UNIVERSITY OF CAMBRIDGE DEPARTMENT OF PHYSICS
Medical Research Council Unit
CAVENDISH LABORATORY
FREE SCHOOL LANE
CAMBRIDGE

TELEPHONE:
CAMBRIDGE 55478

19th October, 1956.

Dr. S. Spiegelman,
University of Illinois,
Dept. of Bacteriology,
362 Noyes Laboratory of Chemistry,
Urbana, U.S.A.

Dear Sol,

Your McCullum-Pratt paper arrived last week and I have read it with great interest. I particularily liked your introduction. I found only one omission of importance; that was the work of the Berkeley and Tübingen groups on TMV, which shows that at least some of the specificity for the amino acid sequence of a protein can be carried by RNA.

Our own ideas on the subject are very similar to yours, although somewhat more precise on certain points. The only advantage of this is that they suggest rather more experiments. I have made, and enclose, a brief summary of them for your information; I doubt if I would want to put all that into print. I am glad you emphasized the Pardee-Prestidge experiment (also being done by Ycas and by the Pasteur group). I had it in my notes on Ann Arbor, but omitted it in the heat of the moment. I need hardly say that our views are relatively fluid, and that the dogmatic tone in the presentation is to make explanation easier.

Some detailed points. How good is the evidence now for blocking of "protein" synthesis (as opposed to active enzyme synthesis) by amino acid analogues? I'm thinking of the recent experiments at the Pasteur. The evidence quoted (pages 5 and 6) does not rule out DNA playing a passive role in the synthesis of some enzymes, and in fact Allfrey's results support this idea. Work tells me that Straub told him recently that the amylase "synthesis" is really an activation, requiring only two amino acids. Finally it always surprises me that a very small attack on RNA does not knock out all protein synthesis. It suggests that some RNA is attacked extensively and other RNA not at all i.e. that the RNA is inhomogenous.

I don't understand your resolved shockates. Nothing exciting at this end.

Yours ever,

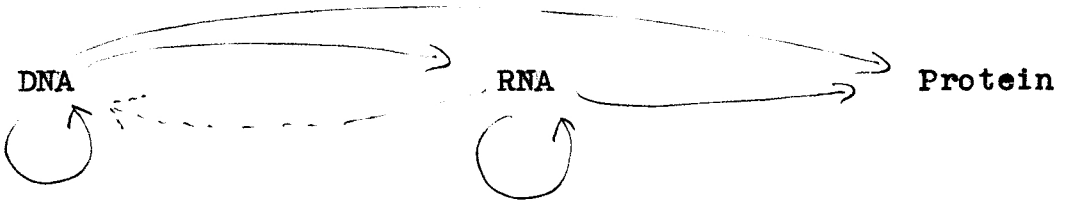
Francis

F. H. C. Crick.

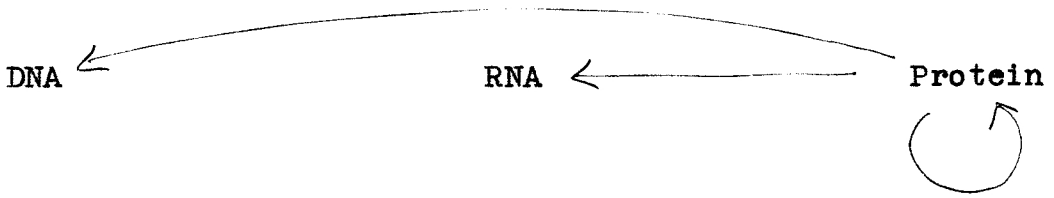
Ideas on Protein Synthesis (Oct. 1956)

The Doctrine of the Triad.

The Central Dogma: "Once information has got into a protein it can't get out again". Information here means the sequence of the amino acid residues, or other sequences related to it. That is, we may be able to have



but never



where the arrows show the transfer of information.

Requirements for protein synthesis.

(a) a passive template i.e. one which does not turn over in the process. This can be RNA or DNA.

(b) mixed intermediates of ribose nucleotides and amino acids. The most favoured ones have the general formula:

Base base base
Sugar - phos - sugar - phos - sugar - phos - phos - amino acid.

DNA makes DNA by a special process not involving RNA and only involving proteins is a non-template manner (e.g. as enzynes, or

as structural supports). Presumably the Kornberg system.

DNA is held in a configuration by histone so that it can act as a passive template for the simultaneous synthesis of RNA and protein. None of the detailed "information" is in the histone. (My guess is that in this configuration the DNA bases have been unpaired).

RNA only acts as a template for protein synthesis when in a microsomal particle. The protein of the particle carries none of the detailed "information"; it is made of identical sub-units. Different particles (i.e. making different proteins) contain different RNA but (usually) the same protein sub-units. They hold the RNA by its phosphate-sugar backbone, not by the RNA bases.

New RNA is usually produced in protein synthesis, but unless it is stabilized by combining with the structural protein to make a microsomal particle, it is broken down. Chloramphenicol uncouples the joining up of the protein.

Thus of the arrows shown in the first diagram all but the dotted one ~~is~~ are allowed in this scheme. It is implied that the configurations of the passive templates, whether RNA or DNA, are always much the same, so that the same ribotide-amino acid intermediates can always be used to absorb onto them.

This scheme explains the majority of the present experimental results!

F.H.C.C.