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edited by

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Dedication—Erwin Chargaff

The composition of this volume is somewhat extraordinary, in that the first six contributions in it are, or are based upon, the presentations at a symposium honoring Erwin Chargaff on the occasion of his retirement from Columbia University after four decades of continuous service. Inasmuch as Chargaff is, in a way hinted at in the preface to Volume 15, the godfather of this serial publication as well as a major influence in the scientific area defined by its title (Nucleic Acids and Molecular Biology), it seemed appropriate that a volume containing the aforementioned presentations, as were the latter themselves, should be dedicated to him.

Five of these contributions are from those for whom Chargaff filled directly the role of teacher, in that they were predoctoral graduate students with him. However, there are many, many more presently active scientists for whom he filled that role in a less direct way. His approach to his subject, the logic of his analysis, and the concise yet elegant exposition of his findings and interpretation—he is a past master in the art of self-expression—taught something to each reader of his many scientific papers. In a competitive age, he competed only with nature, all the while realizing that "even the most exact of our exact sciences floats above axiomatic abysses that cannot be explored" (*1*). His insistence upon proceeding stepwise from the known to the unknown, avoiding the all-too-popular tendency to pile assumption upon assumption (or to avoid calling a spade a spade) may have cost him the priorities and the headlines cherished by many, but they have gained him the respect and the following of those concerned with the quest for truth.

Perhaps the best way to learn of Chargaff's view of science and his place in it is to read his own perception of himself as "the outsider at the inside" in several essays he has written (*1–6*). The most recent (*1*) is autobiographical and deals with his youth and early career before he came to Columbia University in 1935 at the age of 30. His views of himself may not coincide entirely with the high regard in which he is held by others, especially by his colleagues and students. According to these recollections, Chargaff was deeply influenced in his early years by "Karl Kraus, the greatest satirical and polemical writer of our times . . . a fearless critic of the war [World War I] and of the society that had given rise to it. . . . This apocalyptic writer . . . who made me sensitive to platitudes . . . to take care of words as if they were little children . . . to weigh the consequences of what I said . . . was truly my only teacher." Chargaff's early education, "limited in scope, but on a very

high level," encompassed languages, philosophy, history and mathematics, a little physics, but no chemistry. From that time on, even beyond the acquisition of a doctorate in chemistry at age 23, he thought of himself as a writer. More or less drifting into chemistry ("I chose chemistry for essentially frivolous reasons—knowing least about" it, and because it was "the only natural science offering hope of employment"), he continued to think of himself as a writer, having actually published some creditable items, and made a distinction between his profession ("what would feed and sustain me") and "what one did with one's head." His own postdoctoral period, during which he "floated from one thing to the next," and even his predoctoral associations, did not, in his mind, make him "the pupil . . . of any of the great establishment figures of the past. . . . I must say that I have not learned much from my teachers [for], in the strictest sense of the word, I have had none. During almost my entire life, I have been much more of a teacher than a pupil."—Greatness, he says, "can certainly not be transferred by what is commonly called teaching. What the disciples learn are mannerisms, tricks of the trade, ways to make a career, or perhaps, in the rarest of cases, a critical view of the meaning of scientific evidence and its interpretation. A real teacher can teach through his example—or, most infrequently, through the intensity and originality of his view, or his vision, of nature."

At the symposium, and referring to the accomplishments of his students, Chargaff remarked (as recorded on tape): "I couldn't help feeling that I really had very little to do with the whole thing. My definition of a teacher has always been that he's a man who helps a student to find himself. If there's nothing to find, of course, there's trouble, and even the best teacher won't make a good scientist out of a blockhead. I was really blessed in my career here at Columbia by having many, many students, almost all my students, whom I could help to find themselves. This is the only function that I see a teacher can have at a university."

Aaron Bendich (see p. 43) remarks, "His impact and influence, at the time I joined him in January 1940, were serious since he was, and is, a very serious scholar and an uncompromising investigator. His appreciation of precision and accuracy in describing biochemicals, especially of large molecular weight, left no room for ambiguities [see ref. 5: What is DNA?]. "Hence, when the analytical composition of the nucleic acids from several tissues and animal species became clear, then, and only then, could he state that DNA appeared to reflect the species of origin, while RNA was characteristic of the tissue of origin. This was back in 1950–51, and is, in my judgment, the most important interpretation made until then regarding the chemical basis of differentiation and speciation.

The intervening 25 years have provided numerous bases for confirmation of this fundamental concept, which guides so much current biochemical and molecular biological work and thought."

It was never my privilege to work with, or close to, Erwin Chargaff, but more than once I have found myself the recipient of direct, useful, and sharply worded advice that has been, or that might have been, if heeded, valuable. These need not be recounted here; rather, I would recall two among his many works that particularly impress(ed) me. One, which formed a critical link in the reasoning that (following the discovery here of 5′-nucleotides in RNA hydrolysates) led to the establishment of a 3′–5′ phosphodiester link in RNA (versus the previously accepted 2′–3′ structure), was the clever use of ^{32}P, then more novel than now, to show that the appearance of isomeric glycerol phosphates upon alkaline hydrolysis of the phosphodiester of either one of them resulted from a migration of phosphorus via a cyclic intermediate. The other is, of course, the famous "Chargaff base ratios" that exist in most well-bred DNAs. These, as Bendich indicates above, were not only instrumental in the perfection of their model by Watson and Crick, but clearly foretold the spin-off (or "bonus," as Crick describes it) that came out of the structural work: the chemical basis for the accuracy of replication and transcription.

Much as one is tempted to speculate upon the origins of the concepts that led to these and others of Chargaff's contributions, or perhaps simply to list others, or to analyze the thought processes and reasoning that went into them, it is better that these be left to one who is better qualified to know and express them, namely, the man himself. Fortunately, exercising his early developed literary talents, he has set these down in writing for all to enjoy (*1–6*). A self-styled "outsider at the inside of science," he complies with his "own definition of a good teacher: he learned much, he taught more." In the summarizing and para-scientific writings listed below (and quoted above), there is much that can teach all of us, not only about scientific facts but about scientific reasoning, about scientists, and about the larger world of which science is only a part.

It is with admiration and affection, and perhaps a bit of trepidation lest we stray from his own well-defined standards of truth and reason, that this volume is dedicated to Erwin Chargaff by the Editor, the publisher, and by the contributors to the symposium, who speak for the many students, postdoctoral associates, and others who have been influenced by him.

W. E. C.

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1. "A Fever of Reason: The Early Way." *Annu. Rev. Biochem.* **44**, 1 (1975).
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3. "Essays on Nucleic Acids." Elsevier Amsterdam, 1963.
4. Quotation, *in Science* **190**, 135 (1975).
5. "What Really in DNA? Remarks on the Changing Aspects of a Scientific Concept." This series, Vol. 8, 297 (1968).
6. "Profitable Wonders: A Few Thoughts on Nucleic Acid Research," *The Sciences* **15** (No. 6) 21 (1975).

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 $-^4S-$ = 4-thiouridine; $-ac^4Cm-$ = 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*).

(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 $(A_3,C_2)_n$, a *random* copolymer of A and C in 3:2 proportions;

poly(deoxyadenylate-deoxythymidylate) = poly[d(A-T)] or poly(dA-T) or $(dA\text{-}dT)_n$ or $d(A\text{-}T)_n$, 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.

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.:

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

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 the 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
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 editors, 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).

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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.

2. *EJB* 15, 203 (1970); *JBC* 245, 5171 (1970); *JMB* 55, 299 (1971); and elsewhere.*
3. "Handbook of Biochemistry" (H. A. Sober, ed.), 2nd ed. Chemical Rubber Co., Cleveland, Ohio, 1970, Section A and pp. H130–133.
4. "Enzyme Nomenclature," Elsevier Scientific Publ. Co., Amsterdam, 1973.
5. "Nomenclature of Synthetic Polypeptides," *JBC* 247, 323 (1972); *Biopolymers* 11, 321 (1972); and elsewhere.*

Abbreviations of Journal Titles

Journals	*Abbreviations used*
Annu. Rev. Biochem.	ARB
Arch. Biochem. Biophys.	ABB
Biochem. Biophys. Res. Commun.	BBRC
Biochemistry	Bchem
Biochem. J.	BJ
Biochim. Biophys. Acta	BBA
Cold Spring Harbor Symp. Quant. Biol.	CSHSQB
Eur. J. Biochem.	EJB
Fed. Proc.	FP
J. Amer. Chem. Soc.	JACS
J. Bacteriol.	J. Bact.
J. Biol. Chem.	JBC
J. Chem. Soc.	JCS
J. Mol. Biol.	JMB
Nature, New Biology	Nature NB
Proc. Nat. Acad. Sci. U.S.	PNAS
Proc. Soc. Exp. Biol. Med.	PSEBM
Progr. Nucl. Acid Res. Mol. Biol.	This Series

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