonplace to ridicule by unsupported generalizations that which one does not understand, and in both respects Nicholls has succeeded beautifully. In the spirit of substituting light for heat, I shall comment on the several issues he has raised.

1) The biological world certainly contains classes of components that obey the laws of mechanics. A finite number of sardines or of college students can be packed into a can or a telephone booth, respectively; gravity keeps most of us in our place, and modifications of the kinetic theory of gases have been applied meaningfully

to such component interactions as antigen-antibody agglutination, phage-bacterium adsorption, sperm-egg fertilization, and ciliate-ciliate mating.

2) With respect to similarities between organelles, there is no evidence that all cilia are derived from one common progenitor cilium. One of the important hypotheses expounded in my article is that of the *de novo* origin of such organelles by means of physically limited developmental processes from genetically limited sub-organellar-level macromolecular pools.

3) That the topological play is far-fetched is merely Nicholls' unsupported value judgment.

4) The reasons favoring the term *one-envelope system* over *free-living nucleus* are developed in the article. It is not clear to me from Nicholls' letter in what way he supposes them to be inconsistent with the recent work in bacterial biochemistry.

5) In addition to not citing some elegant works in biochemistry, I also elected to consider irrelevant to the crux of the argument much of the important contemporary work in sociology (people-people interrelations) and in nuclear physics (particle-strange particle interactions).

6) The concept of niche-filling is well understood in many professions. The tree cavity preempted by the starling will not be occupied at one and the same time by a flicker; an old French railway car will hold eight horses or 40 men; a simple keystone in an arch may be of marble or of brick or of wood, but not of all simultaneously. A more general concept of space-filling is appreciated by most physically minded people, including architects, city planners, and traffic managers. The important point is that, irrespective of the specific qualitative nature of the unit employed, fundamental geometrical and topological relationships are established between the units. It is at this level that we "intuitively" appreciate the shapes of things and many of the interrelationships in biology and society at large. In a rigorous analytical sense, we may evaluate a termite colony, a hardwood climax forest, an infantry regiment, or a political congress in session without once mentioning adenosine triphosphate or oxidative phosphorylation yet without underestimating their indispensability. In my article I have done this for the shapes of cells in terms of organelles. In other worlds, higher-level interrelationships might be formally similar to ours, but the molecular machinery might be quite different.

7) The possible role of organelles as receivers or transducers of electromagnetic energy was suggested from observations of their ultrastructure by

Fernández-Morán and seems inescapable from a knowledge of these objects. An important unanswered question is simply, "How much?"—a question provoked in the open mind by such knowledge.

8) The concept of organelle isotopy is structurally correct from both physical and etymological standpoints. Plant and animal, microorganismal and metazoan cilia have basically the same form. This similarity does not impose the limitation of common evolutionary origin on the structure itself in the developmental sense.

9) On or off the earth, "non-atoms" represent the subatomic particles. The term stems from the well-known philosophical device of *differentia and negative* and denotes a subset class that relates logically to the higher levels in the figure.

10) The lifetimes of such units as the enzyme-substrate complex are sufficiently short that ingenious instrumental measures, such as those conceived and brilliantly executed by Britton Chance, have been needed for their measurement. As pointed out in the article, the very organelles in or on which these fleeting events occur may be observed in vivo by cytologists at relative leisure. The qualification "relatively" was used by me deliberately and precisely to emphasize comparative lifetimes.

11) I cannot explain Nicholls' failure to find a need for a bridge or a link. A current key concern in physiological genetics and developmental embryology is the construction and testing of hypotheses that relate directly to the ascent from the macromolecular level that is experienced in the lifetime of every organism. If authoritarianism must be resorted to, it is well known that eminent experimentalists since Altmann and Hertwig have grappled with this problem along lines closely analogous to mine. That Nicholls' general accusation—that I have underestimated the contributions of biochemistry at the one extreme or of evolutionary theory at the other—is unfounded may be seen from a careful reading of my article and of the contextually relevant sections of the references cited.

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Dream Deprivation

William Dement tentatively concludes from an interesting study of "The effect of dream deprivation" [*Science* **131**, 1705 (1960)] that "a certain amount of dreaming each night is a necessity." A different interpretation of