Origins of Molecular Biology

Roots of the molecular approach to biology penetrate the past more deeply than many appreciate.

Eugene L. Hess

With almost every new monograph on a biological subject paying homage to molecular biology, it seems appropriate to inquire further into the origin of the term and the substance of this popular approach to biology. Some are inclined to consider the term a shibboleth—a slogan for getting more research funds. Chargaff (*1*) describes molecular biology as "the practice of biochemistry without a license." Others, who speak of the "tyranny of molecular biology" and allege its reductionist approach is a threat to holistic aspects of biology, would consider perhaps "intellectual teratology" a more appropriate description (*2*). Waddington of the Institute of Animal Genetics, in Edinburgh, has suggested (*3*) that "molecular biology" be considered a segment of a larger entity which he calls "ultrastructural biology."

The molecular approach to biology has provided, nevertheless, a unifying paradigm to guide an active and productive group of researchers, and, as Kuhn has argued ably (*4*), it is hard to find another criterion which so clearly proclaims a field of science. I have searched for both the origins of the term and for the source of the ideas which led to the study of biological phenomena at the molecular level, and I propose to show that the roots of the molecular approach penetrate the past far more deeply than many appreciate.

Structurists and Informationists

In his review of the Festschrift volume entitled *Phage and the Origins of Molecular Biology* (*5*) in honor of Delbrück's 60th birthday, Kendrew pointed out that there are two groups of molecular biologists—structurists and informationists (*5*). Kendrew went on to say, "The fact is that in the early days the two schools were almost entirely isolated from each other. On the one hand was the phage group of Delbrück and Luria, concerned primarily with the problem of interpreting the genetics of microorganisms at the molecular level in terms of a one-dimensional molecular information carrier that only by degrees emerged as the molecule of DNA. On the other hand the pupils of Astbury and Bernal were developing methods of elucidating the three-dimensional structure of all kinds of biological macromolecules but with strong emphasis on the proteins. For them the aim of interpreting function was a goal dimly discerned for the future, and they had little knowledge of, or interest in, the problems of genetics" (*5*).

Stent (*6*), in an essay entitled "That Was the Molecular Biology That Was," reflects the informationist viewpoint. Stent did not consider what seems to me were important contributions physical and organic chemists imparted to its early development.

The term seems to have originated in the imaginative and fertile mind of Astbury who worked at the University of Leeds from 1928 until the time of his death in 1961. "When the history of molecular biology comes to be written, it will be seen that the work of Astbury from its beginnings in 1926 was, so to speak, the main line of progress of molecular biology. It started with his appreciation of the alpha-fold, as he called it, the alpha-helix as we call it now" (*7*). These words of Bernal perhaps reflect the parochialism of one pioneer in x-ray diffractometry viewing the work of another. Bernal goes on to say, "His monument will be found in the whole of molecular biology, a subject which he named and effectively founded" (*7*).

Astbury himself seems less certain that he coined the term. When he gave his Harvey Lecture in 1950, he stated, "The name 'molecular biology' seems to be passing now into fairly common use, and I am glad of that because, though it is unlikely I invented it first, I am fond of it and have long tried to propagate it. It implies not so much a technique as an approach, an approach from the viewpoint of the so-called basic sciences with the leading idea of searching below large-scale manifestations of classical biology for the corresponding molecular plan." In 1961, however, he stated, ". . . , as I believe, I was responsible for first propagating the name 'molecular biology,' and its widespread adoption seems to date from my 1950 Harvey Lecture . . ." (*8*). When the University of Leeds inaugurated the department of biomolecular structure and appointed him professor in 1945, Astbury preferred the title molecular biology but the committee thought it was asking too much to describe him as a biologist (*8*). In 1950, it was clear, at least to Astbury, that molecular biology is concerned with conformation and structure of molecules, especially macromolecules, and that molecular structure is a central and crucial feature for understanding the functioning of living organisms. Edsall has suggested that although he spoke of "molecular" biology, Astbury really thought in terms of "macromolecular" biology (*9*). Eleven years later Astbury tolerated a somewhat broader viewpoint and included molecular genetics within the rubric of molecular biology (*8*).

The earliest use of the term in the literature that I have found is in Astbury's summary of papers presented at the Röntgen Celebrations held at the Royal Institution in November 1945 (*10*). In a summary entitled "Progress of X-ray Analysis of Organic and Fibre Structures," Astbury states, " . . . if only for the sake of molecular biology, where perhaps more than anywhere else the great future of x-ray analysis lies."

When Astbury gave the Silvanus Thompson Memorial lecture at the British Institute of Radiology in 1948, in keeping with his descriptive talents, he referred to biological fibers as "molecular yarns," compared the keratin molecule to a "molecular spring," and pointed prophetically to molecular phylogeny.

The author is head of the Molecular Biology Section at the National Science Foundation, Washington, D.C. 20550.

The Molecular Concept in Biology

An indispensible condition for development of molecular biology was the recognition that biological structures are, indeed, organized on a molecular basis. While the molecular viewpoint may seem axiomatic to most of us, there was a long and difficult period of gestation for this concept. Chargaff, Edsall, Flory, and Pirie have discussed the historical development and vicissitudes of the molecular concept in biology in lucid detail, and each has illuminated some of the intellectual aberrations and technological limitations which delayed the development of a molecular approach (*11–14*).

Despite the fact that hemoglobin crystals were observed as early as 1840 and that by the year 1900 a large number of proteins could be prepared as crystals (*15, 16*), the mystique "protoplasm" prevailed into the third decade of this century. Crystallographic data on the hemoglobins of more than 100 species of mammals, amphibians, reptiles, birds, and fish appeared in a monograph by Reichert and Brown in 1909 (*16*). Crystals from plant seed globulins were reported (*17*) as early as 1850, and, in 1892, photomicrographs of crystalline globulins from Brazil nut, hempseed, flaxseed, oats, squash, and castor beans were published by Osborne (*17*). In 1889 ovalbumin was crystallized by Hofmeister and in 1894 serum albumin by Gürber (*18*).

The crystallization of proteins should have directed thinking to a molecule with a fixed and definite configuration. Crystallinity requires that a substantial fraction of component molecules must be fundamentally alike in size, composition, and configuration. Although it is now clear that molecules which organize in a lattice array have regular size and definite shape, its importance was overlooked by most biologists until the middle of the 20th century.

With crystals available it was natural to examine the spectroscopic properties of hemoglobin. The interests of Stokes in spectroscopy led to his discovery in 1864 of the changes in the absorption spectra of blood treated with a reducing agent (*19*). Stokes, a professor of mathematics at the University of Cambridge, also associated the red and purple forms of the pigment with arterial and venous blood and thereby established the function of hemoglobin. Sorby, a geologist, reported (*20*) in 1876 that both the absorption spectra and the stability to acid and alkali differed in hemoglobins from different sources, a fact for which an explicit explanation is still lacking.

One of the earliest workers to inquire into the physical state of intracellular constituents was Tswett (*21*). Tswett, a botanist by training, obviously was remarkably astute and competent in physical chemistry also. His monumental paper entitled "Adsorption Analysis and Chromatographic Methods: Application to the Chemistry of the Chlorophylls," a truly outstanding contribution to the scientific literature, has been translated into English by Strain and Sherma (*22*). In a prefatory paper these authors discuss Tswett's contributions to chemistry and, it goes without saying, to biochemistry and molecular biology (*22*). Synge has suggested that if Tswett's monograph on chromatography, published in Warsaw in 1910, had enjoyed wider circulation, it would undoubtedly have changed the whole course of biochemistry (*23*).

Molecular Weights

From an elementary analysis, Zinoffsky (*24*) obtained, in 1885, an empirical formula which gave a minimum molecular weight of 16,730 for horse hemoglobin. With the formulation of the Raoult and van't Hoff relations in 1887, methods became available for measuring molecular weights of substances in solution. Using the method of freezing-point depression, Brown and Morris reported 30,000 as the molecular weight of amylodextrin (*25*). In 1891 Sabanejeff and Alexandrow reported a molecular weight based on freezing-point depressions of 14,000 for ovalbumin (*26*). In 1900, employing osmotic pressure procedures, Rodewald and Kattein obtained a value of 40,000 for the molecular weight of starch (*27*). Reid in 1905, also using osmotic pressure methods, determined a molecular weight of 48,000 for hemoglobin (*28*).

With molecular weights of such magnitude, and the concept although not the term polymerization already advanced, it should have been realized that many biopolymers were indeed giant molecules. Hlasiwetz and Habermann (*29*) appear to have recognized the polymeric nature of proteins as early as 1871. Curtius seems to have been the first to suggest in 1883 a peptide linkage and the theoretical possibilities of linking amino acids in chains to form polypeptides (*30*).

Even before the existence of the peptide linkage in proteins had been clearly established by Fischer (*31*), there were efforts to polymerize natural amino acids. In 1871, Schaal had condensed asparagine and aspartic acid and obtained a mixture of several polymeric products (*32*). Schiff, in 1897, heated aspartic acid to 200°C and isolated, in addition to products reported by Schaal, an octaspartic acid (*33*). The preparation of polyglycine by heating glycine in glycerol described by Balbiano and Trasciatti (*34*) produced a water insoluble product which upon hydrolysis yielded glycine quantitatively. Fischer prepared, in 1907, a mixed octadecapeptide containing three leucine and fifteen glycine residues (*31*).

Although the precepts of structural chemistry clearly allowed the formation of large covalently linked molecules, there was great reluctance to accept the concept (*11–14*). Organic chemists either disliked the idea or were uninterested in molecules of such complexity. Physical chemistry, as a distinct field of chemistry, was in its incipient stages of development between the years 1880 and 1900 (*35*). In 1887, Wilhelm Ostwald at the age of 34 took the chair of physical chemistry at Leipzig, at that time the only chair of physical chemistry in the world. Supremely self-confident, he founded the *Zeitschrift für Physikalische Chemi* that same year and edited the *Zeitschrift* for several decades thereafter.

Wolfgang Ostwald, a son who was educated and spent his entire academic career at Leipzig, became Professor of Colloid Chemistry in the famous institute built and directed by his father. In 1907, Wolfgang Ostwald founded the *Kolloid Zeitschrift* and edited this journal until his death in 1943. Bancroft, an American who obtained his doctorate at Leipzig in 1892, founded the *Journal of Physical Chemistry* in 1896 and continued to edit this journal until 1932. Bancroft served as a professor at Cornell from 1895 until 1937.

Colloid chemistry, which began in 1861 when Graham (*36*) distinguished colloids from crystalloids in terms of diffusion behavior, provided ideas which pervaded the science of the period. At the turn of the century many of the best known colloids were hydrated oxides of metals, colloidal sulfur, and other substances which were also known to exist as small molecules. In

these reversibly dissociable systems, the colloidally dispersed phase is an aggregate of smaller units held together by secondary forces. Many chemists spoke of a "colloidal state of matter," and a belief developed that any substance, under appropriate conditions, could be converted to a "colloidal state." A logical extension of this view was the converse notion that all colloids were aggregated clusters of small molecules. Colloidal "solutions," whether proteins or iron oxide sols, were considered biphasic systems to which the solution laws of van't Hoff were thought inapplicable. As pointed out by Flory (*13*, p. 5) the concept of a colloidal state as a physical state of organization is inapplicable to the very substance for which the term colloid was chosen.

Wolfgang Ostwald and Bancroft were not only vigorous protagonists of the concept of a colloidal state of matter, but as editors of important journals they undoubtedly exerted considerable influence on editorial content of these journals as well as on patterns of thought of the period. Although a distinction between crystalline proteins and nonprotein aggregates of colloidal dimensions was perceived as early as 1892 by Picton and Linder (*37*), hemoglobin and the seed globulins, the only crystalline proteins known at the time, were thought to be unique in being crystallizable. The interval between 1890 and 1925 can be considered an obfuscated period for the molecular viewpoint in biology. A few perceptive and independent thinkers held the view, nevertheless, that proteins and other biopolymers were giant molecules of colloidal dimensions. Included in this group were Adair, Cohn, Henderson, Loeb, Osborn, van Slyke, and Svedberg.

Macromolecules

One of the conspicuously constructive contributions during this period was the work of Sörenson on ovalbumin (*38*). In 1917, Sörenson defined the *p*H scale, developed the means for measuring *p*H, and demonstrated the necessity of controlling *p*H, in addition to salt concentration and temperature, before solubility studies could be made reproducible. He also established that ovalbumin solutions were "true solutions," as judged by the applicability of Gibbs' phase rule, and carefully measured osmotic pressure relations from which he calculated a molecular weight of 34,000 for ovalbumin (*39*). The impact of Sörenson's work was delayed by World War I, and biochemists had considerable difficulty digesting his findings. Abderhalden, for example, suggested as late as 1924 that, based on their physical and chemical properties, proteins were association structures held together by partial valences (*40*). Another incisive contribution was the osmotic pressure study of Adair (*41*) which indicated a molecule of hemoglobin with four iron atoms and a weight of 67,000; also a severe blow to the "colloidal state" viewpoint.

Staudinger (*42*) beginning in 1920 proposed long-chain linear structures for rubber and polystyrene, persistently and persuasively advocated the molecular or primary valence viewpoint, introduced the term "macromolecule," and attributed the constitutive property of intrinsic viscosity to the size of the molecule. The slow death of the "association polymer" concept and the delayed triumph of the macromolecular viewpoint is indicated by the fact that the Nobel Prize in Chemistry was withheld from Staudinger until 1953, the year Flory published his classic monograph, "Principles of Polymer Chemistry" (*13*). It was unequivocally clear to Pauli (*43*) and Cohn (*44*) that globular proteins consisted of a mixed array of amino acids as repeating structural units assembled with covalent bonds into large molecules of definite size and shape. From 1925 on, the association viewpoint became increasingly untenable.

The theoretical foundations for the determination of molecular weights by ultracentrifugation were published in 1926 by Svedberg and Fähraeus (*45*) who showed that hemoglobin sedimented in a remarkably uniform fashion. Svedberg, although initially a believer in the "association complex" concept was soon converted to the molecular viewpoint (*45*). The ultracentrifuge provided biologists a new and remarkably incisive tool, the potentialities of which are even now not fully exploited. The ultracentrifuge was at the time the most powerful tool available for studying biopolymers. Nevertheless I heard one distinguished biochemist, while he was lecturing to graduate students in 1937, disclaim Svedberg and his centrifuge, and another equally distinguished biochemist during one of his lectures to graduate students berate the ultracentrifuge and all those foolish enough to believe this instrument had any relevance to biology.

The crystallization of an enzyme urease in 1926 by Sumner (*46*) was an additional blow to those who considered proteins to be association complexes. When Northrop crystallized pepsin in 1930 (*47*) it became generally accepted that enzymes were proteins, although this too was disputed for another decade.

Proteins Are Condensation Polymers

Carothers (*48*) was the first to recognize clearly the nature of the chemical structure of condensation polymers. He defined the term polymer (*48*) in modern context (*49*), formulated the theory of condensation polymerization, and indicated that linear polymers consisted of an array of recurring structural units. He stated that cellulose and proteins were probably high-molecular-weight condensation polymers. In the same paper, Carothers stated explicitly that the objective of his future research was to discover how the physical and chemical properties of high polymers of the condensation type are related to the nature of the structural units. It is clear that by 1931 organic chemists (*50*) recognized proteins as being linear mixed condensation polymers of high molecular weight. A monograph by Meyer and Mark (*51*) indicates that, by 1930, physical chemists also regarded many naturally occurring macromolecules as being linear polymers. The realization that the properties which distinguished polymers from other structures resulted from the number and the sequence of monomeric units was beginning to germinate by the middle of the 1930's. A long-chain covalently linked molecule endowed with a capacity to assume, through rotations about its valence bonds, a great many configurations also interested theoreticians, and attempts were made to explain viscosity and flow birefringence (*52*) as well as stretching, elasticity, and other properties (*53*) by means of a statistical treatment of a theoretical model.

Another early development of great significance to molecular biology was that of electrophoresis. Tiselius advanced moving boundary electrophoretic procedures to a level where the technique became a powerful tool both for the evaluation of fractionation steps and for characterization of proteins (*54*) as well as a sensitive criterion of homogeneity at a molecular level (*55*). Our understanding of homogeneity has

shifted over the years, and the concept of molecular homogeneity considered from a chemical, a physical, and a biological viewpoint has been discussed in greater detail (*11*, *12*, *14*).

With the introduction, in 1941, of paper chromatography by Martin and Synge (*56*), biochemists were offered a remarkably sensitive tool capable of incisive resolution. When exploited by Sanger and Tuppy (*57*), the technique helped unravel the first primary or topological structure of a protein molecule—that is, the sequence of the amino acid residues.

Structure in Three Dimensions

Almost immediately upon the discovery in 1912 by von Laue, Friedrich, and Knipping that x-rays can be diffracted by crystals, Sir William and Sir Lawrence Bragg established the basic features of x-ray crystallography and determined the structure of the main type of simple crystals, for example, rock salt, zinc blende, diamond, and fluorspar. The earliest diffraction pattern of a protein was the report of Herzog and Jancke (*58*) who examined hair. Within a decade the structure of the fibrous protein wool and of muscle were being pursued by Astbury, and the globular proteins and viruses by Bernal; both trained with the Braggs. Sir Arthur Eddington is said to have remarked, however, in 1927, that more was known about the interior of a star than about the interior of a table. Although chemical evidence for a linear polymeric structure in cellulose was available as early as 1913 (*59*), 13 years elapsed before, on the basis of x-ray diffraction evidence, a linear structure was proposed explicitly (*60*).

Bernal and Crowfoot measured the size of the unit cell of pepsin, in 1934, and established that protein crystals were composed of identical molecules (*61*). Astbury (*62*) introduced the notion of helical secondary structure soon after these early explorations of biopolymers. Huggins (*63*) and Mirsky and Pauling (*64*) surmised as early as 1936 the importance to protein structure of optimum hydrogen bonding between carbonyl and imide groups, and helical models were proposed, in 1943, by Huggins (*65*) and, in 1950, by Bragg and co-workers (*66*). These early helical models assumed an integral number of residues per turn. Bragg, Kendrew, and Perutz, for example, worked out all possible helical structures compatible with two-, three-, four-, and sixfold axes of symmetry. More exact information about interatomic distances and bond angles in amino acids and their derivatives revealed the limitations of earlier models and led Pauling, Corey, and Branson to propose, in 1951, the alpha or 3.7 residue helix (*67*).

A striking development in molecular biology was the discovery of hemoglobin S associated with sickle cell anemia (*68*). The observation of Ingram in 1958 (*69*) that the abnormality of this hemoglobin resulted from the exchange of a single amino acid exposed a fascinating facet of human genetics.

These early studies contributed significantly to our present understanding of conformational changes which can take place in proteins. It was learned that protein chains could exist in characteristically folded forms which extend into straighter forms upon stretching. The stretched forms are similar to the structures normally found in feather keratin and silk fibroin. A variety of evidence supports the viewpoint that the folded fiber in hair and wool are helices organized into fibrils. The significance of conformational changes in enzymic reactions, what are now called "allosteric effects," was suggested by Wyman and Allen (*70*) nearly 20 years ago. They stated, "It seems possible that, once the substrate is combined with the protein, whether or not through the medium of a prosthetic group, changes involving activation of the substrate may be induced in connection with favoring entropy changes involving widely extended structural alterations in the vast protein molecule. A protein, with its enormous complexity of possible configurations and corresponding richness of entropy effects, would on this basis be uniquely fitted to play the role of an enzyme."

The use of a heavy atom to determine relative phase angles for different x-ray reflections was first demonstrated in a somewhat special case by Robertson and Woodward (*71*). An extension to more general cases instigated a revolution in determining the structure of crystals of organic substances (*72*). Extremely complex structures can be elucidated by this method and the related isomorphous replacement technique. These developments laid the foundation for elucidating the complete structure of a crystalline protein. It was appropriate, therefore, that the first three-dimensional structural analysis of a protein was achieved in Britain by individuals trained in a tradition of x-ray diffractometry initiated 40 years earlier by the Braggs (*73*).

The Nucleic Acids

While our understanding of the structure and properties of proteins, rubber, and some polysaccharides advanced greatly, interest in nucleic acids was not widespread and progress was slow. Glass (*74*) has examined the circumstances which delayed progress in understanding the structure and function of nucleic acids. A nucleic acid–protein complex found in cell nuclei was associated with the physical basis of heredity by Wilson, Delage, Kölliker, and Sachs as early as the last decade of the 19th century (*74*). Despite promising beginnings the concept of nucleic acids as information carrying macromolecules aborted early in the 20th century. The tetranucleotide hypothesis of Levene prevailed until Chargaff showed that the proportions of purines and pyrimidines excluded a tetranucleotide structure (*75*). Those familiar with the tremendous viscosity and other physical properties associated with carefully prepared deoxyribonucleic acid (DNA) samples could not, however, accept the tetranucleotide as a unit molecule.

Since the historical origins of the informationist approach have been discussed by Stent (*6*), there is no need to repeat this aspect of molecular biology. As Stent indicated, an early phase of development was the quest for the physical basis of the game. A remarkable advance in this quest came in 1944 when Avery, MacCleod, and McCarty (*76*), reported that DNA directed genetic properties and suggested that DNA might provide the chemical and physical basis of heredity. The findings of Avery and his associates, although not immediately accepted, dispelled forever the earlier notions that proteins carried the genetic information (*11*, *14*). It was not until 1952, however, when Hershey and Chase (*77*) demonstrated that phage DNA enters the bacterium carrying the genetic information that nearly all dissident voices were silenced.

Northrop has suggested (*78*) that if the transforming principle had been discovered and isolated before the dis-

covery of viruses, the latter would have been classified with the transforming principle and earlier controversies surrounding the nature of viruses would not have arisen. Avery's failure to be awarded the Nobel Prize was an unfortunate oversight, as Tiselius has conceded (*79*). The discovery of the biological activity of DNA and its recognition as the physical basis of the gene stimulated enormous interest in the nucleic acids. The ingenious interpretation by Watson and Crick (*80*) of Wilkins' x-ray data (*81*) provided a remarkably fruitful model for a multitude of projected experiments.

An article written nearly 100 years ago suggests that germinal ideas often lie buried for many years awaiting experimental techniques. "The chemical differences of various species and genera of animals and plants are certainly as significant for deciphering their origins as the differences of form. If we could define clearly the differences in molecular constitution and functioning of different kinds of organisms, we should be able to perceive the evolutionary patterns of development more readily than from morphological considerations" (*82*). Here, perhaps, was the first flicker of biochemical systematics or molecular phylogeny as Astbury described it, a facet of biology already developing rapidly.

Now that it is possible to make proteins and nucleic acids which either never existed or which in the course of evolutionary development long since disappeared, molecules with odd permutations, with new and exotic monomeric units, polymers designed to perform tasks beyond the capabilities of the naturally occurring biopolymers, the future of molecular biology may be more spectacular than its present and its past.

Summary

The term molecular biology originated some time before 1945 in the fertile mind of Astbury, Professor of Biomolecular Structure at the University of Leeds. As conceived by Astbury the salient feature of this approach to understanding living systems was "searching below large scale manifestations of classical biology for the corresponding molecular plan."

An indispensible condition for the development of molecular biology was the recognition that biological structures are organized on a molecular basis. Although proteins were crystallized as early as 1840 and by the year 1900 a large number of proteins had been prepared in crystalline form, the structural implications of the phenomenon were not fully appreciated until 50 years later. The concept of proteins as linear arrays of mixed monomeric units held together by covalent linkages was already dimly perceived prior to the year 1900. Until about 1925, however, the notion that proteins were "association complexes held together by secondary forces" was more popular. After a long vicissitudinous period the view that proteins were macromolecules consisting of long chains of amino acids held together by covalent bonds gained ascendency. As pointed out by Flory, the concept of a colloidal state as a physical state of organization is inapplicable to the very substances for which the term colloid was chosen.

The analytical ultracentrifuge, moving boundary electrophoresis, chromatography, and x-ray diffractometry, developed during the second, third, and fourth decades of the century, provided important tools for studying macromolecules. The ideas of primary, secondary, and tertiary levels of structure were soon followed by the elucidation of the primary structure of insulin and the complete three-dimensional structure of myoglobin.

The quest for the physical basis of the gene ended with the discovery that the "transforming factor" was also a mixed polymer of macromolecular dimensions called thymus nucleic acid, now more popularly known as DNA. The ingenious interpretation by Watson and Crick of Wilkins' x-ray data provided a remarkably fruitful model for a multitude of experiments which elucidated the function of DNA.

References and Notes

1. E. Chargaff, *Essays on Nucleic Acids* (Elsevier, New York, 1963), p. 176.
2. C. Grobstein, *Amer. Zool.* **6**, 621 (1966).
3. C. F. Waddington, *Nature* **190**, 184 (1961).
4. T. S. Kuhn, *The Structure of Scientific Revolutions* (Univ. of Chicago Press, Chicago, 1962), p. 43.
5. J. Cairns, G. S. Stent, J. D. Watson, *Phage and the Origins of Molecular Biology* (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1966); J. C. Kendrew, *Sci. Amer.* **216**, 141 (1967).
6. G. S. Stent, *Science* **160**, 390 (1968).
7. J. D. Bernal, *Biogr. Mem. Fellows Roy. Soc.* **9**, 29 (1963).
8. W. T. Astbury, *Adventures in Molecular Biology* (Thomas, Springfield, Ill., 1952), p. 3; *Nature* **190**, 1124 (1961).
9. J. D. Edsall, personal communication.
10. W. T. Astbury, *Nature* **157**, 121 (1946).
11. E. Chargaff, *Progr. Nucl. Acid Res. Mol. Biol.* **8**, 304 (1968).
12. J. T. Edsall, *Arch. Biochem. Biophys.*, Suppl. 1, 12 (1962).
13. P. J. Flory, *Principles of Polymer Chemistry* (Cornell Univ. Press. Ithaca, N.Y., 1953), chap. 1.
14. N. W. Pirie, *Arch. Biochem. Biophys.*, Suppl. 1, 21 (1962).
15. F. N. Schulz, *Die Kristallisation von Eiweisstoffen und ihre Bedeutung für die Eiweisschemie* (Gustav Fisher, Jena, 1901).
16. E. T. Reichert and A. P. Brown, *The Crystallography of the Hemoglobins* (Carnegie Institution of Washington, Washington, D.C., 1909), publ. No. 116.
17. T. B. Osborne, *The Vegetable Proteins* (Longmans, Green, London, ed. 2, 1924); *Amer. Chem. J.* **14**, 662 (1892).
18. F. Hofmeister, *Z. Physiol. Chem.* **16**, 187 (1889); A. Gürber, *Sitzber. Physik. Med. Ges. Wurzburg* (1894), p. 143.
19. G. G. Stokes, *Proc. Royal Soc.* **13**, 355 (1864).
20. H. C. Sorby, *Quart. J. Microscop. Sci.* (new series) **16**, 76 (1876).
21. M. Tswett, *Ber. Deut. Botan. Ges.* **24**, 384 (1906).
22. H. H. Strain and J. Sherma, *J. Chem. Ed.* **44**, 235, 238 (1967).
23. R. L. M. Synge, *Arch. Biochem. Biophys.*, Suppl. 1, 1 (1962).
24. O. Zinoffsky, *Z. Physiol. Chem.* **10**, 16 (1885).
25. H. T. Brown and G. H. Morris, *J. Chem. Soc.* **53**, 610 (1888).
26. A. Sabanejeff and N. Alexandrow, *Russ. J. Phys. Chem.* **1**, 7 (1891).
27. H. Rodewald and H. Kattein, *Z. Physik. Chem.* **33**, 579 (1900).
28. E. W. Reid, *J. Physiol.* **33**, 12 (1905).
29. H. Hlasiwetz and J. Habermann, *Ann. Chem. Pharmacol.* **159**, 304 (1871).
30. T. Curtius, *Chem. Ber.* **16**, 753 (1883).
31. E. Fischer, *ibid.* **35**, 1095 (1902); *ibid.* **36**, 2094 (1903); *ibid.* **40**, 1754 (1907).
32. E. Schaal, *Ann. Chem.* **157**, 26 (1871).
33. H. Schiff, *Chem. Ber.* **30**, 2449 (1897).
34. L. Balbiano and D. Trasciatti, *ibid.* **33**, 2323 (1900).
35. W. Jost, *Annu. Rev. Phys. Chem.* **17**, 1 (1966).
36. T. Graham, *Phil. Trans. Roy. Soc. (London) Ser. A* **151**, 183 (1861).
37. H. Picton and S. E. Linder, *J. Chem. Soc.* **61**, 148 (1892).
38. S. P. L. Sörensen, *Compt. Rend. Trav. Lab. Carlsberg* **12**, whole issue (1917).
39. Prof. J. W. Williams has informed me that Sörensen's data later were recalculated by Linderström-Lang. Using more exact thermodynamic relations and correcting for nonideality, Linderström-Lang obtained a quite accurate value of 40.000 for the molecular weight. Williams stated that although he has never seen these calculations in print he was informed of the results by Lang.
40. E. Abderhalden, *Naturwissenschaften* **12**, 716 (1924).
41. G. S. Adair, *Proc. Roy. Soc. London* **A109**, 292 (1925).
42. H. Staudinger, *Chem. Ber.* **53**, 1073 (1920); *ibid.* **57**, 1203 (1924).
43. W. Pauli, *Colloid Chemistry of the Proteins* (Churchill, London, 1922).
44. E. J. Cohn, *Physiol. Rev.* **5**, 349 (1925).
45. T. Svedberg and R. Fähraeus, *J. Amer. Chem. Soc.* **48**, 430 (1926); T. Svedberg, *Kolloid-Z.* **51**, 10 (1930); T. Svedberg and K. Pedersen, *The Ultracentrifuge* (Clarendon, Oxford, 1940), pp. 354, 372, 414.
46. J. B. Sumner, *J. Biol. Chem.* **69**, 435 (1926).
47. J. H. Northrop, *J. Gen. Physiol.* **13**, 739, 767 (1930).
48. W. H. Carothers, *J. Amer. Chem. Soc.* **51**, 2548 (1929).
49. The term polymer was introduced by J. J. Berzelius [*Jahresber.* **12**, 63 (1833)] in 1833 to distinguish compounds with the same elementary composition which differ in molecular weight. Berzelius evidently considered polymerism as a special kind of isomerism.
50. W. H. Carothers, *Chem. Rev.* **8**, 353 (1931).
51. K. Meyer and H. Mark, *Der Aufbau der Hochpolymeren Organischen Natierstoffe* (Akademische Verlags Gesellschaft, Leipzig, 1930).
52. W. Kuhn, *Kolloid-Z.* **68**, 2 (1934).
53. E. Guth and H. Mark, *Monatsh. Chem.* **65**, 93 (1934).
54. A. Tiselius, *Biochem. J.* **31**, 313, 1464 (1937).

55. E. L. Hess, *Science* **113**, 709 (1951).
56. A. J. P. Martin and R. L. M. Synge, *Biochem. J.* **35**, 1358 (1941).
57. F. Sanger and H. Tuppy, *ibid.* **49**, 463, 481 (1951).
58. R. O. Herzog and W. Jancke, *Chem. Ber.* **53**, 2152 (1920).
59. R. Willstatter and L. Zechmeister, *ibid.* **46**, 2401 (1913).
60. O. L. Sponsler, *J. Gen. Physiol.* **9**, 677 (1926).
61. J. D. Bernal and D. Crowfoot, *Nature* **133**, 794 (1934).
62. W. T. Astbury, *J. Chem. Soc. (London)* **1942**, 337 (1942).
63. M. L. Huggins, *J. Org. Chem.* **1**, 407 (1936).
→ A. E. Mirsky and L. Pauling, *Proc. Nat. Acad. Sci. U.S.* **22**, 439 (1936).
65. M. L. Huggins, *Chem. Rev.* **32**, 195 (1943).
66. W. L. Bragg, J. C. Kendrew, M. F. Perutz, *Proc. Roy. Soc. (London)* **A203**, 321 (1950).
→ L. Pauling, R. B. Corey, H. R. Branson, *Proc. Nat. Acad. Sci. U.S.* **37**, 205 (1951).
68. L. Pauling, H. A. Itano, S. J. Singer, I. C. Wells, *Science* **110**, 543 (1949).
69. V. M. Ingram, *Biochim. Biophys. Acta* **28**, 539 (1958).
70. J. Wyman and D. W. Allen, *J. Polymer Sci.* **7**, 499 (1952).
71. J. M. Robertson and I. Woodward, *J. Chem. Soc. (London)* **1940**, 36 (1940).
72. C. H. Carlisle and D. Crowfoot, *Proc. Roy. Soc. (London)* **A184**, 64 (1945).
→ J. C. Kendrew, R. E. Dickerson, B. E. Strandberg, R. G. Hart, D. R. Davies, D. C. Phillips, V. C. Shore, *Nature* **185**, 422 (1960).
→ B. Glass, *Proc. Amer. Phil. Ass.* **109**, 227 (1965).
75. E. Chargaff, *Experientia* **6**, 201 (1950).
76. T. Avery, C. M. MacCleod, M. J. McCarty, *J. Exp. Med.* **79**, 137 (1944).
→ A. D. Hershey and M. Chase, *J. Gen. Physiol.* **36**, 39 (1952).
78. J. H. Northrop, *Arch. Biochem. Biophys.*, Suppl. 1, 7 (1962).
79. R. J. Litell, *Sci. Res.* (October 1967), p. 53.
80. J. D. Watson and F. H. C. Crick, *Cold Spring Harbor Symp. Quant. Biol.* **18**, 123 (195→ *Nature* **171**, 737, 964 (1953).
81. M. H. F. Wilkins, A. R. Stokes, H. R. Wilson, *Nature* **171**, 738 (1953).
82. R. Lankester, *Pflugers Arch. Ges. Physiol.* **4**, 318 (1871).
83. I acknowledge my indebtedness to E. Chargaff, J. Edsall, P. J. Flory, B. Glass, N. W. Pirie, J. H. Northrop, and R. L. M. Synge, who have illuminated and brilliantly developed various aspects of this topic. References to their work have been cited. I thank J. W. Williams for having made available to me a nearly complete set of reprints of the publications of W. Astbury. In particular I thank Professors Edsall and Williams for generous and helpful comments and suggestions which not only eliminated errors but clarified and improved portions of the text. I accept full responsibility, however, for all errors, ambiguities, and aberrations which remain.

Language, Name, and Concept

Language expresses a human mode of analyzing experience into conceptual units and the rules that link them.

J. Bronowski and Ursula Bellugi

The experiment of teaching a young chimpanzee to use American sign language (*1*) is an important advance on previous attempts to test the linguistic potential of primates. For the first time, a primate's capacity for a language used by some humans has been clearly separated from his capacity for making the sounds of human speech. In the nature of things, this pioneer study has been made under special conditions, and (like any single study) cannot be assumed to be perfectly representative. Nevertheless, it does offer evidence of a new kind, in the light of which it is timely to reexamine the relation between human language and the signals that animals use or can learn to use.

Chimpanzee and Child

It has never been in doubt since the time of Aristotle that language is a characteristically human accomplishment, and that some of the capacities which it demands are either absent in other animals or are present only in the most rudimentary form. Among these is the fundamental capacity to make and interpret the intricately modulated continuum of speech sounds. Lieberman *et al.* (*2*) have stressed the differences between the articulatory apparatus of the chimpanzee and that of man. Thus the Gardners' decision to bypass the articulatory problems of the chimpanzee and undertake instead to teach a gesture language was a good one. They reasoned that the use of the hands is a prominent feature in the behavior of chimpanzees, who have a rich repertoire of gestures both in the wild and in captivity. By contrast, the futile efforts to teach the chimpanzee Viki to talk (*3*) had already shown that a vocal language is not appropriate for this species. In 6 years of intensive training, Viki had learned to make only four sounds that grossly approximated English words. The results of the Gardners' efforts with Washoe are spectacular by comparison. By the time Washoe was about 4 years old she had been taught to make reliably more than 80 different signs. This comparative success therefore poses a question of substance: What is the true nature of the language performance that has been achieved by a chimpanzee (under these special conditions of training and environment) and how does it differ from that of humans?

We first describe some of the characteristics of the gesture language which Washoe was taught. The Gardners had learned sign language from dictionaries and from a teacher of sign, expressly for their experiment. They used gestures and manual configurations to represent the concepts in sign language and avoided the use of finger spelling as much as possible. All signs are arbitrary to some degree (although some have iconic origins and aspects), and American sign language has many highly arbitrary and conventionalized signs which must be learned. With the addition of finger spelling, it can be used by a literate signer as a direct translation of English in order to communicate with hearing signers; but it generally is not so used among the deaf themselves, whose rules of use may vary in different areas and may not necessarily derive from English. However, the Gardners state that, as far as they can judge, there is no message which cannot be rendered faithfully in translating from English to sign (apart from the usual problems of translating from one language into another). They also report that they tried to follow the word order of English in their signed sequences.

It might be held that ideally Washoe's progress should be compared

The authors are affiliated with the Salk Institute for Biological Studies, San Diego, California 92112.