PROGRESS IN

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Volume 19

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mRNA: The Relation of Structure to Function

edited by

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Preface

This is not the first time that this series has broken with the tradition of including only a group of invited review-type essays, none of which is directly related to its neighbors, inasmuch as the first half of Volume 17 is comprised of papers presented at a symposium honoring Erwin Chargaff on the occasion of his retirement, and that volume was dedicated to him. However, the present volume is the first to be devoted to a symposium on a single topic, including only papers presented at that symposium, and the first to be dedicated *ex post facto*, for the reasons given in the statement that follows, to the memory of one who first proposed its subject.

The decision to make a volume out of this symposium* was quite opportunistic. The subject matter obviously falls within the purview of this series, and the principal invited participants included many whose fields and ideas would qualify them to be invited as contributors to any of its volumes. The nearness of the site, which enabled the undersigned to attend and to discuss matters with the individual contributors, was a factor, as was the long-time association with the chief organizer, the co-editor of this volume.

One of the problems encountered was how to fit in the shorter contributions, both planned and spontaneous, which are the natural concomitants of all such symposia. Decisions were made by the two editors on the basis of length, pertinence, and the submission of manuscript; no attempt was made to record and include the brief questions and answers or other give-and-take that occurred. If this omission loses some flavor or detail, it is more than made up by the fact that each contributor tells his story as he wishes; no attempt has been made to eliminate overlap, or to summarize the results of parallel or complementary investigations (with the single exception of the final paper, which does attempt an overview of the entire symposium: papers, discussions and all). Each of the several major sections may be considered a mini-symposium in itself, rather than the single-author review.

A second editorial decision involved nomenclature. Here the freedom allowed each contributor in the telling of his story was sharply abrogated in order that identical substances should be named identically, and, insofar as possible, in accord with international Recommendations and Rules.

* "mRNA: The Relation of Structure to Function," 29th Annual Symposium of the Biology Division of the Oak Ridge National Laboratory, held at Gatlinburg, Tennessee, April 5–8, 1976.

While most nomenclatural items are covered in "Abbreviations and Symbols" (see p. xxix), there were a few regarding which arbitrary decisions were made. The term "cap" for "5′-terminal sequence" was allowed throughout Section I. However, the terms used by various authors to describe RNA with or without a poly(A) sequence at the 3′ terminal were so diverse and potentially confusing, as well as quite long and often repeated, that we converted them into the short and explicit terms "RNA(A_n)" for RNA containing a poly(A) sequence, and "RNA(no A_n)" for RNA devoid of a poly(A) sequence, where the differentiation is important. (By the Rules, RNA-A_n and RNA should suffice, but the hyphen may be confused with a minus sign.) We also converted X and Y (for "unspecified nucleotide residues") to N′, and N″, and SAM and SAH to AdoMet and AdoHcy, in accordance with the Rules (p. xxix).

It is our hope that readers will find this volume a proper addition to the series, and we welcome, as always, comments—critical or otherwise —on it or on any facet of the series.

W. E. C.
E. V.

Dedication—Jacques Monod

Fifteen years ago, Jacob and Monod presented their ideas on the regulation of gene activity (*1, 2*), introducing several concepts and terms that were as novel as they were prescient (operon and operator; structural gene and regulatory gene; and messenger RNA). They pointed out the necessity for conceiving the existence of a short-lived, rapidly-turning-over chemical entity that could carry the information encoded in the genetic material to the ribosomal "factory," until then considered to be programmed directly by the genetic material, and indicated that the RNA fraction demonstrated several years earlier by Volkin and Astrachan (*3*) had the required properties to make it the logical "candidate" for the messenger role their concept demanded.

In discussing their concept, Jacob and Monod stated "This model may appear rather abstract and complex. It is, however, precise enough to imply very distinctive predictions by which its validity can be tested." Although their ideas were based entirely on results from the study of prokaryote systems, they asked "to what extent are the mechanisms that operate in bacteria also present in tissues of higher organisms; what functions may such mechanisms perform in this different context; and may the new concepts and experimental approaches derived from the study of micro-organisms be transferred to the analysis and interpretation of the far more complex controls involved in the functioning and differentiation of tissue cells?"

The explosion in recent years of research along these lines with eukaryotes enable one to say with confidence that these questions were essentially rhetorical. The messenger RNA-regulator gene concept has had influence far beyond molecular biology. It has had a major impact on developmental biology and embryology. The vistas it opened up, by its brilliant combination of experiment, deduction, and prediction, underlie the Nobel award of 1965 to Lwow, Monod, and Jacob (*4, 5*).

Rather early in the development of the concept of this volume, the subject and content of which flow so naturally out of the above, we asked Jacques Monod to contribute a short historical essay on the conception and development of the mRNA hypothesis. This he agreed to do, but shortly thereafter he became gravely ill and advised us that "I have to admit that this serious state of health is not yet over, and that its being a constant preoccupation has prevented me from meeting many of my obligations." Within days, he was dead.

As a scientist, Monod was blessed with the ability to conceive of the right experiment at the right time, but however thoroughly devoted to

his scientific work, he always had time to help, inspire and discuss with students and other beginning scientists, from the time of his first chairmanship in 1954 through to his later years (from 1971 on) as director of the Pasteur Institute, an appointment that, to his regret, took him out of the laboratory to serve science and help others in another capacity. A generation of now well-known scientists, mainly American, benefited from his training and collaboration from the earliest years onwards.

"In Jacques Monod one met a rare combination of eminent gifts: a harmony between his natural gifts and the task at hand; a balance between intuition, creative imagination, and reason; a logical exigency in all the great undertakings; and a rigorous concern for his responsibilities" (*6*).

It is in appreciation of the high esteem in which he is held, both as a scientist and as a man (*6*), and of the seminal influence he has had on the subject of this symposium and, indeed, on the subject of this series, that we dedicate this volume to the memory of Jacques Monod.

W. E. C.
E. V.

1. F. Jacob and J. Monod, *JMB* **3**, 318–356 (1961).

2. F. Jacob and J. Monod, *CSHSQB* **26**, 193 (1961); J. Monod and F. Jacob, *ibid.* **26**, 389 (1961).

3. E. Volkin and L. Astrachan, *Virology* **7**, 149 (1956).

4. G. S. Stent, *Science* **150**, 462 (1965).

5. J. Monod, *Science* **154**, 475 (1966).

6. Articles by A. Lwow, F. Gros, and others in *Le Monde* (Paris), pp. 1, 19 (June 2, 1976). See also *Trends in Biochemical Sciences*, **1**, N-208 (1976).

Abbreviations and Symbols

All contributors to this Series are asked to use the terminology (abbreviations and symbols) recommended by the IUPAC–IUB Commission on Biochemical Nomenclature (CBN) and approved by IUPAC and IUB, and the Editor endeavors to assure conformity. These Recommendations have been published in many journals (*1*, *2*) and compendia (*3*) in four languages and are available in reprint form from the NAS–NRC Office of Biochemical Nomenclature (OBN), as stated in each publication, and are therefore considered to be generally known. Those used in nucleic acid work, originally set out in section 5 of the first Recommendations (*1*) and subsequently revised and expanded (*2*, *3*), are given in condensed form (I–V) below for the convenience of the reader. Authors may use them without definition, when necessary.

I. Bases, Nucleosides, Mononucleotides

1. *Bases* (in tables, figures, equations, or chromatograms) are symbolized by Ade, Gua, Hyp, Xan, Cyt, Thy, Oro, Ura; Pur = any purine, Pyr = any pyrimidine, Base = any base. The prefixes S–, H_2, F–, Br, Me, etc., may be used for modifications of these.

2. *Ribonucleosides* (in tables, figures, equations, or chromatograms) are symbolized, in the same order, by Ado, Guo, Ino, Xao, Cyd, Thd, Ord, Urd (Ψrd), Puo, Pyd, Nuc. Modifications may be expressed as indicated in (1) above. Sugar residues may be specified by the prefixes r (optional), d (=deoxyribo), a, x, l, etc., to these, or by two three-letter symbols, as in Ara-Cyt (for aCyd) or dRib-Ade (for dAdo).

3. *Mono-, di-, and triphosphates of nucleosides* (5′) are designated by NMP, NDP, NTP. The N (for "nucleoside") may be replaced by any one of the nucleoside symbols given in II-1 below. 2′-, 3′-, and 5′- are used as prefixes when necessary. The prefix d signifies "deoxy." [Alternatively, nucleotides may be expressed by attaching P to the symbols in (2) above. Thus: P-Ado = AMP; Ado-P = 3′-AMP.] cNMP = cyclic 3′:5′-NMP; Bt_2cAMP = dibutyryl cAMP; etc.

II. Oligonucleotides and Polynucleotides

1. Ribonucleoside Residues

(a) Common: A, G, I, X, C, T, O, U, Ψ, R, Y, N (in the order of I-2 above).

(b) Base-modified: sI or M for thioinosine = 6-mercaptopurine ribonucleoside; sU or S for thiouridine; brU or B for 5-bromouridine; hU or D for 5,6-dihydrouridine; i for isopentenyl; f for formyl. Other modifications are similarly indicated by appropriate *lower-case* prefixes (in contrast to I-1 above) (*2*, *3*).

(c) Sugar-modified: prefixes are d, a, x, or l as in I-2 above; alternatively, by *italics* or **boldface** type (with definition) unless the entire chain is specified by an appropriate prefix. The 2′-*O*-methyl group is indicated by *suffix* m (e.g., -Am- for 2′-*O*-methyladenosine, but -mA- for *N*-methyladenosine).

(d) Locants and multipliers, when necessary, are indicated by superscripts and subscripts, respectively, e.g., -m^6_2A- = 6-dimethyladenosine; -s^4U- or -^{4}S- = 4-thiouridine; -ac^{4}Cm- = 2′-*O*-methyl-4-acetylcytidine.

(e) When space is limited, as in two-dimensional arrays or in aligning homo-

logous sequences, the prefixes may be placed *over the capital letter,* the suffixes *over the phosphodiester symbol.*

2. Phosphoric Acid Residues [left side = 5′, right side = 3′ (or 2′)]

(a) Terminal: p; e.g., pppN . . . is a polynucleotide with a 5′-triphosphate at one end; Ap is adenosine 3′-phosphate; C > p is cytidine 2′:3′-cyclic phosphate (*1, 2, 3*); p < A is adenosine 3′:5′-cyclic phosphate.

(b) Internal: hyphen (for known sequence), comma (for unknown sequence); unknown sequences are enclosed in parentheses. E.g., pA-G-A-C(C_2,A,U)A-U-G-C >p is a sequence with a (5′) phosphate at one end, a 2′:3′-cyclic phosphate at the other, and a tetranucleotide of unknown sequence in the middle. (**Only codon triplets are written without some punctuation separating the residues.**)

3. Polarity, or Direction of Chain

The symbol for the phosphodiester group (whether hyphen or comma or parentheses, as in 2b) represents a 3′-5′ link (i.e., a 5′ . . . 3′ chain) unless otherwise indicated by appropriate numbers. "Reverse polarity" (a chain proceeding from a 3′ terminus at left to a 5′ terminus at right) may be shown by numerals or by right-to-left arrows. Polarity in any direction, as in a two-dimensional array, may be shown by appropriate rotation of the (capital) letters so that 5′ is at left, 3′ at right when the letter is viewed right-side-up.

4. Synthetic Polymers

The complete name or the appropriate group of symbols (see II-1 above) of the repeating unit, **enclosed in parentheses if complex or a symbol,** is either (a) preceded by "poly," or (b) followed by a subscript "n" or appropriate number. **No space follows "poly"** (*2, 5*).

The conventions of II-2b are used to specify known or unknown (random) sequence, e.g.,

polyadenylate = poly(A) or $(A)_n$, a simple homopolymer;

poly(3 adenylate, 2 cytidylate) = poly(A_3C_2) or $(A_3,C_2)_n$, an *irregular* copolymer of A and C in 3:2 proportions;

poly(deoxyadenylate-deoxythymidylate) = poly[d(A-T)] or poly(dA-dT) or (dA-dT)$_n$ or d(A-T)$_n$, an *alternating* copolymer of dA and dT;

poly(adenylate,guanylate,cytidylate,uridylate) = poly(A,G,C,U) or $(A,G,C,U)_n$, a random assortment of A, G, C, and U residues, proportions unspecified.

The prefix copoly or oligo may replace poly, if desired. The subscript "n" may be replaced by numerals indicating actual size, e.g., $(A)_n \cdot (dT)_{12-18}$.

III. Association of Polynucleotide Chains

1. *Associated* (e.g., H-bonded) chains, or bases within chains, are indicated by a *center dot* (not a hyphen or a plus sign) separating the *complete* names or symbols, e.g.:

poly(A)·poly(U) or $(A)_n \cdot (U)_m$

poly(A)·2 poly(U) or $(A)_n \cdot 2(U)_m$

poly(dA-dC)·poly(dG-dT) or $(dA\text{-}dC)_n \cdot (dG\text{-}dT)_m$.

2. *Nonassociated* chains are separated by the plus sign, e.g.:

$$2[\text{poly(A)}\cdot\text{poly(U)}] \xrightarrow{\Delta} \text{poly(A)}\cdot 2\ \text{poly(U)} + \text{poly (A)}$$

or $2[A_n \cdot U_m] \rightarrow A_n \cdot 2U_m + A_n$.

3. Unspecified or unknown association is expressed by a comma (again meaning "unknown") between the completely specified chains.

Note: In all cases, each chain is completely specified in one or the other of th two systems described in II-4 above.

IV. Natural Nucleic Acids

RNA	ribonucleic acid or ribonucleate
DNA	deoxyribonucleic acid or deoxyribonucleate
mRNA; rRNA; nRNA	messenger RNA; ribosomal RNA; nuclear RNA
hnRNA	heterogeneous nuclear RNA
D-RNA; cRNA	"DNA-like" RNA; complementary RNA
mtDNA	mitochondrial DNA
tRNA	transfer (or acceptor or amino-acid-accepting) RNA; replaces sRNA, which is not to be used for any purpose
aminoacyl-tRNA	"charged" tRNA (i.e., tRNA's carrying aminoacyl residues); may be abbreviated to AA-tRNA
alanine tRNA or $tRNA^{Ala}$, etc.	tRNA normally capable of accepting alanine, to form alanyl-tRNA
alanyl-tRNA or alanyl-$tRNA^{Ala}$	The same, with alanyl residue covalently attached. [*Note:* fMet = formylmethionyl; hence $tRNA^{fMet}$, identical with $tRNA_f^{Met}$]

Isoacceptors are indicated by appropriate subscripts, i.e., $tRNA_1^{Ala}$, $tRNA_2^{Ala}$, etc.

V. Miscellaneous Abbreviations

P_i, PP_i	inorganic orthophosphate, pyrophosphate
RNase, DNase	ribonuclease, deoxyribonuclease
t_m (not T_m)	melting temperature (°C)

Others listed in Table II of Reference 1 may also be used without definition. No others, with or without definition, are used unless, in the opinion of the editor, they increase the ease of reading.

Enzymes

In naming enzymes, the 1972 recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature (CBN) (*4*), are followed as far as possible. At first mention, each enzyme is described *either* by its systematic name *or* by the equation for the reaction catalyzed *or* by the recommended trivial name, followed by its EC number in parentheses. Thereafter, a trivial name may be used. Enzyme names are not to be abbreviated except when the substrate has an approved abbreviation (e.g., ATPase, but not LDH, is acceptable).

References*

1. *JBC* **241**, 527 (1966); *Bchem* **5**, 1445 (1966); *BJ* **101**, 1 (1966); *ABB* **115**, 1 (1966), **129**, 1 (1969); and elsewhere.†

* Contractions for names of journals follow.

† Reprints of all CBN Recommendations are available from the Office of Biochemical Nomenclature (W. E. Cohn, Director), Biology Division, Oak Ridge National Laboratory, Box Y, Oak Ridge, Tennessee 37830, USA.