

SOUTHERN ILLINOIS UNIVERSITY

C A R B O N D A L E

I L L I N O I S

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Dear Francis,

Your answer to my letter was particularly interesting, especially your statement "... we all tacitly assumed that it was ribosomal RNA which was the genetic message." In this instance, the "we" must mean molecular biologists because your statement carries with it the implicit assumption that all DNA is genic. It has been apparent, however, for nearly four decades to cytologists and geneticists that most of the chromatinic nucleic acid (DNA) is heterochromatinic and nongenic, and, hence, that only a very small fraction of the DNA (or the RNA produced from it) could be involved in gene action sensu strictu. It has been very difficult to explain this fact to molecular biologists because they have been so absorbed with the relation between genes and nucleic acids that they have excluded the relationship of nongenic DNA to the cellular economy from their thinking. But the involvement of heterochromatin in the cellular economy was obvious, of course, to Jack Schultz, because of his deep interest in heterochromatin, and he must have made it obvious to Caspersson in the late 30's. Hence, the limited involvement of genic DNA in protein synthesis could hardly be considered a new idea 30 years later. (I should have mentioned Jack in my letter to Science.)

Knowledge of this kind dates back to the time when it was first demonstrated that the Y-chromosome which carries the largest slug of nucleic acid in the *Drosophila* genome is essential to male fertility in spite of the fact that it carries no genes. The more recent demonstration that the inactivation of the extra X in the female is due to overloading it with DNA makes it clear that both the physiological competence of the total genome and the inactivation of genes are associated with nongenic functions of the heterochromatinic DNA. The heterochromatinic DNA must be presumed to function in the production of RNA at a much higher quantitative level (90-95%) than the genic DNA (5-10%, or even less). Heterochromatin probably acts as a means of making what I would call "constructional" protein essential for cell walls, ribosomes, mitochondria, spindle and all the multitude of other cellular organelles of very ancient origin, but not for the construction of gene-controlled enzymes.

Because the nongenic functions of DNA are performed by the host when virus infection occurs, one may not properly draw a parallel between viral DNA and chromosomal DNA. I am inclined to think that the most interesting really new idea in RNA metabolism is your concept of adaptor RNA which seems to have been totally unexpected.

But the idea that only a very small fraction of the RNA produced by chromosomes is under genic control was certainly obvious to Caspersson. His courage in defending his completely unorthodox views in the face of the fierce opposition of biochemists (especially Lindstrom-Lang) has never been properly recognized.

I did not intend so much to stress the question of the origin of the idea of messenger RNA as to ask for a clear idea of the consensus among molecular biologists on the priorities involved. You have answered this question very precisely. I gather that you do not think there has been any hanky-panky in this connection. If I read your final paragraph correctly, it says that these priorities are only the business of the insiders, but we outsiders are also deeply interested because this great revolution has fired the interests of the entire scientific community, and we would all like to know the history of the development of the ideas. I don't think we should be deprived of this knowledge because it might hurt the feelings of some of those immediately concerned. Your advice to consult the original papers is really not helpful because it is just another way of saying that we should all become biochemists, and this, of course, is out-of-the-question.

I was primarily interested in the priority of the operator concept, and there has been hanky-panky here. Monod stated that the first discovery of the gene-controlled adaptive enzymes in bacteria was in his laboratory. This statement with its qualification is precise and correct. But he knew very well that I reported gene-controlled adaptive enzymes in yeast three years earlier. I did not choose to argue this point, but I think that the substitution of "operator" for "activator" is a matter of deep concern for all those interested in scholarliness.

Sincerely yours,

Carl

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P.S. I was in a front seat and listening very closely, and my memory is very good. I suspect that Sydney had stage fright.

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