Letters

Nucleotide Sequence of a Gene: First Complete Specification

Readers of *Science* should have their attention called to the fact that the marvelous achievement of Holley *et al.* (*1*) in determining the complete nucleotide sequence of an alanine transfer RNA isolated from yeast probably reveals for the first time the complete primary structure of a gene, an implication which is doubtless taken for granted by many who are familiar with the field, but which may not be immediately evident to others. Previous work (*2*) has shown that s-RNA molecules have base sequences complementary to those of DNA of the same organism. This is virtually equivalent to saying that cistrons or genes make s-RNA, and that the base sequence in one strand (*3*) of the genic DNA is complementary to the base sequence in its s-RNA product. Current knowledge (*4*) further indicates that the methylated bases in s-RNA acquire their modifications after transcription from their DNA gene. It is assumed that other modified bases in s-RNA are also modified after transcription. Hence, we may write out in full from Holley *et al.*'s base sequence of their alanine RNA the base sequence of the yeast cistron or gene that produced it, as in Fig. 1.

```
                                    Di    Di      Di
                         Me         H     H       Me
ala-sRNA:       GGGCGUGU G GCGCGUAG U CGG U AGCGC G CUCCCUUIGC

DNA cistron:  { CCCGCACA C CGCGCATC A GCC A TCGCG C GAGGGAACCG
              { GGGCGTGT G GCGCGTAG T CGG T AGCGC G CTCCCTTGGC

                Me
                          *
                I ψGGGAGAGUCUCCGGTψCGAUUCCGGACUCGUCCA : CCA

                C ACCCTCTCAGAGGCCAAGCTAAGGCCTGAGCAGGT : GGT
                G TGGGAGAGTCTCCGGTTCGATTCCGGACTCGTCCA : CCA
```

Fig. 1. Primary structure of an alanine transfer RNA (from Holley *et al.*) and of the gene from which it was obtained. Symbols in ala-sRNA represent the 3′-phosphates of: G, guanosine; C, cytidine; U, uridine; MeG, 1-methylguanosine; A, adenosine; DiHU, 5,6-dihydrouridine; DiMeG, N^2-dimethylguanosine; I, inosine; MeI, 1-methylinosin; ψ, pseudouridine; T, ribothymidine. U* is a mixture of U and DiHU. The A, C, G, and T in the DNA cistron have the standard meanings of deoxyadenylate, deoxycytidylate, deoxyguanylate, and deoxythymidylate, respectively.

Whether the terminal CCA is coded by the cistron is doubtful since this can be enzymatically added to or removed from s-RNA in general (*5*). Hence the last three nucleotide pairs, those to the right of the dotted line, probably do not belong on the gene. There are of course some assumptions as to generality underlying the preceding argument.

All of the supplementary evidence referred to in the citations above is based on studies of viruses and bacteria which are, of course, simpler than the eucaryotic yeast. If we may assume that these discoveries on viruses and bacteria are applicable to yeast, then the formula for the DNA cistron given above is the formula for the first fully specified cistron or gene.

T. M. SONNEBORN

Department of Zoology,
Indiana University, Bloomington

References

1. R. W. Holley, J. Apgar, G. A. Everett, J. T. Madison, M. Marquisee, S. H. Merrill, J. R. Penswick, A. Zamir, *Science* **147**, 1462 (1965).
2. H. M. Goodman and A. Rich, *Proc. Nat. Acad. Sci. U.S.* **48**, 2101 (1962); D. Giacomoni and S. Spiegelman, *Science* **138**, 1328 (1962).
3. S. Spiegelman and M. Hayashi, *Cold Spring Harbor Symp. Quant. Biol.* **28**, 161 (1963) gives a review on this.
4. E. Borek, *ibid.*, p. 139; M. Gold and J. Hurwitz, *ibid.*, p. 149.
5. L. L. Hecht, M. L. Stephenson, P. C. Zamecnik, *Biochim. Biophys. Acta* **29**, 460 (1958).

Stratigraphy and Evolution

Edward S. Deevey, in his review (5 Feb., p. 592) of *Approaches to Paleoecology* (J. Imbrie and N. Newell, Eds., Wiley, New York, 1964), says: "In stratigraphy, for example, the classical or evolutionary work being largely finished. . . ." A most amazing statement. This kind of study has hardly begun. The following basic problems, among others, are virtually unexplored: (i) evolution of taxa in samples obtained in direct superposition, that is, in one continuous section; (ii) quantitative assessment of how many forms in an assemblage show directional evolution, any evolution, or none at all; (iii) under what circumstances (factual, not theoretical) evolution (rapid, directional, otherwise) takes place; (iv) whether direction of evolution and direction of natural selection coincide (Kurtén method).

Deevey's sentence continues: ". . . the problems of correlation that remain are ecological problems. . . ." The complete confusion existing with regard to correlation within the Tertiary is occasioned, in my opinion, by a lack of sufficient data on the role played by parallel evolution proceeding at different rates in different lineages.

H. J. MAC GILLAVRY

Geological Institute,
University of Amsterdam,
Amsterdam, Netherlands

I am sorry that Mac Gillavry has taken my innocent statement as indicating either ignorance of or animus against evolutionary studies. I agree that evolutionary work of many exciting kinds is just beginning, now that classical stratigraphy has provided the temporal framework. Confusing as it must sometimes be to those who practice both, paleontology and stratigraphy are different subjects, and my reference was to stratigraphy in the narrow, literal sense—the recording of strata. Evolutionary change offers the best basis for ordering strata, and the stratigraphic units—stages, series, and systems—that can be ordered in evolutionary time are the classical ones. A different methodology is required, however, for unfossiliferous rocks, and for units that are too short to have witnessed appreciable evolutionary change. It is for these shorter or fossil-poor units, and especially for correlation between coeval units of different lithology *and* fossil content, that ecological insight is proving most useful. That is