General Virology

S. E. LURIA
PROFESSOR OF BACTERIOLOGY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

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Preface

This book is the outgrowth of a course on viruses that I have been teaching since 1946, first at Indiana University, more recently at the University of Illinois. The problem that faced me in 1946 was planning a course in virology for graduate and advanced undergraduate students in biology and biochemistry, who had no medical orientation and no background in histopathology, in a university that was justly proud of its reputation as a center of experimental biology. I could teach either a watered-down course in virus diseases or organize a new type of course, in which virology would be presented as a biological science, like botany, zoology, or general bacteriology. My choice of the second alternative was, I think, justified. My classes in virology have been well attended and have attracted excellent students. Similar courses have since been established in other institutions.

Virology is fast becoming an important field of science, in which geneticist, cell physiologist, and biochemist find, in the ground plowed by the pathologist, a fertile soil for new approaches to fundamental problems of cell function and organization. The interest of "outsiders" in viruses has grown continuously since the middle 1930's, stimulated at first by the progress of physicochemical work on virus particles, later and more powerfully by the recognition of viruses as keys to the study of cellular integration. The eagerness with which modern bacteriophage work has been seized upon by biophysicists, geneticists, and biochemists, and the conscious efforts to create a comparative virology (whose heuristic value can be seen by perusing, for example, the proceedings of a symposium on *The Nature of Virus Multiplication* held at Oxford in 1952) are signs of the healthy growth of the new science.

In attempting to teach general virology, I was faced with the problem of the lack of a textbook. In 1946, the best books dealing with viruses were devoted to the description of virus diseases. The main exceptions were Doerr and Hallauer's *Handbuch der Virusforschung*, a bilingual treatise of vast scope, and Bawden's excellent *Plant Viruses and Virus Diseases.* Both were unsuitable as textbooks, although invaluable as reference books. In spite of many important additions to virological literature, no single volume suitable for classroom use has appeared. This book is an attempt to fulfill the need for a textbook in general virology.

My teaching of virology, and this book as a result of it, have been built around a central concept, that of the dual nature of viruses as inert particles on the one hand, and as operating constituents of functional cells on the other hand. In the light of this concept, I have tried to present the physical and chemical approach to virus particles and the biochemical and cell-physiological approach to virus-infected cells as two separate but integrated aspects of virology. In the limited space of one semester or of a book of this size, one can hardly hope to make a biochemist or a physicochemist out of a biology student, or a biologist out of a chemist. I have covered such background information as I found useful in teaching, from the logarithms to the embryology of the chick embryo, but I have given no details of actual techniques. Any description of individual virus diseases has deliberately been omitted. The pathogenicity of a virus is, of course, less incidental to virus biology than, say, the pathogenicity of *Streptococcus pyogenes* is to bacteriology, since the virus, an integrated intracellular parasite, "lives" the life of the host as its own only life. Thus each virus disease is potentially a different form of virus life. Yet, I feel justified, both on didactic and on conceptual grounds, in assuming a priori as much uniformity and community of mechanisms as the known facts do not contradict. This assumption stems, of course, from a belief in the intrinsic simplicity of nature and from a feeling that the ultimate contribution of science resides in the discovery of unifying and simplifying generalizations, rather than in the description of isolated situations—in the visualization of simple, overall patterns, rather than in the analysis of patchworks.

Facts about individual viruses are presented as model systems or as examples, without any attempt at extensive coverage. The choice of examples reflects my limited knowledge of many areas of virology. Being myself a specialist, I shall count on the tolerance of other specialists whose field I may have misinterpreted, and on their willingness to suggest improvements for future editions of this book. The selection of references was dictated not only by the accidents of my limited knowledge but also by an attempt to single out articles with further references, with descriptions of important methods, or with new ideas and timely syntheses.

In a science developing as fast as virology, any book is bound to be somewhat out of date by the time it appears in print. In fact, original work is proceeding at such a pace that interpretations presented in research articles must often be revised in galley proof. Yet, virology has reached the stage where we may be justified in attempting at least a provisional integration. It will be gratifying if this book contributes to such an integration.

Many friends and colleagues encouraged me to write this book, friendly periodic reminders from the publishers over a period of three years helped me fight the frequent temptation to forget about it. Special thanks go to Dr. Zella Luria, who read the whole manuscript and contributed many improvements of language, style, and reasoning, and to Mrs. Mary Delbrück, who in the summer of 1949 typed under dictation the first draft of several chapters. My friends Drs. L. M. Black, E. Caspari, M. Delbrück, G. K. Hirst, K. Maramorosch, S. M. Rose, R. W. Schlesinger, and R. Y. Stanier read some chapters at various stages of writing and made valuable suggestions. The Graduate School of Indiana University provided in 1949 a grant for secretarial help. I wish especially to thank my very good friends the students in the virology courses at Indiana University and at the University of Illinois, who stimulated and shared my enjoyment of virology and submitted themselves sympathetically to my early and recent experiments in developing an approach to this growing science.

S. E. L.

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VIROLOGY AS A BIOLOGICAL SCIENCE

Virology has become a fundamental biological science in its own right. Just as bacteriology has emerged as a biological science out of the practically important but scientifically constricting borders of its medical applications, so has virology begun to become a body of knowledge and of generalizations, with its own perspectives and its own internal development. Having originated as a branch of pathology—human and animal pathology on the one hand, plant pathology on the other hand—the new science of virology, developed at first in response to practical needs, has reached a point where progress is dictated at least as much by the logic of its internal development as by the demands of applied areas. Analogy with other fields teaches us that the emergence of virology as a fundamental science from an applied one will actually make virology more adequate to handle those practical problems from which it arose, even though it may sometimes appear to lose sight of them. The years between 1945 and 1950 saw an increasing integration of various areas of virology, particularly under the impact of advances in the study of bacterial viruses (*172*). Nevertheless, the attempts to present virology in a coordinated way, or at least in an all-inclusive way, have been few (*187; 610*). Still today, the methodological and semantic barriers between plant, animal, and bacterial virologists are slow in yielding before the recognized need for joint efforts and for cross-fertilization of ideas.

What kind of biological science is virology? We may subdivide somewhat artificially the fundamental biological sciences (as distinct from applied sciences, like medicine, and from ancillary sciences, like biometrics) according to the nature of their subject matter, into *taxonomic*, *integrative*, and *interpretative* sciences. A taxonomic science (for example, botany, mycology, entomology, ichthyology, mammalogy) is characterized by the fact that its subject matter is a group of organisms with a recognized taxonomic unity, that is, a common ancestry and a historical development unique to that group. Integrative sciences (physiology, ecology, genetics) analyze the common or specialized properties of living organisms in their historical dynamic relations and transformations. Interpretative sciences (biochemistry, biophysics) analyze elementary processes and functions of organisms in terms of the behavior of the pieces (molecules, atoms, electrons) that are the common material basis of all matter, living and nonliving.

A definition of viruses. Does virology fit into any of the above categories? This question has no precise answer. The subject of virology is not one immediately definable by common-sense criteria verified by taxonomic or methodological analysis. Viruses, the subject matter of virology, themselves require a definition. This, like all definitions, should be operational, that is, it should provide factual criteria for inclusion or exclusion of given objects in terms of observable properties and performable tests. Such a definition always has a certain arbitrary quality. Its value will depend on the number and size of the areas of uncertainty it leaves.

We shall adopt for viruses the following definition: *Viruses are submicroscopic entities, capable of being introduced into specific living cells and of reproducing inside such cells only.* This definition provides practical, restrictive criteria, and at the same time emphasizes the fact that virology, although it covers a group of biological entities, is not a taxonomic science in the usual sense. Indeed, there are no grounds for assuming that all objects that fulfill our definition belong to one distinctive branch of the evolutionary tree. There is not even general agreement as to whether any or all viruses can be considered as "organisms." Our definition of viruses stresses the *methodological* rather than *taxonomic* unity of the subject matter of virology. Yet it stresses the fact that viruses, although possibly not constituting a taxonomically valid group, possess the basic properties that can be validly accepted as an operational basis for defining "organisms"—the properties of individuality and of homologous reproduction. Reproduction—together with its inseparable counterpart, heritable variability—makes possible the historical continuity and perfectibility of the pattern of specificity embodied in the individual and gives it potential immortality.

We must point out, however, that the reproduction referred to in our definition is purely descriptive, stating that more virus similar to the original one is produced. No specific mechanism of reproduction is postulated in the definition.

Let us examine our definition more closely. We shall discuss the meaning of its various parts and see how the elimination of any one of them suggests possible natural relationships between viruses and other biological elements.

The requirement for ability to be introduced into host cells emphasizes the external derivation of the virus. This constitutes a requirement for the recognition of a virus as such. A virus does not need to enter every host from outside. It may be transmitted internally from generation to generation of its host, even intracellularly at cell division and in the formation of germ cells. But, to be observed, a virus must be capable at some time of entering some host organism or cell from the outside. Elimination of this requirement would identify viruses with all "self-reproducing" protoplasmic components of cells, such as genes and other units endowed with genetic continuity. As we shall see in chapter 18, the view is rather widely held that some or even most viruses may have originated by the acquisition of infectivity (that is, of external transmissibility) on the part of self-reproducing cell components. At any rate, we may emphasize from the start that, once inside the host cell, a virus appears indeed to behave as a protoplasmic element, distinct, however, from other such elements by its actual or potential transmissibility to new host cells.

The "submicroscopic" requirement is more arbitrary, but is methodologically convenient. The effective resolving power of the light microscope being around 2000 A, the definition restricts the virus field to the study of agents that at some time in their development consist of elements, *recognizable in isolated form,* with at least one linear dimension equal or smaller than 2000 A (43). There is, of course, no fundamental reason behind the choice of this borderline value for size. It simply turns out empirically to be an adequate point of separation. This size limit happens to be reasonably close to the limit of porosity of ordinary bacteriological filters, which can therefore be used to separate bacterial cells from virus particles without much loss of the latter (*filtrable viruses*). Several agents, however, which have dimensions greater than 2000 A are included among viruses. Our definition should really state: "submicroscopic or nearly submicroscopic entities."

Elimination of the submicroscopic size requirement would include among viruses a variety of obligate intracellular parasites, such as some bacteria (e.g., *Mycobacterium leprae*), the rickettsiae, and some algae and possibly fungi. There are sound taxonomic reasons for including such organisms with groups other than viruses. The rickettsiae (see chapter 19), according to the most accepted view, represent a special group of obligate parasitic Gram-negative bacteria. The possibility that some of the obligate parasitic microorganisms are related to viruses and the hypothesis that some viruses originated from them or from their ancestors by "regressive evolution" through parasitism are very popular among virologists (*114; 271; 395*).

The requirement for reproduction "inside living cells only" excludes all saprophytic, free-living organisms. A number of submicroscopic free-living organisms are known to exist. Many bacteria, especially in unfavorable environments, can go through submicroscopic stages or L forms, which may reproduce as such and later return to the typical bacterial morphology (*179*). Several submicroscopic free-living organisms, without known bacillary stages of development, have been described. Among them are the "pleuropneumonia organisms" originally described by Nocard and Roux (see *571*), similar in many respects to L forms of bacteria; the sewage and soil organisms of Laidlaw and Elford (*396*) and of Seiffert (*589*); and the serum organisms of Barnard (*39*). The pleuropneumonia and sewage organisms have well-defined and not too complex nutritional requirements for growth (*519*). This in itself differentiates them from viruses, whose growth, as we shall see, appears to depend on the host cells not for a supply of nutritionally required compounds or growth factors, but for the use of the integrated enzymatic machinery of the cell, which provides energy and synthetic machinery for the virus. Indeed, viruses in the free state appear to be completely inert metabolically.

The requirement for "host specificity" included in our definition of viruses, although not excluding any known group of organisms, emphasizes again the fact that the virus-host relation is one of integration rather than of supply of nutrients. If we were to encounter an intracellular parasite apparently unable to reproduce in the free state but capable of reproduction in living cells of any kind, we could reasonably suspect that growth of this parasite in the free state would be possible if we were able to isolate and supply in cell-free form some hitherto unidentified, perhaps unstable, nutrient. On the other hand, we shall see that the relation of true viruses to their host cell is so intimate and integrative that the hope for cell-free virus reproduction is about on the same level as the hope for artificially constructed, self-reproducing cells.

The relation of virology to other biological sciences. Virology's relation to bacteriology stems on the one hand from the common technical problems of handling very small biological objects (microscopy, filtration techniques, sterilization), and on the other hand from the common interest in pathogenic microbes. Both pathogenic bacteriology and applied virology belong to the wider field of pathology. The study of pathological changes in host organisms, however, is more intimately connected with the study of viruses than with that of pathogenic bacteria, because the detection, the recognition, and the titration of viruses depend almost exclusively on observations of abnormal changes produced in some host. Fundamentally, however, virology should be concerned primarily with virus properties and functions. It should ultimately be possible to interpret all pathological changes of a host, directly or indirectly, in terms of the mechanisms by which a virus alters the infected cells.

Virology has become closely allied to protein chemistry and physicochemistry and has borrowed the techniques of these sciences, because the small size of viruses places them in the colloidal range and gives them many properties in common with proteins and other macromolecular substances. Methods for purification and for determination of the size, homogeneity, and state of dispersion of particles are similar for viruses and proteins. The overlapping size ranges of viruses and proteins do not a priori imply a similarity of organization or of chemical complexity. Such a similarity can only be tested by structural analysis. Thus, the relation of virology to protein chemistry is, at least in principle, purely technological.

THE DEVELOPMENT OF OUR KNOWLEDGE OF VIRUSES

Like all sciences, virology has not developed in a straight path, but rather by a slow accumulation of empirical knowledge. Some unity and general perspectives have only emerged in the last 10 years. Some diseases now known to be caused by viruses have been recognized for thousands of years. A Chinese description of a pestilence dating from the 10th century B.C. apparently refers to smallpox. Yellow fever, known for centuries in tropical Africa and as a scourge of ships in the African trade, was probably responsible for the legends of cursed ships, such as those of the Ancient Mariner and the Flying Dutchman *(114)*. Plant virus diseases, such as potato leaf-roll, have been traced to records of several hundred years ago; and tulips with the ornamentally appreciated color variegation known as tulip break, caused by a virus, have been cultivated since the 16th century (*43*).

The transmissibility of smallpox has been known for centuries, and vaccination against smallpox by extracts containing vaccinia virus (cowpox) was introduced as a medical practice by Jenner at the end of the 18th century (Jennerian vaccination, *361*). The transmissibility of tobacco mosaic by mechanical inoculation of sap of infected plants was demonstrated by Mayer in 1886.

During the last decades of the 19th century, the successes that had attended the search for bacterial agents of many diseases drew increasing attention to various diseases for which this search had remained fruitless. The idea of submicroscopic, nonbacterial pathogens, however, was slow in finding an experimental basis. In 1892 Iwanowsky reported the transmission of tobacco mosaic by means of sap filtered through bacteriological filters which were supposed to retain all bacteria. His report went unnoticed; its significance was apparently not fully clear to the author himself. In 1898–1899 Loeffler and Frosch (*428*) for foot-and-mouth disease and Beijerinck (*58*) for tobacco mosaic succeeded in proving serial transmission by bacteria-free filtrates in which no microscopic organism could be detected. Impressed by this unexpected finding, Beijerinck described the agent of tobacco mosaic as a *contagium vivum fluidum,* meaning by this an agent which reproduced, and therefore had life, but which was in a state of dispersion different from that of organisms. In reality, there is no clear-cut difference in the state of dispersion of small organisms and of large molecules. Moreover, the fact that virus reproduction and its pathological consequences can be initiated by a single virus particle make the state of dispersion of viruses irrelevant for their mode of action.

There followed an intense period of discovery of virus pathogens or "filtrable viruses," to employ a now obsolete expression. The early years of virology saw the development of methods permitting the microscopic visualization of the largest types of virus particles or elementary bodies. Following pioneer observations by Buist (*106*), many workers, and especially Paschen (*514*), greatly developed the art of virus staining. Meanwhile, rapid progress was made in the study of the cellular pathology of virus diseases, with the recognition of specific intracellular inclusions (see *217*).

On the one hand, the work on the size and properties of virus particles contributed to the development of modern techniques of ultrafiltration, ultracentrifugation, and other physicochemical procedures, culminating in the successful purification, crystallization, and chemical characterization of virus particles (*405; 622*). On the other hand, research on cellular pathology of virus infections gave a great stimulus, first, to the study of tissue cultures, and second, to the study of chick-embryo techniques as means of investigating viruses in simplified systems. The study of tissue cultures provided direct evidence of the need for contact with living, metabolizing cells as a prerequisite for virus reproduction. Frozen, killed tissue, or tissue separated from virus by membranes impermeable to the virus would not support virus reproduction. The discovery in 1910 of a virus that produces malignant tumors in chickens (*562*) and the generalization of this discovery to a whole group of fowl cancers in subsequent years opened the way for the realization that viruses are a major agent of neoplastic transformations, both in animals and in plants (*83*).

The discovery of bacteriophages or bacterial viruses by Twort (*653*) and by d'Hérelle (*306*) and the deliberate use of bacteriophages as models for the study of the virus-cell relation (*65*) provided perhaps the most important single factor for the present integration of virology into a unified science.

The recognition of the specificity of host-virus relations, of its limitations, and of its determination by genetic and developmental factors (host specificity and tissue specificity) assumed increasing importance as a result of efforts to conquer the virus diseases of man and of economically important animals and plants (see *265*). From the epidemiological standpoint, the most salient developments have been the recognition of the role of arthropod vectors in the transmission of many virus diseases of animals and plants (*547*), the analysis of complex host-vector-virus cycles (*601*), and the clarification of the role of latent infections of reservoir hosts in perpetuating pathogenic viruses. The analysis of spontaneous mutability in viruses (*310; 361a; 457*) not only contributed to the epidemiological understanding of virus diseases but also established the nature of viruses as independently evolving and therefore taxonomically independent genetic systems. Similarly, the analysis of the serological properties of viruses (*121*) established their nature as chemically specific, host-independent structural elements, while providing a basis for a multitude of diagnostic tests for virus diseases.

PLAN OF THE BOOK

It will be our aim to study viruses as a group, in spite of the recognized uncertainty as to the extent of taxonomic kinship among what we call viruses. We shall not attempt the description of individual virus diseases nor of individual viruses, but shall rather deal with the facts and methods of virology as a whole. We shall, however, undertake whenever possible the interpretation of certain phases of applied virology in terms of fundamental virus properties. For example, a discussion of virus ecology will of necessity be closely allied to a general discussion of the epidemiology of virus diseases. We shall subdivide our subject matter as follows:

1. Survey of viruses; range of existence; nomenclature and classification (chapter 1).

2. Detection and titration of viruses (chapters 2 and 3).

3. The properties of viruses outside the host: size, structure, composition, organization of virus material; chemical and serological analysis; effect of physical and chemical agents (chapters 4–7).

4. Virus-host interaction: analysis of the simplest and most thoroughly investigated host-virus systems; study of virus reproduction; interaction among viruses in common hosts (chapters 8–14).

5. Viruses in nature: variation, ecology, survival, transmission; virus latency and relation of viruses to growth and morphogenesis; tumor viruses (chapters 15–17).

6. Origin and nature of viruses; relation to other biological systems (chapter 18).

7. Rickettsiae (chapter 19).

RANGE OF EXISTENCE OF VIRUSES

It is customary and reasonable to subdivide viruses, according to the major subdivisions of their hosts, into bacterial viruses (bacteriophages), plant viruses, and animal viruses. We must realize, however, that even such broad subdivisions may create ambiguities, as in "plant viruses" that reproduce in their insect vectors. We must remember that, because of their nature, viruses are detected and discovered as pathogens, that is, as agents causing abnormalities in some hosts. It is therefore logical to list them in terms of their "major host," that is, of the host whose manifestations are of the greatest importance to man—economical, medical, or otherwise. In general, each virus will have a variety of hosts, more or less related organisms, in which it can reproduce. Some of them, often those in which damage caused by the virus is slight or absent, are more important in assuring the survival and evolutionary success of the virus than the major host which arouses man's interest. In tables 1 and 2 we present an extensive though by no means complete list of animal and plant viruses.

There are several important aspects to be considered in taking stock of the range of organisms that have been found to be hosts for viruses. As far as bacterial viruses are concerned there is hardly a group of readily cultivable bacteria for which bacteriophages are not known. The bacteria for which no phage has been described (spirochetes; myxobacteria; iron, sulfur, and nitrifying bacteria) present major technical problems to bacteriologists. Our knowledge of them is quite inadequate. It is likely that every thoroughly investigated bacterial group will be found to be the host of some phages. It is interesting to note that the host range of phages does not cut across well-established taxonomic boundaries between bacterial groups. Phages active on micrococci will not grow on streptococci; phages of enteric bacteria do not attack *Pseudomonas*. Specificity can go far beyond the rather flimsy classification boundaries that separate genera and species. It reaches down to individual strains or "clones." The explanation for this great specificity resides in the fact that phage resistance in bacteria is acquired by discrete mutational steps, so that a strain sensitive to a phage may give rise to stable mutants resistant to that specific phage.

Among animal viruses, the only invertebrates in which virus diseases have been observed are the insects. These represent, of course, the economically most important and therefore scientifically most prominent group. The study of insect virus diseases was stimulated in France in the 19th century by the losses due to diseases of the silkworm, the protagonist of the natural silk industry. Virus diseases of insects, especially Lepidoptera and Hymenoptera, are today a most important area of virology.

Among vertebrates, virus diseases have been recognized in fish (carp pox, infectious tumors) and in amphibia (virus tumor of the kidney in the leopard frog). In birds we find virus diseases of great economic importance: Newcastle disease of fowl, laryngotracheitis and many others. The main importance of some virus diseases of birds is their occasional transmission to man (psittacosis, ornithosis). Certain neoplastic virus diseases of birds, fowl sarcomas and fowl leukemia, have a tremendous interest for the virologist because of their role in the study of the relation of viruses to tumors. They represent in some respects the most thoroughly investigated cases of tumors caused by viruses.

In mammals, virus diseases have been recognized in most domestic animals and in several wild ones, particularly in rabbits, whose virus

Table 1. Representative animal viruses

Virus	Major Host	Other Natural Hosts	Transmission	Typical Reactions in Major Host	Diagnostic Reactions
Coxsackie group	Man	—	Contact	Meningitis; myalgia	Virus neutralization
Dengue	Man	Monkeys	Mosquitoes	Fever; rash; leukopenia	Complement fixation; virus neutralization
Encephalitis group					
Equine encephalomyelitis (Eastern, Western, Venezuelan)	Horse	Man; fowl	Mosquitoes; mites	Meningo-encephalitis	Complement fixation; virus neutralization
Japanese (type B) encephalitis	Man	Chicken; mammals?	Mosquitoes	Meningo-encephalitis	Complement fixation; virus neutralization
Lymphocytic choriomeningitis	Man	Mouse	Contact (vectors?)	Meningitis	Complement fixation; virus neutralization
Russian (Spring-Summer) encephalitis	Man	Wild mammals and birds?	Ticks	Meningitis; encephalitis	Complement fixation; virus neutralization
St. Louis encephalitis	Man	Chicken; other birds? wild mammals?	Mites, mosquitoes	Encephalitis	Complement fixation; virus neutralization
Herpes simplex	Man	—	Contact	Cold sore (fever blister); stomatitis	Complement fixation; virus neutralization
Herpes zoster (shingles)	Man	—	? (Possibly from varicella infection)	Vesicular eruption of skin along nerves	Complement fixation; agglutination of elementary bodies
Inclusion conjunctivitis	Man	—	Contact	Conjunctivitis (especially in infants)	Intracellular inclusions
Infectious hepatitis	Man	—	Contact	Jaundice	—

Influenza (A, B, C)	Man	—	Contact	Flu; pneumonia	Hemagglutination inhibition; virus isolation in egg
Lymphogranuloma venereum	Man	—	Contact (genital)	Primary blister; lymph-node swelling	Staining for elementary bodies; complement fixation; skin test
Measles	Man	—	Contact	Skin rash; Koplik spots in mouth	—
Molluscum contagiosum	Man	—	Contact	Skin nodules	Intracellular inclusions
Mumps	Man	—	Contact	Parotitis	Hemagglutination inhibition; complement fixation; skin test
Poliomyelitis (Types I, II, III)	Man	—	Contact	Motor paralysis	Virus neutralization; complement fixation; (cytotoxic effect in tissue culture)
Rubella (German measles)	Man	—	Contact	Skin rash	—
Trachoma	Man	—	Contact	Chronic conjunctivitis	Intracellular inclusions
Varicella (chicken pox)	Man	—	Contact	Skin rash	Complement fixation; agglutination of elementary bodies
Variola (smallpox, alastrim)	Man	Related to cowpox (vaccinia), horsepox, sheep pox	Contact	Skin vesicles	Complement fixation; intracellular inclusions (Guarnieri bodies)
Yellow fever	Man	Monkeys	Mosquitoes	Jaundice; liver and kidney necrosis	Isolation of virus; virus neutralization
Warts (verrucae)	Man	—	Contact	Skin, genital, and laryngeal warts	—
Cowpox (vaccinia)	Cattle	Man	Contact	Skin vesicles	Complement fixation

Table 1. Representative animal viruses (*Continued*)

Virus	Major Host	Other Natural Hosts	Transmission	Typical Reactions in Major Host	Diagnostic Reactions
Foot-and-mouth (aphthous fever)	Cattle	Swine; sheep; man	Contact	Vesicles on oral mucosa and skin	Complement fixation
Pseudorabies (mad itch)	Cattle	Swine; cat; dog	Contact	Skin itch; pharyngeal paralysis	—
Rinderpest (cattle plague)	Cattle	Sheep; goat; buffalo	Contact	Inflammation of digestive tract	Rabbit inoculation
Louping ill	Sheep	Man?	Ticks	Meningo-encephalitis	Complement fixation; virus neutralization
Rift valley fever	Sheep	Goat; cattle; man	Mosquitoes	Liver necrosis	Virus neutralization
Hog cholera	Swine	—	Contact	Hemorrhages; leucopenia; encephalitis	Skin test
Swine influenza	Swine	—	Contact, lungworm	Pneumonia	Hemagglutination inhibition
Swamp fever (equine infectious anemia)	Horse	—	Flies; mosquitoes; contact	Destructive anemia; hemorrhages	—
Distemper (canine and fox)	Dog	Wolf; fox	Contact	Pneumonia; meningitis	Ferret inoculation
Rabies (hydrophobia)	Dog	Cat; wolf; fox; man	Contact (bite)	Throat paralysis; encephalitis	Intracellular inclusions in brain (Negri bodies); complement fixation
Feline infectious enteritis (panleucopenia)	Cat	—	Contact	Enteritis; leucopenia	—
Fowl plague	Fowl (chicken, turkey, duck)	Wild birds	Contact	Hemorrhages; edema	Chicken inoculation