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Genetic Memory

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Genetic memory resides in specific molecules of deoxyribonucleic acid. The DNA alphabet consists of four letters, the bases, A, T, G, and C. The sequence of letters in a nucleic acid message corresponds to a sequence of the 20 amino acid species in protein. Two molecules of DNA interact with one another by hydrogen bonding between bases on opposite chains. As proposed by Watson and Crick,[1] adenine pairs with thymine, and guanine with cytosine. Information is retrieved by transcribing the DNA message in the form of ribonucleic acid and then translating the RNA message into protein. Triplets are translated sequentially, from left to right.

The information encoded in a nucleic acid template enables the reading mechanism to select one from many species of molecules, to define the position of the molecule relative to the previous molecule selected, and to define the approximate time of the event relative to previous events. Hence the nucleic acid functions both as a template for other molecules and as a biological clock.

Although the genetic information is encoded in the form of a one-dimensional string, the polypeptide products fold in a specific manner predetermined by the amino acid sequence. In effect, a complex, three-dimensional object is created by first fabricating a linear string of letters that folds upon itself, in a fairly specific manner. Probably the principle of unidimensional sculpturing could be used by man for the construction of certain kinds of objects.

Often, one molecule of messenger RNA (mRNA) contains the information for many molecules of protein, so the RNA message must also contain information for the initiation and termination of the polypeptide chain. The translation must be initiated properly since selection of the first word also phases the translation of subsequent words. At least three enzymes are required for the initiation process, three additional enzymes for the formation of the peptide bond and movement of the ribosome along the message, and one or more enzymes for the termination of protein synthesis. In addition, specific enzymes are required for the synthesis and repair of DNA, for the synthesis of mRNA, aminoacyl-transfer RNA (AA-tRNA), and for the modification of tRNA and ribosomal RNA. The process of protein synthesis, illustrated diagrammatically and in highly abbreviated form, is shown in Fig 1.

The chromosome of a relatively primative organism, such as *Escherichia coli*, consists of approximately 3 million base pairs. Sufficient information is present to determine the sequence of 1 million amino acids in protein which is approximately the amount required for 3,000 species of protein. The human genome is 1,000 to 2,000 times larger than that of *E coli*, ie, information for the synthesis of 3 to 6 $\times$ 10^6 species of protein could be present. However, multiple copies of essentially the same gene frequently are stored; hence much information probably is redundant.

The precise number of enzymes required for the storage, retrieval, and transmission of genetic information has not been determined. Perhaps 200 species of protein would suffice. However, as much as 25% of the total protein synthesized by rapidly growing *E coli* is utilized for the construction of new ribosomes.

The Rate of Reading.—The average *E coli* ribosome can read approximately 1,000 mRNA triplets per minute. The reading rate therefore is quite slow compared to a man-made computer. However, protein is synthesized simultaneously at many sites within the cell. *Escherichia coli* with a generation time of 25 minutes contains approximately 15,000 ribosomes per chromosome. Hence, 15 million amino acids may be incorporated into protein per minute per chromosome. The RNA message usually is covered by a train of ribosomes; hence one molecule of mRNA is translated simultaneously at different sites. A single molecule of mRNA may serve therefore as a template for the synthesis of many molecules of protein. It seems likely though, that some species of mRNA are destroyed earlier than others.

Some genes are transcribed more frequently than others. It is clear that retrieval of genetic information often is regulated selectively. Some regions of *E coli* DNA may be transcribed 1,000 times per generation; others may be transcribed only one or two times per generation.

Deciphering the Genetic Language.—The experimental approaches that eventually led to the deciphering of the genetic code came from the study of in vitro synthesis of protein. The demonstration that mRNA is required for the in vitro synthesis of protein and that synthetic polynucleotides such as poly U serve as templates for the synthesis of polyphenylalanine provided a means of exploring many aspects of the code and the translation process.[2] Polynucleotides composed of different combinations of bases in random sequence were synthesized with the aid of polynucleotide phosphorylase, discovered by Grunberg-Manago and Ochoa.[3] Synthetic mRNA preparations then were used to

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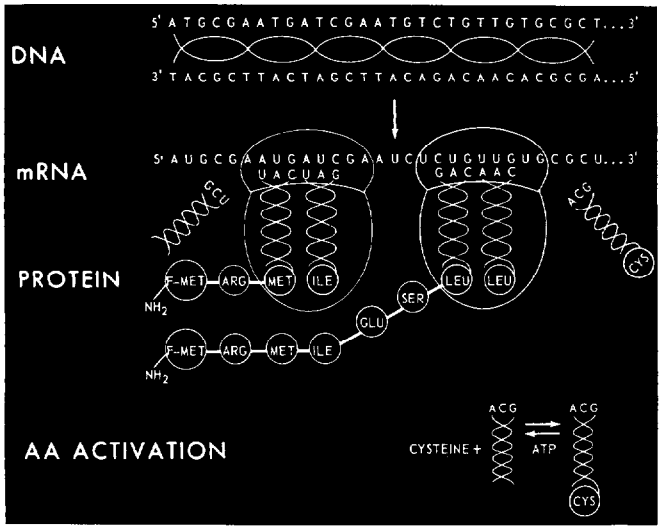


1. The retrieval of genetic information is illustrated in a condensed and diagrammatic form.

direct cell-free protein synthesis. The base content of the mRNA can be correlated with the amino acid content of newly synthesized protein. In this manner the base compositions of 53 RNA codons were assigned to amino acids.[4,5] It was also found that three sequential bases in mRNA correspond to one amino acid in protein, that AA-tRNA is required for the translation of mRNA,[6] and that codons for the same amino acid sometimes require different species of AA-tRNA for their translation.[7] Analysis of the coat protein of mutant strains of tobacco mosaic virus provided evidence that triplets in mRNA are translated in a nonoverlapping fashion, because the replacement of one base by another in mRNA usually results in only one amino acid replacement in protein.[8]

Alternate codons for the same amino acid were shown in most cases to contain two bases in common. Common bases were assumed to occupy the same base position of synonym triplets.

Base Sequence of Codons.—Codon base sequences were established in several ways: by directing in vitro protein synthesis with polyribonucleotides containing repeating doublets, triplets, or tetramers of known sequence as described by Khorana in the accompanying communication, and by stimulating the binding of aminoacyl-tRNA to ribosomes with trinucleotides of known sequence.[9] Since aminoacyl-tRNA binds to ribosomes prior to peptide bond formation, the process of codon recognition can be studied without peptide bond synthesis. A simple method for determining ^{14}C-aminoacyl-tRNA bound to ribosomes was devised that depends upon the selective retention of ^{14}C-aminoacyl-tRNA bound to ribosomes by disks of cellulose nitrate; unbound ^{14}C-aminoacyl-tRNA is removed by washing.

At the time that the trinucleotide template approach to codon sequence was devised, most of the 64 trinucleotides had not been prepared. Elegant

Table 1.—The Genetic Code*

	UUU		UCU		UAU	UGU	
		PHE			TYR		CYS
	UUC		UCC		UAC	UGC	
				SER			
	UUA		UCA		UAA TERM	UGA	TERM
		LEU					
	UUG		UCG		UAG TERM	UGG	TRP
	CUU		CCU		CAU	CGU	
					HIS		
	CUC		CCC		CAC	CGC	
		LEU		PRO			ARG
	CUA		CCA		CAA	CGA	
					GLN		
	CUG		CCG		CAG	CGG	
	AUU		ACU		AAU	AGU	
					ASN		SER
	AUC	ILE	ACC		AAC	AGC	
				THR			
	AUA		ACA		AAA	AGA	
					LYS		ARG
MET_F	AUG	MET	ACG		AAG	AGG	
	GUU		GCU		GAU	GGU	
					ASP		
	GUC		GCC		GAC	GGC	
		VAL		ALA			GLY
	GUA		GCA		GAA	GGA	
					GLU		
MET_F	GUG		GCG		GAG	GGG	

*Nucleotide sequences of RNA codons were determined by stimulating binding of *E coli* AA-tRNA to *E coli* ribosomes with trinucleotide templates. F-Met corresponds to N-formyl-Met-tRNA, the initiator of protein synthesis. TERM corresponds to terminator codons.

chemical methods for oligoribonucleotide synthesis, devised by Khorana and his colleagues, are described in the accompanying communication. We have employed enzymatic methods for oligoribonucleotide synthesis. Leder and co-workers showed that primer-dependent polynucleotide phosphorylase, in the presence of a dinucleoside monophosphate primer and nucleoside diphosphate, catalyzes the synthesis of oligonucleotides of low chain length[10]; a similar method was also reported by Thach and Doty.[11] Another enzymatic method for oligonucleotide synthesis, reported by Bernfield,[12,13] is based upon the demonstration by Heppel et al[14] that RNase A catalyzes the synthesis of oligonucleotides from pyrimidine-2′,3′-cyclic phosphate moieties in the presence of mononucleotide or oligonucleotide acceptors.

The 64 trinucleotides were synthesized and assayed for template specificity in stimulating binding of *E coli* aminoacyl-tRNA to ribosomes.[15,16] A summary of the code is shown in Table 1. Almost all triplets were found to correspond to amino acids. In most cases, synonym codons differ only in the base occupying the third position of the triplet. Thus synonym codons are *systematically* related to one another. Only four unique patterns of degeneracy were found, each pattern determined by the bases that occupy the third positions of synonym triplets. Patterns of alternate third bases are as follows:

(1) G
(2) U = C
(3) A = G
(4) U = C = A

A fifth pattern, U = C = A = G, was found also, but may be formed by combining two or more simpler patterns such as [(U = C) + (A = G)] or [(U = C = A) + (G)].

Codons specifying the initiation of protein synthesis differ in that alternate bases occupy the *first* rather than the third position of the codons. For example, N-formyl-Met-tRNA responds to AUG and GUG. Three triplets, UAA, UAG, and UGA, serve as terminator codons. Hence the degeneracy pattern again is unusual (discussed under Punctuation).

One consequence of logical degeneracy is that mutations resulting from the replacement of one base pair in DNA by another often do not result in the replacement of one amino acid by another in protein. Hence, many mutations are "silent." The code appears to be arranged so that the effects of error often are minimized. Amino acid replacements in protein that result from an alteration of one base per triplet can be derived from Table 1 by moving horizontally or vertically from the amino acid in question, but not diagonally.

Punctuation

Codon Position.—Each triplet can occur in three structural forms: as a 5′-terminal-, 3′-terminal-, or internal-codon. Substituents attached to terminal or internal ribose hydroxyl groups can influence the template properties of codons profoundly. Relative template activities of oligo U preparations, at limiting oligonucleotide concentrations, are as follows: p-5′-UpUpU > UpUpU > CH_3O-p-5′UpUp > UpUpU-3′-p > UpUpU-3′-p-OCH_3 > UpUpU-2′, -3′-cyclic phosphate. Trimers with (2′-5′) phosphodiester linkages, (2′-5′)-UpUpU and (2′-5′)-ApApA, do not serve as templates for phenylalanine- or lysine-tRNA, respectively. The relative template efficiencies of oligo A preparations are as follows: p-5′-ApApA > ApApA > ApApA-3′-p > ApApA-2′-p.[17]

Many enzymes have been described that catalyze the transfer of molecules to or from terminal hydroxyl groups of nucleic acids. It is possible therefore that modifications of terminal hydroxyl groups sometimes regulate the reading of RNA or DNA.

Initiation.—Two species of methionine-tRNA are found in *E coli;* one species, Met-$tRNA_f$ is converted enzymatically to N-formyl-Met-$tRNA_f$,[18] and functions as an initiator of protein synthesis in extracts of *E coli* in response to the codons AUG or GUG; the other species, Met-$tRNA_m$, does not accept formyl groups and responds only to AUG.[19,20]

Translation of mRNA is initiated near the 5′-terminus of the RNA and proceeds three bases at a time toward the 3′-terminus. The first amino acid to be incorporated into protein is the N-terminal amino acid; the C-terminal amino acid is the last to be incorporated.

At least three nondialyzable factors are required for the initiation of protein synthesis.[21-23] However the reactions have not been clarified fully. It seems probable that one factor, the C protein, is required for the attachment of the 30S ribosomal subunit to the 5′-terminus of the nascent chain of mRNA prior to the detachment of the mRNA from the DNA template.[21] Another factor is required for binding of N-formyl-methionyl-tRNA to the 30S ribosomal subunit in response to AUG or GUG.

Termination.—Results obtained by Stretton and co-workers[24] and by Garen[25] demonstrate that UAA, UAG, and UGA are terminator-codons. Capecchi has reported that a protein, termed the release factor, is required for terminator-codon dependent release of polypeptides from ribosomes.[26]

Terminal events in protein synthesis have recently been studied with trinucleotide codons.[27] Initiator and terminator trinucleotides sequentially stimulate N-formyl-methionyl-tRNA binding to ribosomes and the release of free N-formyl-methionine from the ribosomal-intermediate. The release factor and a terminator trinucleotide is required for this reaction. The release factor has been fractionated into two components; R1, which corresponds to the terminator codons UAA and UAG; and R2, which corresponds to UAA and UGA.[28] The specificity of R therefore is related to the codon. These results suggest that terminator codons may be recognized by release factors. However, the mechanism of termination remains to be clarified, and it is certainly possible that terminator-codons are recognized by components that have not been detected thus far.

Mechanism of Codon Recognition

Cells often contain multiple species of tRNA for the same amino acid. Soon after the code was found to be degenerate, the specificity of separate species of $tRNA^{leu}$ for codons was examined. Randomly ordered poly UG and poly UC preparations are templates for different species of Leu-tRNA.[7] Thus alternate codons for the same amino acid sometimes are recognized by different species of tRNA. When base sequences of synonym codons were established, it became abundantly clear that synonym codons are logically related to one another. Since only a few general degeneracy patterns were found, each pattern was thought to represent a general mechanism for codon recognition.

Evidence that one molecule of AA-tRNA can respond to two kinds of codons was obtained by showing that >99% of the available molecules of ^{14}C-Phe-tRNA bind to ribosomes in response to poly U, and >65% of the molecules also bind in response to UUC.[29] Hence >65% of the Phe-tRNA molecules respond *both* to UUU and UUC. Additional evidence was obtained by fractionating AA-tRNA and determining the responses of the separated fractions of ^{14}C-AA-tRNA to trinucleotide codons.

Results obtained thus far in our laboratory with purified fractions of AA-tRNA from *E coli,* yeast, and guinea pig liver are summarized in Fig 2. It is clear that one species of tRNA may recog-

Table 2.—Alternate Base Pairing*

tRNA Anticodon	mRNA Codon
U	A
	G
C	G
A	U
G	C
	U
I	U
	C
	A

Alternate base pairing. The base in a tRNA anticodon shown in the left-hand column forms antiparallel hydrogen bonds with the base(s) shown in the right hand column, which usually occupy the third position of alternate mRNA codons. Relationships are "wobble" hydrogen bonds suggested by Crick.[30]

nize 1, 2 or 3 synonym codons that differ only in the base occupying the third position of the codon. Five unique patterns of degeneracy were found, each pattern determined by alternate third bases of synonym triplets recognized by a tRNA species. Patterns of alternate third bases of synonym codon sets are as follows:

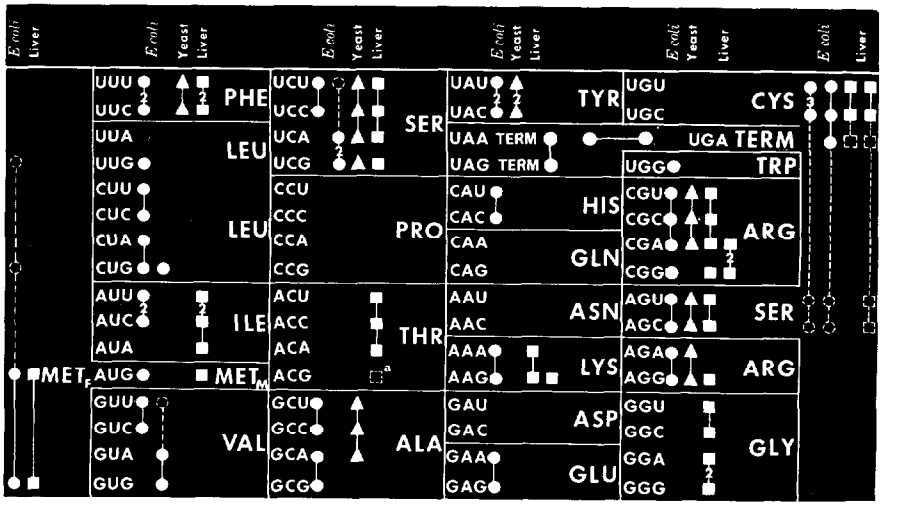
(1) G
(2) U = C
(3) A = G
(4) U = C = A
(5) A = G = U

Crick proposed a mechanism that would enable a base in the tRNA anticodon to pair with alternate bases occupying the third position of synonym mRNA codons.[30] By changing positions slightly, that is, by wobbling, bases in the appropriate position of the tRNA anticodon form alternate pairs with bases occupying the third position of synonym mRNA codons. Antiparallel Watson-Crick hydrogen bonds form between the first and second bases of the mRNA codon and corresponding bases in the tRNA anticodon and wobble hydrogen bonds form between bases occupying the third positions of synonym mRNA codons and a corresponding base in the tRNA anticodon as shown in Table 2. Hence, U in a tRNA anticodon pairs with A or G in the third position of synonym mRNA codons; C pairs with G; G pairs with C or U; and I pairs with U, C, or A. Additional evidence supporting this mechanism of codon recognition stems from the elucidation of base sequences of tRNA anticodons. The data are fully consistent with wobble base pairing.

In summary, degeneracy patterns for amino acids observed with unfractionated AA-tRNA often result from recognition of several codons by a single species of tRNA and from the presence of multiple species of tRNA for the same amino acid that respond to different sets of codons.

Universality

Although the results of many studies indicate that the genetic code is largely universal, the fidelity



2. Responses of purified AA-tRNA fractions to trinucleotide codons. Joined symbols adjacent to codons represent synonym codons recognized by a purified AA-tRNA fraction from ● *E coli*, ▲ yeast, and ■ guinea pig liver. The number between symbols represents the number of redundant peaks of AA-tRNA found responding to that set of codons. The open symbols represent ambiguous AA-tRNA responses; MET_f corresponds to N-formyl-Met-tRNA, the initiator of protein synthesis; MET_m corresponds to Met-tRNA; TERM corresponds to termination of protein synthesis. Release factors 1 and 2, rather than RNA, correspond to UAA and UAG, or UAA and UGA, respectively (*a* signifies uncertain).

of translation can be altered in vivo and in vitro by altering components or conditions required for protein synthesis. The extent of such alterations was examined by studying the fine structure of the code with tRNA from different organisms. Almost identical translations of nucleotide sequences of amino acids were found with bacterial, amphibian, and mammalian aminoacyl-tRNA. However, *E coli* tRNA did not respond detectably to certain codons. Therefore aminoacyl-tRNA preparations were fractionated by column chromatography and responses of tRNA fractions to trinucleotide codons were determined.[31] A summary of the results is shown in Fig 2.

Many "universal" species of aminoacyl-tRNA were found, however seven species of mammalian tRNA were not detected with *E coli* preparations; conversely, five species of tRNA from *E coli* were not found with mammalian preparations. The results also suggest that some organisms contain little or no aminoacyl-tRNA for certain codons (AUA, AGA, or AGG).

The remarkable similarity in codon base sequences recognized by bacterial, amphibian, and mammalian AA-tRNA suggests that most, perhaps all, forms of life on this planet use essentially the same genetic language. The code probably evolved more than 5×10^8 years ago.

It is possible that some species-dependent differences in the codon recognition apparatus serve as regulators of protein synthesis. The possibility that embryonic differentiation may be dependent upon changes in codon recognition remains to be explored. At the present time, the biological conse-

quences of a modifiable translation apparatus are largely unknown.

Fidelity.—Since multiple species of tRNA for the same amino acid often recognize separate sets of codons, the synthesis of two proteins with similar amino acid compositions may require *different* species of tRNA. Some codons probably occur more frequently in mRNA than others for the same amino acid.

Most codons probably are translated with little error (0.1% to 0.01%). However, with some codons the level of error may be as high as 50%. Therefore, the accuracy of codon translation can vary at least 5,000-fold. Errors usually are specific ones, because two out of three bases per codon often are translated correctly. The code seems to be arranged so that the consequences of error often are minimized.

The biological significance of a flexible, easily modified codon translation apparatus is not known. One intriguing possibility is that the codon recognition apparatus is modified in an orderly, predictable way at certain times during cell growth and differentiation and that such modifications selectively regulate the kinds and amounts of proteins synthesized. In accord with this hypothesis, many factors have been found that influence the rate and the accuracy of protein synthesis in vitro. In addition, one may also consider the structural heterogeneity of components required for protein synthesis. For example, it seems probable that tRNA may be extensively modified by enzymes *after* the tRNA polynucleotide chain has been synthesized. Since tRNA contains many trace bases, a spectrum of intermediates probably exists for each species of tRNA. Whether such reactions play a role in regulating gene expression remains to be determined. One intriguing possibility is that infection of a cell by a virus may result in the production of a factor that modifies tRNA and, in consequence, alters the rate of synthesis of mRNA or protein.

It is clear that the translation apparatus of the cell will accept and follow in robot-like fashion any instructions written in the appropriate molecular language. Since the language has been deciphered, the informational properties of the genetic message can be defined in terms of molecular structure. It seems probable that synthetic messages will eventually be used to program cells and their descendants.

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