DEPARTMENT OF MICROBIOLOGY

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(Fyr) Glad Italy.

Dear Francis:

I'm about to make what for me is an important and nearly irreversible decision, and would be grateful to you for any thoughts you have on the matter and for any backing (largely moral) you could give me.

If we are ever to unravel the course of events leading to the evolution of the procaryotic (i.e., simplest) cells, I feel it will be necessary to extend our knowledge of evolution backward in time by a billion years or so--i.e., backward into the period of actual "Cellular Evolution". There is a possibility, though not a certainty, that this can be done by using the cell's "internal fossil record"--i.e., the primary structures of various genes. Therefore, what I want to do is to determine primary structures for a number of genes in a very diverse group of organisms, on the hope that by deducing rather ancient ancestor sequences for these genes, one will eventually be in the position of being able to see features of the cell's evolution--i.e., by knowing what features of the primary structures are "locked-in", what regularities (repeats, etc.) existed, and how one ancient primary relates to another ancient primary structures (which gave rise to some different cellular function).

The obvious choice of molecules here lies in the components of the translation apparatus. What more ancient lineages are there? A priori it seems impossible to evolve any structural gene without the capacity to translate the gene--making the evolution of some rudimentary translation machine necessarily a very early happening. Hopefully that machine was a direct lineal ancestor (both functionally and structurally) of the present one. Also, I feel (and you may too) that the RNA components of the machine hold more promise than (most of the) protein components. For example, how can we get activating enzymes--as we now have them--without a good deal of evolution, and how can these evolve without translation, etc?

What I propose to do is not elegant science by my definition. (Elegant science is that which generates the minimum of excess information in answering a question(s).) However, I feel that the approach is necessary for the time being--in view of our paucity of concepts. In addition what I propose will need a rather large laboratory set up to do RNA sequencing. Since I have a low level of

administrative capacity, frankly I'm afraid I'll encounter some difficulties in setting up such a laboratory. Here is where I'd be particularly grateful for your advice and help. What I need to do is probably to become associated with some energetic young product of Fred Sanger's lab, whose scientific capacities complement mine. Together, we could probably get the operating going. In fact, it is struggling along at present; I've inherited all of Sol's extensive sequencing set-up and have one or possibly two students coming along nicely, but these are obviously not (yet) at the level of sophistication required to run such a lab. If you know any young scientist who has training along these lines, I'd be grateful for your suggesting the idea to him. What I feel I have to offer here is a rather sound view of evolution and a well equipped laboratory.

In the longer run, my plans tend toward setting up (probably not at Illinois) in collaboration with a number of others in this area, a much larger grouping, that would include a larger RNA sequencing operation and a protein sequencing operation, and allied laboratories, all in the framework of an Evolution Institute. This, of course, is a wholly different situation, in that financing then becomes a major problem. Nevertheless, this is the eventual goal, and at that time I shall need all the backing I can get.

I have the general feeling that the average scientist (particularly some of those inhabiting the granting committees) are not really aware of what sorts of problems lie ahead in the area of evolution. Hence, monies are hard to get in this area. As a consequence, I and others will be forced to make numerous propaganda gestures in order to rouse the requisite amount of interest. Your last article on the code may have helped somewhat here, and my response to it was partly motivated by keeping the general interest up in the area.

Incidentally, thanks for the reference on the three forms of $tRNA_{tyr}$; I was particularly struck by the difference that one substitution on A can make. Recently I've had some more discrete ideas about the "error evolution" of the decoding machine and may write them up. If so I'll send you a copy; if not write you about them (this letter is too long already).

Thanks for any advice or help you can give me.

Kindest regards,

Carl

C. R. Woese
Associate Professor of Microbiology

CRW:jh