Human perception of orientation and symmetry depends on mental transformation analogous to actual motor exploration of different aspects of the thing perceived. We gain a stronger sense of bisymmetry or balance by centering and aligning the axis of symmetry of a pattern, motorically or mentally, with an internal mental axis of uprightness, one that represents the gravitational axis about which the body must normally be balanced.

Cerebral asymmetry has evolved in humans in relation to a unique development of cooperative intelligence and communication. The main factor at the outset seems to have been a bias to choose one hand for gestures of communication, and this has led to a one-sided control for speech and for sequencing in all signal movements. Subhumans seem not to have developed a consistent handedness. Asymmetries recently found in the anatomy and behavior of apes seem to fit the hypothesis that, in evolution, watching to see what another is doing or expressing created the need for a consistent or near-consistent sidedness.

When social factors favoring right-handedness are accounted for, 90 percent of humans, even as newborns, appear to be inherently right-handed. This correlates with unilateral anatomical features of the cerebrum that emerge in the fetus. Cortical organs are, in turn, directly involved in speech, understanding of speech sounds, and ability to read and write. But all these intelligent skills elaborate after birth, becoming deeply molded by experience, and all express discoveries and inventions of culture.

In this book, data from human clinical studies on the lateralization of functions in the brain and the spate of recent research on asymmetry of perceptions and movements with normal subjects are given disappointingly superficial treatment. The authors add little that is original on these matters.

They review well the development of a sense of left and right in children and the peculiar inherent failure of lateralization of mental functions as well as right-handedness in some 2.5 percent who do not learn to read or write at the normal rate. Children under 5 seem, in psychological tests, like animals, having at most a vague sense of left and right. Corballis and Beale propose that the development of a left-right sense is due to growth of an asymmetry in the brain. They present a not-fully-worked-out idea that homotopic nerve connections between the hemispheres cause left-right reflection of images at the level of memory, beyond the immediate "here and now" of the percept and remote from the primary sensory regions of the cortex. Unfortunately, the interhemispheric conduction theory for mirror confusion, though plausible if one accepts that the higher mental functions are laid down in somatotopic (body-shaped) arrays, has no direct evidence. We must wait on anatomical research to see if this form of the notion is correct.

Most children 5 to 10 years of age thrive under formal school instruction and gradually become irreversibly left-brained for skilled use of words. Before that, their right brains have a limited potentiality to take over the same skills, and afterward the adaptability is lost. The whole conventional plan of Western education comes into collision with many left-handers and is especially hard on the unlateralized dyslexics. Man's native brain is clearly not prepared for total regimentation by society.

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Personal Recollections

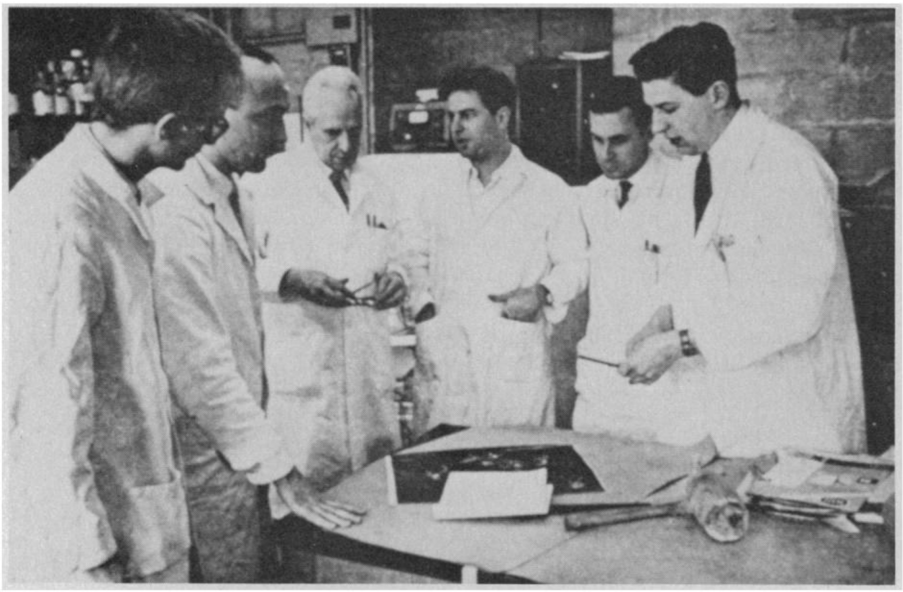
Reflections on Biochemistry. In Honour of Severo Ochoa. Papers from a symposium, Barcelona and Madrid, Sept. 1975. A. KORNBERG, B. L. HORECKER, L. CORNUDELLA, and J. ORÓ, Eds. Pergamon, New York, 1976. x, 466 pp., illus. Cloth, $25; paper, $9.50.

The incredibly fast advance in many areas of biochemistry makes for equally rapid obsolescence of previous findings. Even the basic observation on which a new advance is based is rapidly forgotten because it has become common knowledge. What may be irretrievably lost in this natural course of events is really something else. It is the passion, the art, the very flavor which characterizes a particular scientific period that quickly sinks into oblivion together with the men and women who were the participants.

So Carl Cori writes near the beginning of this volume, which is indeed an endeavor, by a group of notable biochemists, to recapture some of the personal aspects of past achievements and to pay tribute to one of the major biochemists of our time.

Severo Ochoa's career spans nearly half a century and continues actively today. As pupil, colleague, director of research, and friend, he has been closely associated with a large proportion of the major contributors to biochemistry in the era of its most rapid growth. The symposium from which this book arises was held in honor of his 70th birthday. The central themes concern enzymatic mechanisms in biosynthesis and cell function. The contributors were asked to prepare not papers of the sort commonly found in journals but reflections on the development of a subject, a concept, or an approach to biochemistry. Most of the authors consider the development of one or more of their own researches, tracing origins of the work, significant influences not yet recorded in print, as well as errors and misleading clues, and the working out of conclusions. The subjects include much of the most important biochemical research of the last 40 years. Styles naturally differ greatly from one biochemist to another, and some papers are concerned with more personal recollections or with reflections on science in our time. Personal characteristics of the authors and differences in approach to difficult problems emerge more clearly than they generally do in formal research reports. Thus there is much that will be valuable to the historian of science, who will, however, be watchful for distortions and omissions in recollections of past activities set down many years thereafter. I return to this point later.

Ochoa's career, outlined in the opening article by F. Grande and C. Asensio, has indeed covered an extraordinary portion of the range of biochemical research. Born in 1905 in the northern Spanish province of Asturias, he published his first paper from the physiology department of the University of Madrid in 1929. The head of the department was Juan Negrin, who was later to become president of the Spanish Republic at the height of the civil war. From 1929, for two years, Ochoa worked in Otto Meyerhof's Institute of Physiology in Heidelberg. As he said later: "Meyerhof was the teacher who most contributed toward my formation, and the most influential in directing my life's work." Meyerhof's concern as an experimentalist was with the biochem-



"The RNA synthetase research team at New York University (1964). From left to right: Piet Borst, Ted Abbot, Severo Ochoa, Charles Weissman, Martin Billeter, and Roy Burdon. On the table: the wooden mallet used in the first step of synthetase purification and the scheme of phage RNA replication." [From *Reflections on Biochemistry*]

istry of muscle and the interconversion of chemical and mechanical energy and with the mechanism of fermentation in yeast and other organisms, which involved many of the same underlying processes that were found in muscle. He was one of the few early biochemists who were well grounded in thermodynamics and were aware of the distinction between the free energy yield of a chemical process and the heat of reaction. He had a philosophic breadth of outlook on the problems of biology, and his laboratory was one of the three or four greatest centers of biochemical research in the world. Ochoa worked there on muscle biochemistry and continued such research on his return to Madrid in 1931.

The outbreak of civil war in 1936, however, ended all hope of continuing scientific research in Spain. Ochoa, with his wife, Carmen, returned to Heidelberg to resume work in Meyerhof's laboratory, then moved to England and joined the department at Oxford headed by Rudolph Peters. Here he made a major contribution to the resolution of a central problem of bioenergetics, the coupling of oxidation with phosphorylation and the formation of adenosine triphosphate, the major reservoir of free energy for biochemical processes. This phenomenon had just been observed independently by H. M. Kalckar in Denmark and V. A. Belitser in the Soviet Union; Ochoa first established evidence concerning the number of phosphate bonds formed per atom of oxygen consumed.

The outbreak of war in Europe in 1939 led the Ochoas to migrate again, this time across the Atlantic to the laboratory of Carl and Gerty Cori in St. Louis, which was then in the midst of major researches on glycolysis and phosphorylation, and the isolation of the enzyme phosphorylase in pure form. In the latter achievement the protein chemist Arda A. Green, recently arrived from Harvard Medical School, played a major role, together with the Coris. In the preceding 15 years, J. B. Sumner and J. H. Northrop had prepared the first pure crystallized enzymes, and the validity of their work had been gradually accepted in the face of much disbelief. Otto Warburg and Hugo Theorell, in Berlin and Stockholm, had prepared pure enzymes with associated coenzymes that were involved in biological oxidations. With the preparation of purified phosphorylase, the study of enzymes involved in intermediary metabolism entered a new phase; this was an important influence in Ochoa's subsequent career, in which he was deeply involved in isolating and characterizing enzymes.

In 1945 he came to New York University, his home for the next 30 years, and became professor in the department of pharmacology and later in the department of biochemistry. Here he and his collaborators worked out many aspects of the Krebs tricarboxylic acid cycle, purifying the enzymes involved and determining their mechanisms of action. In the study of fatty acids his outstanding achievement was the elucidation of the metabolism of propionic acid by reactions involving coenzyme A, biotin, and vitamin B_{12} coenzymes, and connecting propionic with succinic acid, a component of the tricarboxylic acid cycle.

A new turning point came with his discovery, with Marianne Grunberg-Manago, of polynucleotide phosphorylase from *Azotobacter vinelandii*, an enzyme whose biological function is still uncertain but which is capable of making polynucleotides in random sequence from almost any mixture of nucleoside diphosphates. Despite its uncertain biological role, it proved a powerful tool in the next development—the use of these polynucleotides for the elucidation of the genetic code. The concept that a code must exist for translating nucleotide sequences in nucleic acids into amino acid residue sequences in proteins had of course been compellingly advanced by Francis Crick and others; the first clear-cut experimental evidence came from Marshall Nirenberg at the National Institutes of Health, just as the work in Ochoa's laboratory was beginning to achieve similar results. For several years there was a competitive race between the two laboratories, as the code for all the 20 amino acids of proteins gradually emerged. The most decisive evidence of all came from the laboratory of H. G. Khorana, at the University of Wisconsin and later at M.I.T., who prepared polynucleotides of completely defined sequences by a combination of classical organic chemistry and skillful use of enzymatic synthesis of polynucleotides. In this volume Khorana tells of this work, and of his more recent remarkable synthesis of a gene that directs the synthesis of tyrosine transfer RNA of *Escherichia coli*.

More recently the focus of work in Ochoa's laboratory has been on the replication of RNA bacterial viruses and on the mechanism of protein biosynthesis, including the isolation of three proteins essential for initiating the formation of the peptide chain. The complexity of these researches is beyond any comment that can be offered here; there are some excellent accounts of aspects of these subjects in several papers in the latter part of this volume.

Ochoa's research career, from the early studies on metabolism in muscle to the recent work on protein biosynthesis and the genetic code, spans an era of extraordinary development in scientific outlook. The questions with which his recent work has been concerned could not have been asked, could not even have been conceived, at the time he began his work. The transformation, one of the most far-reaching in the history of biology, has changed genes from postulated entities of unknown nature to definite chemical structures. It has established the nature of the directed programs that specify the exact order of the nucleotides in nucleic acids and of the amino acid residues in proteins, subject to occasional mutations and to very rare random errors in replication; and it has revealed subtle and powerfully effective regulatory mechanisms that control the production of enzymes when they are needed and turn on and off the flow of production of metabolites. These advances are associated with such names as Beadle, Tatum, Delbrück, Luria, Pauling, Avery, Watson, Crick, Wyman, Monod, Jacob, Pardee, Sanger, Stein, Moore, Perutz, and Kendrew. Most of them are not mentioned in *Reflections on Biochemistry*, or are mentioned only incidentally; there is so much to be told that inclusion of all this background would be impossible. There is of course much discussion of certain aspects of biochemical regulation—some of the contributors, such as E. R. Stadtman, have been leaders in this field—and Charles Yanofsky gives an excellent account of his brilliant researches into the relation between a gene and the enzyme whose structure the gene determines.

There are some 46 papers here by colleagues and present and former collaborators of Ochoa. Amid their great diversity one can mention only a few. The paper by Carl Cori, already quoted at the beginning of this review, stands apart from the others as a study of developments over nearly two centuries in the study of lactic acid, from Scheele, Berzelius, and Liebig up to the beginning of the modern era. It supplies a valuable historical perspective.

H. M. Kalckar, one of the discoverers of oxidative phosphorylation, supplies some of the early background that led to that discovery; and E. C. Slater reflects on the past, present, and future of bioenergetics and the future of energy supply for mankind. Efraim Racker, describing his "pathway from psychiatry to cancer," tells of his personal relation with Ochoa and of the interaction between them in thinking and experiment, revealing much that could not have been found from published papers. M. Losada gives a very lucid discussion of photosynthesis.

H. A. Barker tells of the origins of a major discovery, that of the coenzymes related to vitamin B_{12}, which eventually emerged from some surprising findings he made in A. J. Kluyver's laboratory in 1936 concerning the fermentation of glutamate by certain clostridia. This problem was put aside for many years before it was again taken up and eventually solved. This is an important piece of biochemical history that might never have been pieced together if Barker had not set it down here. Stadtman, in another paper, notes Barker's remarkable insight in formulating a theory of fatty acid oxidation from the data available in 1951—a scheme that later proved correct in nearly every detail but has not received adequate recognition by later workers.

H. L. Kornberg gives an illuminating account of the origins of the "glyoxylate cycle," which he discovered and which forms a means of bypassing some of the steps in the Krebs tricarboxylic acid cycle and supplying some essential precursors for cellular biosynthesis. He brings out well the difficulties and confusion that preceded ultimate clarification; the story should be valuable to historians, as well as scientists, as conveying an impression of how a research actually progresses.

Fritz Lipmann and Konrad Bloch, in separate articles, reflect on the nature of the evolutionary transition from prokaryotes—the bacteria and blue-green algae—to the eukaryotic higher organisms. Bloch's thoughts arise from his work on the biosynthesis of sterols, which are ubiquitous in eukaryotes but are found in prokaryotes only in extremely rare instances. Consideration of the pathways of biosynthesis and the stereochemistry of the intermediates provides some clues to this puzzling problem in biochemical evolution, which has received too little attention by those concerned with evolution.

The origin of the Pasteur effect—the decreased consumption of carbohydrate by cells in the presence of oxygen—has been a matter of debate for half a century. Dozens of proposals have been advanced. Alberto Sols here presents an interpretation in terms of a sequential series of feedback mechanisms, subject to allosteric control. Other researchers may still debate his views, but they will have to take account of the evidence he adduces.

Arthur Kornberg considers his varied experience with enzymes and outlines a long-range proposal for reconstituting a successful viral infection in a molecularly defined cell-free system. His faith, from past experience, leads him to believe in the almost unlimited possibilities of what one can do with enzyme systems. Paul Berg looks at the past achievements and the future prospects of genetic manipulation, that storm-tossed subject, for which—having duly warned of the scientist's responsibility for preventing possible biohazards—he predicts a probably glorious future.

C. Weissman tells, in lively fashion, of his adventures with MS2 phage in Ochoa's laboratory; and E. Viñuela and M. Salas give a very good account of another phage, $\phi 29$, that they have investigated in Madrid.

The six contributors who deal with protein biosynthesis all present interesting material; P. C. Zamecnik and also M. Nomura provide material of both historical and current interest about the development of their pioneer researches; H. G. Wittman writes on ribosomes and H. Weissbach on peptide chain elongation, both about as lucidly as is possible with these complicated subjects. In the following section, on cell biology and neurobiology, S. Udenfriend's account of his work on collagen and fibrosis was of particular interest to this reviewer.

In the final section, along with personal recollections of Ochoa by E. Chain and D. Nachmansohn, L. Leloir reflects on the nature of discovery; unfortunately he quotes the account by Sir Richard Gregory (1923) of Galileo's alleged experiment in dropping different weights from the leaning tower of Pisa. Modern historians of science all agree that there is no evidence whatever that Galileo ever performed such an experiment. J. Oró writes interestingly on prebiological chemistry and the origin of life. H. A. Krebs considers the factors that promote, and those that obstruct, continued scientific productivity of the sort strikingly exemplified by Ochoa—and, one may add, by Krebs himself. The book ends with a tribute to Ochoa by Salvador Dali, whose striking cover picture decorates the book.

Recollections of past events can be deceptive, as has been well shown by recent studies of some of Claude Bernard's greatest discoveries by M. D. Grmek and by F. L. Holmes. The direct record in Bernard's notebooks shows a much more complex and irregular pattern of research than Bernard recalled many years later in writing his *Introduction to the Study of Experimental Medicine*. Such facts serve as warning to the historian that he must reconstruct past events, so far as possible, from the evidence provided by the participants at the time and should use later recollections with due caution. Nevertheless, recollections of the sort recorded here can illuminate much that would otherwise be forgotten or unknown and provide much absorbing reading for those who are interested in understanding scientists and the ways in which they work, think, and sometimes dream.

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