THE VIRUSES

Biochemical, Biological, and Biophysical Properties

Edited by

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Volume 1

GENERAL VIROLOGY

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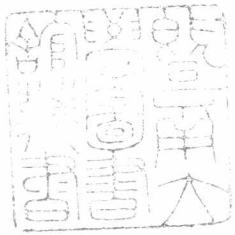

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Preface

Experimental biology at the present time is approaching a particularly interesting stage. It is probably true to say that in recent years biochemical concepts have dominated all general thinking on the fundamental problems of biology. There has been an uninterrupted succession of important discoveries and there is as yet no sign of any drying up of the flow of discovery. It is orthodox to believe that the way is now open to a comprehensive understanding of the basic living process in terms of biochemistry, with perhaps only an inspired continuation of progress along present lines being necessary. There are some, however, who are more impressed with the mounting difficulties of applying the methodology of chemistry to the complex macromolecules of living systems and their interactions than with the inevitability of their being overcome.

Clearly the crux of biological thought today is the applicability of chemical and physical approaches to the typical macromolecules, protein and nucleic acid, of living substance. In this context virology seems to occupy a key position among the biological sciences. Viruses are the smallest biological units which manifest all the essential characteristics of life and many are now known to be built up only of nucleic acid and protein. With the development of new biochemical techniques useful in attacking the problems of macromolecular structure viruses have become the material *par excellence* for fundamental study. The very great discovery that nucleic acid preparations possessing virus activity can be obtained from virus-infected tissues and from pure viral nucleoproteins has focused attention on nucleic acid as the key material in virus activity, in genetic activity, and in the synthesis of proteins and of nucleic acids. It would appear, therefore, that nucleic acid structures contain the codes for the fabrication of every individual of every species. Since some viral nucleic acid preparations can be obtained quite pure, chemically as well as genetically, in lots of hundreds of milligrams, it is obvious that the viral nucleic acids offer an especially favorable and perhaps unique possibility of breaking the code and of approaching the synthesis of a replicating structure. These represent great challenges in virology and are, of course, of the greatest importance to science and to mankind.

There have been many systematic compilations of knowledge on viruses as agents of disease in man, in animals, or in plants. To our knowledge, however, the present work is the first to be published in English in which a systematic attempt is made to cover the significance of experimental work on viruses for general problems within and on the borderlines of biochemistry, biology, and biophysics. Since it would be impossible for one or two persons

to write authoritatively about all of the important aspects of virology, it has been necessary to seek the assistance of experts in different areas of virology. The editors have been quite fortunate in securing contributions from 34 of the leading virologists in 8 different countries. Almost two-thirds of the contributors are from American laboratories and this mirrors with reasonable accuracy the relative activity in virology during the past several years. However, there is presently a great upsurge of research activity in virology in several countries and significant new information is now almost world-wide with respect to source.

The plan of "The Viruses" has deliberately followed that of the works on "The Proteins," "The Nucleic Acids," and "The Enzymes" published also by Academic Press. In this treatise on "The Viruses" we are concerned essentially with the chemical and physical characteristics of viruses and with the processes associated with their multiplication in the cell. In general we are not concerned with manifestations of viral infection in multicellular organisms or in populations of susceptible hosts except insofar as they provide information about processes at the cellular level. It is manifestly impossible to treat comprehensively of viruses without consideration of their behavior at the genetic level. Particularly with the bacterial viruses there is now much information on record on recombination between viruses and on interaction between the genomes of virus and host cell. In this region we may well find the material from which will come eventually an understanding of the relationships between the genetic and chemical approaches. The discovery of infectious nucleic acid preparations represents a major start in this direction.

It would not be realistic to separate the academic approach to virology sharply from the clinical. In the last analysis the prevention or cure of virus disease will depend on properties of virus and host cell. In the past, success in control has depended almost exclusively on the use of procedures at the immunological or epidemiological levels, but if these are to be refined and fully understood much use will have to be made of the information provided by the essentially theoretical studies which the present work has been designed to systematize and display. Consider, for example, the new immunological problems that one may encounter if, as may emerge, infectious nucleic acid moves directly from cell to cell. This treatise provides the information and the interpretation of this information that will be necessary for a rational experimental approach to such new problems.

One of the main difficulties the editors have encountered has been one inherent in all attempts at biological generalization, namely, the diversity of the material that is available for study and the widely varying intensity and success with which different sections of that material have been studied. It will be found, for instance, that a large proportion of each of the three

volumes is concerned with the properties of one plant virus (TMV), one bacterial virus (T2) and three animal viruses (vaccinia, influenza A, and poliomyelitis viruses). There are large numbers of other viruses in each of the main categories and undoubtedly many show or will show highly significant differences in behavior from those which for one reason or another have been chosen as prototypes. Perhaps one of the important functions of the work will be to show where such significant differences can most hopefully be looked for. Clearly there is no lack of scope for further work in virology.

Melbourne, Australia F. M. BURNET

Berkeley, California WENDELL M. STANLEY
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Chapter I

The Problems of Virology

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I. Introduction

The present work was designed to provide a relatively comprehensive account of current knowledge of viruses regarded, not as agents of disease, but as biological entities whose properties can be studied in the laboratory by the methods of experimental biochemistry, biology, and biophysics. We have interpreted this as broadly limiting our topics to the chemical, physical and, where relevant, genetic structure of the infective units and to what is known of the interaction between virus and the cell it infects. Except where it is necessary to allow definition of some intrinsic quality of a virus, no consideration is given to the pathogenesis of virus diseases nor to clinical, epidemiological, or ecological aspects of such diseases.

Even with this limitation, the field to be covered is enormous and peculiarly difficult to organize satisfactorily. The first difficulty concerns the range and diversity of viruses. If we confine attention to the infective form, we have units ranging in complexity from a relatively simple system of association between two types of macromolecule (tobacco mosaic virus) to large units of complex composition which are more nearly like organisms (vaccinia and psittacosis viruses). Some, such as the smaller plant and animal viruses, possess RNA (ribonucleic acid) only, the bacterial viruses contain DNA (deoxyribonucleic acid) in one group of a unique chemical structure, and some of the larger animal viruses may be found to contain both types of nucleic acid. No direct evidence can be obtained of the ways by which viruses have evolved. It is doubtful whether any biologist would even suggest that all types of virus had a remote common ancestor. Many have suggested, on the other hand, that among the viruses we include a widely heterogeneous group of many different evolutionary origins, the single common feature

being their adoption of the role of strict intracellular parasite. On this view we may find that any treatise on general virology will eventually be reduced to a discussion of the ways by which a living cell can have its metabolic activities diverted to allow the replication of material of alien pattern. As a matter of fact, we have given considerable space to this general area, as may be seen from an examination of the following chapter in this volume. It remains necessary, however, to attempt to discuss at least representative examples of each main group of viruses.

This leads to the second difficulty—the unevenness with which topics bearing on general aspects of virology have been dealt with in the different groups. Following what Sir Charles Harington (1957) has characterized as "the intellectual shock that was administered" to science by the discovery of crystalline tobacco mosaic virus more than 20 years ago, there occurred a great surge of activity in virology. There has, for instance, been a great concentration of biochemical and biophysical work on TMV (tobacco mosaic virus), a moderate amount on some of the other "macromolecular" plant viruses, and virtually none on the larger and less stable plant viruses. Similar work on the animal viruses has lagged behind that on the plant viruses. Details of the process of infection and of the interference by virus with the metabolism of the host are known in much more detail about bacterial viruses, particularly T2 with *Escherichia coli* B as host, than about any other combination. Genetic work is almost limited to a few bacterial viruses and influenza A virus. It is already clear that generalizations about virus behavior cannot safely be drawn on the basis of one or a few well-studied examples. We have, in fact, considerable sympathy with one or two potential collaborators who declined the task on the basis that the time was not yet ripe to undertake a general treatise on viruses. They felt that the study of the bacterial viruses had perhaps gone far enough to give a reasonably clear picture of the process of infection and that attempts to provide a comprehensive description of the processes involved in infection by representative animal, plant, and insect viruses should be deferred until knowledge of these had reached much the same level of completeness as exists for bacterial viruses. The reason for going on with the project is simply our belief that it is of the very nature of science that knowledge must always be incomplete and that the present is a better time to attempt our task than 5, 10, or 20 years ago. We believe, too, that the same two remarks will be made with equal cogency at any time in the foreseeable future.

II. The Double Approach

A. The Infective Particle

Virus research is a segment of experimental biology and inevitably encounters the same methodological and interpretative difficulties that beset