PERSPECTIVES AND HORIZONS IN **Microbiology**

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A SYMPOSIUM EDITED BY

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The addresses of Lewis Webster Jones, Selman A. Waksman, and Albert J. Kluyver, which appear in the Appendix of this book, were first published in the December 1954 issue of The Scientific Monthly. *They are reprinted here by the kind permission of the publishers.*

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Preface

Microbiology has made great strides in the last eight or nine decades. Beginning with studies of microorganisms as causative agents of disease and fermentation, their occurrence in soil and other natural substrates, and life cycles of certain groups of bacteria and fungi, microbiology has grown into a broad science with numerous theoretical and practical applications. This is true of ecology and taxonomy of microorganisms, physiology and biochemistry, genetics and cytology, and applications to virtually every aspect of human endeavor.

This symposium, arranged in connection with the dedication on June 7, 1954, of the Institute of Microbiology, Rutgers University, presents an attempt to analyze the present and possibly some of the future aspects of micro biology. Who would have thought, in the days of Pasteur and Koch, of such problems as "metabolic models" and "metabolic pathways," of "vitamins" and "antibiotics," of "genetics of microorganisms" and "biochemical mutations," of "viruses," and of "steroid transformations," let alone such specialized subjects as "metapoietic integrations"? By presenting a broad outline of these and other phases of microbiology, this symposium on the *Perspectives and Horizons in Microbiology* deals with the many-sided aspects of a science devoted to the study of the microscopic forms of life and their relation to mankind.

The numerous applications of the activities of microorganisms have, for the most part, been omitted from this symposium. They are definitely suggested, however, in their relation to human and animal health, in the problems dealing with viruses and immunological reactions, in the discussion of soil processes and plant growth, and in the outline of nitrogen-fixation and the effects of microbes on plant life. The inclusion of a chapter on antibiotics tends to give emphasis to a new field of microbiology that has made great progress during the last fifteen years. The problems of disease control are suggested in the extensive applications of this advancing science.

Because of their historical interest, three general addresses delivered at the dedication of the Institute are included as an appendix.

It is the sincere hope of those who organized this symposium that it will serve as a milestone in the history of a science that deals with the smallest of living things and with their importance in the cycle of life in nature and especially in the life of man.

SELMAN A. WAKSMAN

September 1, 1954
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THE MICROBE AS A LIVING SYSTEM

Chapter 1

The Microbe as a Whole

By CORNELIS B. VAN NIEL

Until recently, microbiology was the special field of only a few individuals working in comparative isolation. This small minority regretted the tendency to equate microbiology with the study of problems in disease and public health, which commanded attention once the role of microorganisms in food spoilage and as causative agents of many plant and animal diseases had been established. These men were probably no less impressed by the great advances made in the prevention, control, and treatment of disease than were the many who had become medical microbiologists. But they realized that microbes possess a wider range of physiological and biochemical potentialities than do all other organisms combined. Microbes represent forms of life that can persist in nature because the organisms fill particular ecological niches, permitting them under special conditions to compete successfully with other living beings. Hence the few nonmedical microbiologists could envisage the unusual advantages that studies of the microbes as biological entities might offer for the attainment of a better understanding of the fundamental aspects of life. Occasionally they could reiterate their hope that some day the neglected opportunities would attract others to the larger field; meanwhile they continued their work, assured by a long-range point of view and by the fascination of the subject itself.

But during the last fifteen years a marked change has taken place. The number of publications concerned with microorganisms from other than medical points of view has increased enormously, and several new journals have been started to accommodate the swollen current of reports dealing with biochemical studies in which microbes have played a part. One of the chief reasons for this development has been the influence exerted by A. J. Kluyver's masterly synthesis of the information on the vast diversity of metabolic processes carried out by the numerous types of microorganisms. This synthesis revealed that all biochemical events can be interpreted as composites of more or less extended series of step reactions, each step chemically intelligible and representing a special case of simple electron transfer between two different molecules, mediated by a specific enzyme. Depending upon the nature of the participating reactants, this leads to the transfer of atoms or larger units from one molecule to another, as in transhydrogenations, transphosphorylations, transaminations, transmethylations, transacetylations, and transglucosidations.

While emphasizing the fundamental unity in the biochemical behavior of all living beings, Kluyver's contributions also drew attention to the existence among microorganisms of extreme cases of biochemical specialization and of processes that may be characterized as grossly exaggerated examples of phenomena that are encountered elsewhere as quantitatively minor side reactions. That organisms which display such properties are significant for more detailed investigations on the particular reaction mechanisms involved was clearly appreciated.

This concept gave rise to that of "comparative biochemistry," and so broadened the range of useful potentialities of microbes for biochemical studies that it is not surprising to find, in the course of fifteen years, that biochemists interested in fundamental problems became increasingly aware of the advantages offered by Leeuwenhoek's "little animals." Furthermore, the gradual realization that growth factors for yeasts and bacteria bear a close relationship to vitamins required by higher animals soon led to the use of microorganisms for the assay of vitamins and amino acids and for the detection and identification of as yet unknown growth factors. The subsequent proof that several of these substances participate in biochemical processes as coenzymes or building blocks for coenzyme synthesis, a concept first advanced in 1933 by Lwoff in connection with studies on the role of hemoglobin in the nutrition of trypanosomes, increased the usefulness of the microbes still more, especially in view of their high rate of growth and the possibility of controlling the material by the use of pure cultures and chemically defined media. The microbes thus became the material *par excellence* for studies of special nutritional problems and of enzyme systems. And when at last methods were perfected for the extraction of enzymes from bacteria, yeasts, molds, and other microbes—through preliminary drying, disruption of the cells by grinding, shaking with glass beads, supersonic oscillations, or enzymatic dissolution of the cell walls—our understanding of the details of biochemical reaction mechanisms through the use of microorganisms advanced rapidly.

Unquestionably, biochemistry has profited greatly from these developments. Nevertheless, the microbiologist receiving a request for a pure culture of some bacterium, yeast, or alga, and for directions for growing it, from a biochemist who wishes to use it for a specific biochemical investigation cannot always escape the conclusion that the culture in question will be considered as little more than a potential enzyme preparation. And just as the chemist will feel uneasy when a special analytical procedure or method for synthesizing a chemical compound is used by a person with little experience and no more than a rudimentary knowledge of chemistry, unaware of the rationale of the operations and of the possible pitfalls in interpretation, so the microbiologist is likely to be somewhat apprehensive when his material is treated as a chemical reagent, rather than as a mass of living organisms with their own peculiarities and responses to environmental conditions that have to be appreciated for the culture to be used to best advantage. These are aspects that can be learned, and it is comforting to know that many biochemists nowadays are anxious to acquire a sound training not only in biochemistry, but in the general principles of microbiology as well.

Even so, one might argue with considerable justification that there is now developing a strong tendency to equate "general" microbiology, as contrasted to "medical" microbiology, with biochemistry and to consider a study of microorganisms as truly significant only if it is directed towards biochemical investigations. I consider such a tendency regrettable; however, this statement should not be misconstrued to mean that I have little or no interest in biochemical problems, or that I would advocate that the use of microorganisms for biochemical studies be henceforth curtailed. Not only would such an attitude be futile; it would also be unscientific. The biochemist should not be satisfied with our present level of understanding of biochemical phenomena. He must obviously realize that many types of reactions have not yet been analyzed with respect to the nature of the enzymes involved. He must know that the interpretation of enzyme specificity on the basis of the general idea that it is related to the molecular configuration of protein molecules leaves much to be desired and that a satisfactory account of the specificity problem requires a much more refined explanation. Even the mechanism of enzyme action through electron transfer is by no means as well understood as, for example, the reaction mechanisms between diatomic molecules. Probably, more attention gradually will be devoted to such problems, and as long as microorganisms promise to be useful for the isolation of hitherto unknown enzymes or for a more fundamental study of the mechanism of enzyme action, it would be indefensible to discourage the use of microorganisms in enzyme studies.

Nor am I concerned with the question of whether these should properly be called biochemistry or microbiology; I have little interest in definitions and delineations of fields of scientific endeavor. But I should like to emphasize that the microbe is potentially significant also for the study of phenomena that are not directly associated with either disease or enzymology, of phenomena that present problems far less clearly defined or definable but nonetheless equally fascinating. Such problems can perhaps best be indicated by referring to that realm of complexity of organization where a collection of chemical compounds exhibits the properties of a living organism. Again, I shall not attempt to define where the distinction between "living" and "nonliving" should be drawn; in the long run this may become the task for academicians desirous of formulating a useful dictionary type of definition of these terms. What I am concerned with is the attainment of a better comprehension of manifestations of matter on a level of complexity such as characterizes a microbe, implying organization, growth, and responses to environmental factors through irritability, variability, and adaptation, all of which may be combined in the term "individuality." I do not mean to express a belief that such phenomena cannot ultimately be explained on the basis of physicochemical events. But in view of the record of the history of scientific developments, I am inclined to think that these manifestations themselves could not be inferred from studies on isolated fragments of the organism. The mere fact that several examples have recently accumulated to show that an organism cannot use a particular substrate, although its enzymatic composition is such as to justify the conclusion that it should, is a simple case in point. At present this anomaly is attributed to permeability barriers or to enzymatic organization; it must, however, be realized that this explanation does not constitute a satisfactory one in terms of better comprehended mechanisms, but actually is hardly more than a paraphrase of the underlying observations. Let me emphasize that the point at issue is not that our current knowledge of permeability problems is still woefully incomplete, but that the mere detection of the irregularities was the result of studies with living organisms as well as with isolated enzyme extracts. Similarly, the occurrence of adaptations and mutations could not, I believe, have been surmised from experiments with crude or crystalline enzyme preparations, but had to be established by investigations with cell populations.

So far as we can perceive at present, the basis of life is matter, and the scientist must aim at an ultimate interpretation of the manifestations of life in terms of mechanisms that govern the behavior of the elementary particles of matter. To achieve this, we must know the manifestations, however, and it is my contention that we can discover them only by studies on living organisms. The greater the complexity of the latter, the more difficult will be the analysis of particular vital functions. Hence the microorganisms, in view of their relative simplicity, appear to provide promising material for further studies on the fundamental aspects of life.

Much has already been accomplished here, and there are signs of increased activity along several lines. The relatively recent developments demonstrating, for example, that bacteria in general represent organized units com-