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March 31, 1965

Dr. Francis H. Crick
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The Medical School
Hills Road
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Dear Francis:

I was at Madison several days ago, where Khorana now has evidence that AGA = arginine and GAG = glutamic. There are thus increasing hints that A will be found to equal G for most 3rd positions. My impression of the solid facts is shown in the enclosed picture. The only item which really bothers me is the mechanism by which arginine can mutate to serine, a very frequent result observed by Yanofsky. This is a crucial point since it is involved in his genetic data which suggests that the direction of translation is 5' to 3'. I thus wonder if there is any good evidence against believing that AUA or AUG codes for serine. If so, then it is understandable why cell-free extracts from su^- strains incorporate some serine (result of Haselkorn) when an AGU copolymer is used.

Here our main excitement comes from the study (by my students Mario Capecchi and Gary Gussin) of the template activity of RNA from a sus^- mutant of the RNA phage R17. They have an in vitro system which tells us that the CR63 suppressor gene causes the production of a new type of sRNA. This, if added to a sus^- in vitro system, causes suppression (as shown by the production of coat protein).

On the E. coli mutant front, Wally now at last may have evidence that polynucleotide phosphorylase breaks down RNA in vivo. Our hunch now, however, is that it cannot be the sole answer to mRNA breakdown, but that it works only if another enzyme working from the 5' end starts the breakdown process by nibbling off the nucleotides at the 5' end. When this happens, no new ribosomes can attach, thus leading to an absence of ribosomes at the 3' end. Then polynucleotide phosphorylase attacks the 3' end. In this way the polar mutants, as well as modulation, may find a simple explanation. To prove this we must find an E. coli enzyme which works from the 5' end.

I hope by now that Odilie is fully recovered.

Regards to all,

J -
James D. Watson

JDW:jb

GENETIC CODE AS OF MARCH 30, 1965:

	<u>2nd</u>		<u>3rd</u>		
	U	C	A	G	
U	PHE (B)**	SER (B)	TYR (B)	CYS (B)	U
	PHE (B)	SER (B)	TYR (B)	CYS (B)	C
	LEU (B)	SER (B)	(ochre) (amber)	TRYP	A G
C	LEU	PRO (B)	HIS		U
	LEU	PRO (B)	HIS GLUN GLUN		C A G
A	ILEU (B)	THR?	ASPN (B)		U
	ILEU (B)	THR?	ASPN (B)		C
		THR	LYS (B) LYS (B)	ARG	A G
G	VAL (B)	ALA?	ASP	GLY	U
	VAL	ALA?	ASP	GLY	A
	VAL?	ALA?	GLU (B)	GLY	C
	VAL	ALA?	GLU		G

*the order of each triplet is 5' to 3'
 ** (B) denotes sRNA binding data

Copolymer Results of Khorana:

ARG GLU
 AGAGAGAGAGAGAGAGAGAGAG

LEU SER
 CUCUCUCUCUCUCUCUCUCUCUCU

CYS VAL
 UGUGUGUGUGUGUGUGUGUGUG

THR HIS
 ACACACACACACACACACACAC

LYS ARG GLU
 AAGAAGAAGAAGAAGAAGAAG