Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
I. Introduction

Molecular biology has focused attention on viruses as simple models for basic biochemical and genetic processes. However, its very success in this context has tended to obscure the fundamental question, "What is the role played by viruses in Nature?" This article is an attempt to examine this issue. Various factors make the task a difficult one: (1) viral taxonomy is still a subject of controversy (see Lwoff and Tournier, 1971); (2) the amount of available data is now so great that one scientist cannot critically assess the validity of every claim; (3) much of the most pertinent information is so recent that certain key principles must still be regarded as suggestive rather than established; and (4) a further major factor concerning the available information relates to the origins of much of the data. Because of their small size, their haploid state, and their rapid replication rate, the genomes of viruses are in very intimate equilibrium with environmental stress. The act of isolation immediately removes a virus from many of the influences that hitherto determined the character of its genome.
After several thousand passages on indicator cells (themselves often the products of frequent subculturing in vitro) in the "unnatural" universe of the laboratory, the entity available to the experimenter may possibly have lost the genetic features most relevant to its original ecology. For example, much modern knowledge concerning lysogeny has been gained using laboratory stocks of λ coliphage "constructed" by isolation of mutants and outcrossings with other stocks so as to make them more amenable tools for genetic analysis. It is worth remembering that the original λ isolate (Lederberg, 1951) was considered "a rather poor object for genetic studies" because "the plaques were small and differences in plaque morphology difficult to discern" (Campbell, 1969).

Taken together, factors (1) through (4) mean that any attempt to unify the available data into a novel framework is bound to attract criticism from specialists in various areas. However, it is hoped that the theory developed in this article will serve a useful function in stimulating discussion, and will force a re-evaluation of the role played by viruses.

Before the main postulates of this article are presented, it is useful to condense certain data concerning viruses into perspectives. The points made below are not novel, and they are intended as conclusions derivable from available data rather than as postulates.

Although the topics discussed below overlap to some extent, to simplify treatment they have been presented separately.

II. Most Species Have Associated Viruses

Cytolytic viruses are known for most prokaryotes that have been the subject of intensive investigation. The number of distinct virus types per species is considerable. There are 50 known phages able to infect the enteric bacterium Escherichia coli (see Appendix, Part A). Barnet (1972) found 28 distinguishable phages for various strains of the soil organism Rhizobium trifolii. Teh and Reanney (1973) found over 15 morphologically distinct phage types lytic for one strain of another soil microbe, Bacillus pumilus.

As one progresses from unicells to higher organisms, the number of different viruses associated with any one species becomes very large. The best researched vertebrate is man himself. Depending on the criteria used for classification, a figure of about 200 to 500 "different" viruses are known to be associated with human disease (see Appendix, Part A) (Jawetz et al., 1970). This figure ignores passenger viruses with no established pathological effects.

It is difficult to gain meaningful estimates for virus numbers for other eukaryote species, but it is likely that the figures are considerable. Rueckert (1971) states that "it is probably safe to venture that thousands of picornaviral serotypes exist in nature in non-human hosts."
A survey of the major taxonomic groupings shows that, for the main orders, viruses are known in many cases (see Appendix). It is true that no viruses have been reported for certain major phyla such as the Bryophyta (Matthews, 1970). However, where no viruses are documented, it is more likely that the relevant research has not been done or that the particular biology of the group makes it refractory to virus assay than that viruses are completely absent.

These observations lead to the conclusion: Most cellular species, which are themselves not obligately parasitic, have associated with them one or more types of virus.

III. Viruses Are the Most Numerous Genetic Objects in the Biosphere

Few studies have been made on the population biology of viruses in natural environments. Reanney and Marsh (1973) examined the population structure of a phage—D5—attacking the soil organism Bacillus stearothermophilus; in enriched soil where conditions favor virus multiplication, D5 populations often exceeded $10^8$ pfu/gm dry weight of soil. In untreated soil moistened with rainwater, titers were of the order of $10^8$ to $10^4$ pfu/gm. In other untreated environments, such as compost, D5 titers of $10^5$ to $10^6$ pfu/gm were obtained.

Some ecological studies have been carried out on the phages that parasitize the bacteria that ripen milk into cheese, since these phages are of economic importance. When phage was added to Streptococcus lactis in skim milk, the phage titer rose to $10^8$ pfu/ml (Babel, 1962). However, in the natural situation in raw milk containing diverse microbial populations, such wholesale lysis has not been observed. Collins (1952) found that the production of lactate by lactic acid bacteria was little affected by phage, even when susceptible bacteria made up 50% of the total microflora. In a later study, Collins demonstrated that the production of acid by a mixture of three different strains of S. lactis in skim milk was not reduced when any one of the three corresponding phages was added to the culture (Collins, 1955).

To the extent that these results are a true reflection of the natural situation, it follows that the lytic patterns and very high virus titers that fill texts on virology are artificial products of human manipulation. However, it must be remembered that laboratory conditions optimize virus multiplication by providing uniquely favorable conditions for host cell growth. In a natural environment such as soil, when the number of plaque-forming units scored for a given phage in a given sample is small, the metabolizing cell population sensitive to that phage is also likely to be small; phage titer has in fact been used to monitor bacterial activity in soil because of this presumed proportionality (Robinson and Corke, 1959; Reanney, 1968). In view of the fact (Section II) that there can be a large number of virus types lytic for any given species, it becomes apparent that the
number of virus particles in (most) natural environments probably exceeds the number of host organisms. The likelihood that virus populations outnumber those of their hosts is enhanced by the existence of temperate viruses which may only occasionally manifest an infectious character. Few studies on the frequency of occurrence of latent viruses in natural contexts have been made, but it is suggestive that MacPhee et al. (1969) found temperate phages for 5 of 10 strains of *Klebsiella* tested. It should be noted that failure to isolate a temperate virus for a given organism does not prove that no such virus exists.

Data presented in the next section are compatible with the inference that most prokaryote and eukaryote species harbor temperate or cryptic virus genes.

If it is admissible to consider episomal DNA "potential virus," then it is clear that in many (most?) natural environments viruses are the most numerous genetic objects.

While the size of a viral genome is small in relation to that of the cell it infects, the rate of replication of the viral genome is almost always very much faster than that of the host. The chromosome of *E. coli* is about 1.00 mm long. The DNA of T4 is about 0.06 mm long; as a T4-infected *E. coli* cell produces about 200 progeny particles, the total DNA production of an *E. coli* cell is 12 times greater for the virus DNA than for the host DNA generated by the normal division of one cell into two.

When one considers (1) the enormous numbers of viruses present under favorable conditions; (2) the variety of viruses often present for a given species; (3) the rapid multiplication rate of viruses; and (4) as shown in Section IV, the fact that certain genes which act as a part of cellular chromosomes can re-enter an independent existence as virus particles; then a second conclusion seems justified: For a given environment at any given moment, virus genes constitute a sizable fraction of the replicating nucleic acid in that environment.

### IV. Virus Genes Can Enter and Leave Cell Chromosomes

The phenomena of lysogeny and transduction are well documented in prokaryotes (e.g., see, Stent, 1963). It is not yet possible to generalize these processes throughout the rest of biology, but there are now suggestive indications that very similar processes occur in vertebrates.

The oncogene theory (Huebner and Todaro, 1969; Todaro and Huebner, 1972) envisages genes of viral origin as more-or-less normal components of vertebrate chromosomes. A substantial amount of evidence is consistent with this general notion. C-Type RNA viruses have been isolated from cats, rats, hamsters, cows, pigs, monkeys, humans(?), and in addition from chickens and snakes (Todaro and Huebner, 1972). Using hybridization techniques, Baluda (1972) demonstrated that DNA complementary to the RNA of avian leukemia
VIRUSES AND EVOLUTION

Virus occurs widely in chickens. Similarly, Varmus et al. (1972) found avian virus-specific nucleotide sequences in normal chick cells, as well as transformed cells; quail DNA also contained virus-specific sequences. The virus "marker" gs antigen has been found in cells that show no trace of virus particles (Huebner et al., 1970). The most convincing support comes from the fact that apparently "virus-free" cells can be induced to produce C-type virus by treatment with halogenated pyrimidines (Aaronson, 1971a). Rowe et al. (1972) found that all their clonal and subclonal lines could be induced to produce murine leukemia virus (MuLV) by treatment with 5-iododeoxyuridine, indicating that the viral genome was present in unexpressed form in all AKR cells. They also noted that one mouse seemed to carry more than one MuLV strain. Weiss et al. (1971) showed that even cells that lack the gs antigen can be induced to make leukosis-type virus.

Evidence is accumulating which suggests that the herpes virus, Epstein-Barr virus, occurs in latent form in human chromosomes (Hampar et al., 1972; Zur Hausen et al., 1972; Gerber, 1972). At the moment it seems possible that many "normal" cell clones harbor several latent virus genomes.

The analogy with lysogeny is particularly apt in the case of the papova viruses, polyoma and SV40. It seems likely (Watson, 1970) that the circular polyoma DNA integrates with host DNA by a mechanism similar to that proposed by Campbell (1962). The opposite process—encapsulation of host genes by viral capsomeres—has been demonstrated for polyoma. Michel et al. (1967) showed that polyoma pseudovirions contain fragments of mouse genome. Subsequently, Qasba and Aposhian (1971) demonstrated that polyoma pseudovirions could deliver mouse DNA to human cells. Further, Merril et al. (1971) found that phage λ carrying a functional bacterial Gal transferase gene could initiate transferase activity in human fibroblast cells taken from a patient with a congenital lack of α-D-Gal-1-phosphate uridyl transferase. λ-Specific RNA and transferase activity were distinguished at undiminished levels 41 days after infection, suggesting that stable incorporation of the transduced DNA into the human chromosome(s) had occurred. In these "transductions" the DNAs of donor and recipient were separated by many millions of years of evolutionary divergence, so that such interchanges may not occur in nature; but between closely related species or between individuals of the same species, it seems reasonable to assume that such genetic exchanges may occur frequently.

Smith et al. (1972) examined abortively transformed cells for SV40 and found that two out of three clones tested contained virus-specific material, despite the fact that they were phenotypically normal. They suggested that cryptic transformants might represent the most common cell type harboring the viral genome, and implicated virus sequences as a possible source of the new gene families present in eukaryote DNA (cf. Britten and Kohne, 1968).
Conclusion three is perhaps more contentious than the previous two. However, the data just presented are consistent with the inferences (1) that virus genes can and do enter and leave cellular chromosomes, but that (2) at any one time more "virus" genetic material exists in cryptic form integrated with cellular chromosomes than is to be found in the capsids of "infectious" virus particles.

V. Integrated Virus Genomes Are Often Reiterated

One of the facts that has emerged from recent data is that integrated viral genomes in eukaryote cells are seldom present in single copies. Baluda (1972) calculated that cells of leukemic chickens contained 4.95 avian leukosis virus DNA equivalents per cell. Normal cells contained 3.2 DNA equivalents per cell. Gs-negative cells contained as much viral DNA as their gs-positive siblings. Varmus et al. (1972) found multiple copies of avian tumor virus genes in chick and quail cells but not in HeLa cells or salmon sperm. Cells transformed with Rous Sarcoma virus had 15 copies of rapidly reassociating sequences (Varmus et al., 1972). Interestingly, a similar number of viral genes in chick cells was observed regardless of the degree of expression of viral information. Smith et al. (1972) found an SV40 abortively transformed line to contain about five virus genome equivalents per diploid cell. Subclones of this abortively transformed line had 2.7 to 10 viral copies per diploid cell. A similar situation obtains for polyoma, but the number of viral copies has been estimated to be as high as 60 (Watson, 1970).

The presence of reiterated sequences in eukaryote DNA is well-known (Britten and Kohne, 1968). Models such as the master-slave hypothesis (Callan, 1967) emphasize that the tandem alignment of identical (or similar) genes permits frequent crossing-over between the extensive regions of homology thus created, with the result that excision of DNA is facilitated (see Callan, 1967). Thus reiterated DNA favors episome formation (Edelman and Gall, 1969).

By the nature of the crossover events involved, the DNAs excised from repetitive sequences are often circular (see Callan, 1967). Thomas et al. (1970) sheared salmon sperm DNA by passage through fine needles; when these preparations were denatured and annealed and examined by electron microscopy, many circular molecules were observed; similar experiments with prokaryote DNA revealed essentially no circles under similar conditions. Thomas (1970) concluded that the ability to form circles is a general property of all eukaryote chromosomal DNA.

It seems very likely that at least for some viruses, such as adenovirus, the integrated virus genes lie adjacent to reiterated cellular DNA sequences. Thus, in addition to the virus-specific genes, RNA transcripts contain repetitive cell sequences (Tsuei et al., 1972). Wall and Darnell (1971) found that cells transformed with SV40 contain RNA with both viral and cellular sequences. In
cells transformed with SV40 heterogeneous nuclear RNA (HnRNA), molecules of very high molecular weight were shown to contain virus-specific RNA sequences, while polysomal virus-specific sequences were much smaller (see Darnell et al., 1971). HnRNA is thought to be transcribed from the reiterated DNA sequences implicated in regulation (see Darnell et al., 1971).

It also seems likely that such integrated virus DNA can undergo genetic exchanges with adjacent cell sequences. Aaronson (1971b) found that, when serologically distinct murine RNA viruses were grown in human cells, the various viruses acquired common surface antigens. He interpreted these data as signifying genetic exchange between human and viral genomes.

The information summarized in this section seems adequate to sustain the following conclusion: in eukaryotes "episome"-type (circular) DNA containing cellular and/or viral sequences can arise from reiterated DNA not only as a result of "infection" but also as a normal consequence of the processes of DNA replication-recombination-repair.

VI. Cytopathic Viruses May Be Atypical

Cytolytic viruses "broadcast" their presence because of their drastic effects on host cells. It was inevitable that such viruses would be the first to be discovered and investigated, and this has led to a widespread tendency to think of viruses only as destructive agents responsible for disease. However, the fact that cytopathic viruses are often of medical or economic importance to man does not justify the conclusion that such viruses are the norm when the whole ecology of viruses in the biosphere is taken into account.

The points discussed above raise the possibility that the reverse is true, that is, that cytopathic viruses—the ones most familiar to us—are atypical as viruses. This concept seems less drastic when one remembers the accepted dictum that "many infectious agents may remain latent in their natural hosts . . . but . . . may become pathogenic when transferred to other species" (Gross, 1970). For example, SV40 remains latent in its natural carrier Macaca mulatta but can induce a high incidence of sarcomas following inoculation into newborn hamsters (Gross, 1970).

This suggestion calls into question current views on the basic nature of (certain) viruses. The intention of this article is to reinterpret the role of (certain) viruses in terms of evolution.

VII. Some Evolutionary Considerations

There are certain aspects of evolution that have never been fully explained. The dilemma can be illustrated by quoting from Francis Crick (1970): "All biologists believe essentially that evolution is driven by natural selection. But someone from the more exact sciences could well point out that it has yet to
be explained that the rate of evolution can be adequately explained by the processes which are familiar to us. It would not surprise me if nature has evolved rather special and ingenious mechanisms so that evolution can proceed at an extremely rapid rate. . . ."

The possibility that gene exchange mediated by viruses might fit one require-
ment for a "special and ingenious mechanism" demanded by Crick is argued below. However, before this can be discussed it is necessary to examine carefully some of the accepted axioms of evolutionary theory.

The basic issue is the problem of variation. There was initially some doubt as to whether the inferred rates of mutation in certain species were enough to sustain the observed rates of evolution. But expressed rates of mutation are much lower than actual rates of mutation, for reasons summarized by Holmquist (1972).

The premise is accepted in this article that enough variation is provided by spontaneous mutation to account for the rates of evolution of all species in all periods.

However, in considering the dissemination of variation, it is necessary to distinguish carefully between the roles of processes such as recombination and sexual transfer. Significant (from the evolutionary standpoint) recombination can occur only when chromosomes or chromosome fragments of different genetic pedigrees are united in one cell. Thus while molecular recombination plays a basic role in enhancing variability, it is dependent for its effectiveness on the prior existence of mechanisms of gene transfer from cell to cell.

It should also be remembered that, especially in prokaryotes, the gene mate-
rial transferred has already passed the test of natural selection insofar as strongly deleterious mutations usually cause the death of the cell harboring them before any transfer can occur. Thus to a certain extent the numerical value of a given mutation rate is irrelevant to the rate and direction of evolution of a given species. The only "variability" of direct significance to an evolving clone is that which is not immediately selected out in the prevailing environment.

This statement does not presuppose that the variation introduced by mutation and accepted by the environment permits evolution to proceed at the observed rates. The complex enzymology of molecular recombination in all cells and the finely organized cytology of mitosis and meiosis in eukaryotes, underscore the fact that an enormous selective advantage accrues to any biological system able to shuffle preexisting variations into novel genetic mosaics for environmental "editing." This point is fundamental to the rest of the discussion.

VIII. The Role of Viruses in Evolution

There exist three known mechanisms by which gene material can be transferred from cell to cell: (1) transformation, (2) transduction, and (3) sexual
conjugation. It seems logical to assume that the order in which these have been listed reflects the order in which they have been exploited by evolution. **Transformation** is the most random and inefficient process, but it requires nothing more complex than the laws of diffusion and the existing chemistry of the cell membrane, modified in contemporary cells by the development of transport systems which facilitate membrane penetration (Tomaz, 1969). **Transduction** requires the development of genes for capsomere proteins able to encapsidate nucleic acid and/or a sophistication of the process of membrane evagination so as to package nucleic acid into free particles. These are relatively modest genetic adaptations. However, true sexual union as it occurs in modern eukaryotes requires such a high degree of cytological organization that it is inconceivable that it could have operated efficiently during the first billion or so years of cell evolution.

It is characteristic of evolution that the development of a system that more efficiently fulfills a strongly advantageous evolutionary need seldom entirely eliminates the less efficient system that preceded it in time. For example, nerve cells transmit messages from one part of a biological system to another far more quickly than the more "ancient" mechanism of transmission by chemicals, but chemical messengers (hormones) are still of basic importance in physiology.

It may be that the first postulated mechanism of gene interchange between cells—transfer of naked DNA (transformation)—has now been so effectively displaced by the second two that it modifies cell genotypes only in a few rare cases among prokaryotes (this may in fact not be true, as we know very little of the processes of genetic interchange among cells in natural environments). However, the postulate is advanced here that the mechanism of gene transfer by virus vectors played a predominant role in spreading acceptable variation in the long period prior to the effective emergence of eukaryote life, and (2) that because of the advantages discussed below this mechanism continues to influence evolution among most species and in certain situations may still be the dominant "driving force" for adaptive change.

In any sexual union there is always sedentary genetic material (female) and actively transferred genetic material (male). The male "gametes" transferred vary from virtually naked DNA in the case of mating male *E. coli* to the complex structures of vertebrate sperm which possess specialized organs of motility. However, *in essence* sperm are simply packets of DNA encapsidated in lipoprotein covers. The accessory structures (tail, and so on) are related almost entirely to the problem of transfer. The similarity to viruses is obvious; virus infection involves the transfer from one individual to another of packets of nucleic acid encapsidated in protein shells, for example, icosahedra, or in lipoprotein envelopes, for example, C-type viruses. While the **quantity** of information transferred by an individual virus is small, when the huge **numbers** of
viruses obtainable (in infection) are considered along with the rapid replication rate, then the potential effectiveness of viruses as gene vectors is considerable.

The sexual mechanism has the very great advantage that it achieves a full diploid condition. This has made possible the allelic shielding of mutant traits which might otherwise cause the immediate death of the cell harboring them. Sex allows a vast amount of variation to be stored in diploid cells and transmitted without loss or detriment to the cell from generation to generation.

There are many situations, however, in which the more random but more rapid mechanism of viral transduction may have advantages as a means of spreading variation. This postulate can be illustrated by the following example. The genetic map of E. coli can be transferred from one cell to another by mating. But the total genome of E. coli also exists in a lysate of cells infected with a generalized transducing phage such as PI (Ozeki and Ikeda, 1968). Now if it is of selective advantage to spread variation as effectively as possible, then clearly gene markers from one total E. coli genome can be disseminated among a far greater number of cells from the virus lysate than from the mating donor cell which, although it can potentially transfer the entire chromosome, can do so to only one recipient.

Further, it may be possible by transduction to spread genetic variations among species barred from interbreeding by species infertility. While viruses in general are highly specific for particular hosts, several are distributed throughout a surprisingly wide taxonomic range. Alfalfa mosaic virus, for example, is able to infect 222 different species of plants (Crill et al., 1970) (see Table I).

The ability to transfer genetic material is a property of the virus coat. In small, rapidly adapting systems such as viruses with (often) regular repetitious coat structures, it is far simpler to change cell substrate specificity than it is to break down the barriers that prevent two organisms from interbreeding, as a vastly greater number of mutations would be required to effect the latter change than the former.

Anderson (1970), in formulating a theory similar in part to that discussed in this article, postulated that a major evolutionary role of viruses was to carry genes across species and phylum barriers. We dispute this. Irrespective of how genes are transferred from cell to cell, the ability of the recipient to incorporate donor genes effectively into its chromosome depends upon the degree of base homology between donor and recipient DNAs. Clearly, the more closely related any two DNAs from different taxonomic sources, the greater the probability of effective assimilation. This may explain the usually strict specificity shown by viruses for particular cells. What is claimed here is that the more rapid adaptive capacity of viral transductants provides a greater flexibility which has surely been exploited by evolution at certain times in certain contexts.

Specifically then, this article envisages (certain) "viruses" as primarily agents
| Scientific name       | Common name             |
|----------------------|-------------------------|
| *Apium graveolens*   | Celery                  |
| *Ballota nigra*      |                         |
| *Beta saccharifera*  | Sugar beet              |
| *Capsicum* spp.      | Pepper                  |
| *Carthamus tinctorius* | Safflower              |
| *Chenopodium album* | Lambs quarters          |
| *Cicer arietum*      | Garbanzo bean           |
| *Cichorium endivia*  | Endive                  |
| *Crotalaria juncea*  | Sunn hemp               |
| *Crotalaria spectabilis* |                     |
| *Daphne odora*       |                         |
| *Dianthus Caryophyllus* | Carnation              |
| *Dolichos lablab*    | Hyacinth bean           |
| *Glycine javanica*   |                         |
| *Glycine max*        | Soybean                 |
| *Lathyrus odoratus*  | Sweet pea               |
| *Lupinus* spp.       | Lupin                   |
| *Majorana hortensis* |                         |
| *Medicago lupulina*  | Hop clover              |
| *Medicago sativa*    | Alfalfa                 |
| *Menibha piperita*   | Peppermint              |
| *Nicotiana tabacum*  | Tobacco                 |
| *Ocimum basilicum*   |                         |
| *Phaseolus vulgaris* | Bean                    |
| *Physalis sp.*       | Groundcherry            |
| *Pisum sativum*      | Pea                     |
| *Portulaca oleracea* |                         |
| *Solanum melongena*  | Eggplant                |
| *Solanum nigrum*     |                         |
| *Solanum tuberosum*  | Potato                  |
| *Sonchus arvensis*   |                         |
| *Sonchus cornutus*   |                         |
| *Sonchus olearceus*  |                         |
| *Stachys* annua*     |                         |
| *Trifolium pratense* | Red clover              |
| *Trifolium repens*   | White clover            |
| *Viburnum opulus*    |                         |
| *Vicia faba*         | Broad bean or horse bean|
| *Vitis vinifera*     | Grape                   |

* From Crill *et al.* (1970).
of gene exchange between cells. On this basis (certain) viruses and cells have coevolved from a "point" close to the origin of the phylogenetic tree and/or from branch points in the tree. Gilden and Oroszlan (1972) note that, for the gs antigen of the C-type viruses, three of the first four amino acids at the N terminus of cat and mouse gs antigen are the same, while, except for the terminal Pro, the chick sequence is distinct. This is the first experimental evidence for the coevolution hypothesis.

What is the detailed evidence for this postulated role of viruses? The discussion falls into two parts, the first dealing with DNA viruses, and the second with RNA viruses. The reason for this division becomes apparent as the discussion proceeds.

IX. DNA Viruses

The ability of DNA phages such as λ to integrate with cell genomes with the necessary base homology, and conversely to act as vectors of host genes, is well documented. Virtually no ecological work has been done to investigate the extent to which these processes operate in nature.

As a model of a DNA virus for higher cells, which may fulfill some of the requirements of the theory, consider polyoma.

Early experiments seemed to indicate extensive base homology between mouse and polyoma DNA (Axelrod et al., 1964). This homology was subsequently shown to result from the presence of host DNA encapsidated within polyoma virions (Winocour, 1969).

Further experiments have indicated that any host genetic marker can become encapsidated in polyoma protein (Winocour, 1968, 1969). The host DNAs so incorporated have a buoyant density indistinguishable from that of the uninfected cell (Winocour, 1968). Ben-Porat and Kaplan (1967) have concluded that all mouse embryo cell DNA that replicates after infection is eventually degraded to a size similar to that of polyoma DNA. Winocour (1969) concludes that "the breakdown of mouse cellular DNA before encapsidation must be a specific [author's italics] process in view of the relatively restricted size of the fragments that are produced."

These data suggest that the polyoma genome encodes a nuclease specific for the host DNA. To account for the uniform size of the fragments produced, it is tempting to speculate that the five methylcytosine residues that occur in mouse DNA but not in polyoma DNA act as signals for the enzyme, and that these are spaced at "polyoma DNA unit lengths" throughout the mouse genome. It is difficult to see the biological advantage of this specific fragmentation of host DNA if the virus is considered solely as a lytic virus. However, the phenomenon
is quite intelligible if we consider the mouse cell–polyoma genomes part of one
general and interchangeable genetic system.

An alternative hypothesis to explain the data is that the size of the mouse cell
DNA fragments is determined by the capacity of the polyoma capsid to accomo-
date them physically (cf. Streisinger's "headfull" hypothesis for T4). If this is
ture, it means that polyoma capsid subunits must have far less preferential affini-
ity for polyoma DNA than do the capsomeres of another "temperate" virus such
as λ which normally efficiently packages only homologous DNA. Either possibility
leads rather easily to the concept that the encapsidation of host genes by polyoma
protein is more a normal function of the system than an atypical "mistake" in
the assembly of the virus.

If polyoma does fulfill the requirements of the theory, we might expect that
its own DNA could integrate into mouse cell chromosomes. It is known that
multiple copies of polyoma DNA can lie in tandem in cell DNAs (Watson,
1970). The presence of these cryptic copies of virus genetic material has been
detected only because cells harboring it are transformed from normal into can-
cerous. However, if no such medically obvious effect occurred, it is possible
that the virus genes could lie latent in the cell chromosomes without ever being
detected.

One obvious objection is this. The very act of encapsidating an essential host
gene presupposes that this gene will be lost from the host chromosome. Does it
not follow that when such transductions occur the donor chromosome will in-
evitably be damaged or destroyed and the cell killed?

It does follow that such "silent" transducing viruses must preserve the integrity
of cell chromosomes. One way to do this would be for the virus to stimulate
compensating host cell DNA synthesis. In accord with this requirement, polyoma
infection has been shown to overcome the blockages of DNA synthesis arising
from a number of causes (Winocour, 1969). It may be significant that every
cell induced by polyoma to make DNA approximately doubles its DNA content
(Gershon et al., 1965). The DNA made after infection is methylated normally
(Winocour et al., 1965), a point that may be important if five methylcytosine
residues serve as recognition signals for DNA degradation by a virus-encoded
enzyme, as suggested earlier.

It should not be forgotten that polyoma may not be and probably is not a
true representative of the type of silent transducing virus envisaged here. A
truly cryptic virus would have no adverse effect on the cell it enters. However, it
would have to stimulate DNA synthesis to prevent damage to the cell chromo-
some from which genes were being transduced. In a truly cryptic type of virus,
stimulation of DNA synthesis would be a controlled process and may in fact be
coupled to normal replication of the host chromosome. In the case of polyoma,
the usual controls have apparently ceased to operate; from this it follows that laboratory strains of polyoma can cause cancer which arises from uncontrolled DNA synthesis.

**X. RNA Viruses**

**Activator RNA**

Before beginning to discuss the possible role of RNA viruses in evolution, it is necessary to digress.

It is now well established that many DNA sequences in higher organisms are repetitive (Britten and Kohne, 1968). This has led to a widely accepted model of eukaryote cell regulation (Britten and Davidson, 1969). The main features of this model are:

1. Much DNA in the cells of higher organisms serves a regulatory function.
2. Gene sets are switched on by activator RNA, this RNA being produced by a special class of regulatory genes called integrator genes.
3. The regulatory genes are members of families of repeated DNA sequences.

From the Britten–Davidson model, it follows that, during the evolution of higher organisms, few new proteins need enter into the structure and/or physiology of organisms. Rather large morphological changes result from slight changes in the integrative function, by modulating preexisting gene sets. We stress that a key molecule in this scheme is the product of the integrator gene—activator RNA whose function it is to switch on a given gene battery, depending upon the particular signal fed into the system either by the environment or by the product of a previously activated structural gene.

Let us examine RNA viruses in the light of this theory. If one tabulates the viruses that contain RNA as opposed to DNA and lists the taxonomic groups for which these are specific (see Appendix), one very striking fact emerges. Most of the viruses affecting differentiated organisms contain RNA. Almost all plant viruses contain RNA and, according to currently available evidence about 70% of known animal viruses contain RNA. By contrast, in prokaryotes, the vast majority of phages contain duplex DNA. The only RNA viruses that occur in bacteria are specific for cells that may perhaps be considered "differentiated" in that they possess sex factors.

We suggest that there is a direct correlation between the distribution of RNA and DNA viruses and the degree to which a given host genome contains repetitive DNA. In prokaryotes, in which most genes are unique, selection has favored DNA-transducing viruses which act as vectors for structural genes. In differentiated cells, however, as Britten and Davidson have stressed, the probability of utilization of new DNA for regulation is far greater than the likelihood of inven-
tion of a new and useful amino acid sequence. Since a key element in their regulatory model is activator RNA, it becomes possible to see why—if viruses fulfill an essential role in spreading variability through gene pools—viruses specific for differentiated cells normally contain RNA.

Note that this "rule" may not apply to very small viruses whose RNA genomes are the size of cellular mRNAs, for example, among plants TYMV, and so on, and among animals polio, foot and mouth, and so on. In these cases a different and plausible explanation for the RNA character of their genomes is possible, namely, that once selection has simplified a virus genome to the extent that all relevant information can be contained in one polycistronic message a DNA equivalent of this message is uneconomical in terms of packaging and expensive in terms of replication/transcription. We are specifically thinking of viruses whose RNA is relatively large and whose structure seems to be derived in large part from cell membranes. The "budding" process so characteristic of C-type viruses strongly resembles a normal cellular function such as membrane evagination in superficial appearance. However, it is possible that the only host components to enter virus envelopes are lipids, and that virus maturation involves a marked restructuring of the cell membranes to accommodate virus-specified proteins. The status of this question is still open, but it is interesting to note that viruslike particles are known that bud from the membranes of the endoplasmic reticulum but which have no demonstrable infectious ability. These intracisternal A-type particles (Kuff et al., 1972) may be regarded as immature virions, or they may be viewed as mistakes in the process of information flow—for some reason they are not encapsidating activator RNA.

The most striking feature of Part B of the Appendix is that with the exception of the herpesvirus group, no virus whose essential envelope structure is formed by budding from "cell" membranes contains DNA. (Viruses of the herpes group bud from membranes, but the particles are already encapsidated in icosahedral shells.)

Thus the "infectious" viruses that most closely fit the postulates of this article are those like lettuce necrotic yellows and wheat striate mosaic, and so on in plants, and rabies, and so on in animals. Even more relevant are the temperate B- and C-type cancer viruses of animals. However, such viruses have been detected only because of their ability to bring about cell transformation and/or to produce "infectious" virus on treatment with inductive chemicals. The possibility exists that "virus" particles may be found that are not infectious, because they act in part or in whole as vectors of host genetic material (see Section XII).

The efficiency of such a pathway of information flow would be greatly enhanced if the transduced host material could be amplified either before leaving the donor cell or on entry into the recipient cell. This could be achieved (a) by enzymes associated with the structure of the transducing virus particle, (b) by
enzymes encoded in further polynucleotide contained in the transducing particle, (c) by enzymes in the donor or recipient cells.

XI. The Genomes of (Certain) RNA Viruses Can Be Considered Activator RNA

Specifically, it is suggested here that the single-stranded RNA virus genomes are in part activator RNA. While there is no evidence yet that such RNA genomes bind to reiterated cell DNA, it may be significant that the RNA transcript of adenovirus DNA contains reiterated cell sequences, suggesting that the DNA of this virus integrates at such repetitive parts of the chromosome (Tsuei et al., 1972). Sivolap and Bonner (1971) found that chromosomal RNA (cRNA), which may be the homolog of activator RNA, binds chiefly to repetitive DNA. In his model of the eukaryote chromosome, Crick (1971) postulated that unpaired regions of DNA consisting of repeated sequences serve as control elements. Crick noted that the unpaired state of control DNA facilitates selective binding of activator RNA.

One possible experimental prop for the concept of "viral" activator RNA is the existence of viroids such as potato spindle tuber virus (PSTV). Diener (1971) showed that the infectious entity in the disease is a low-molecular-weight RNA of sufficient size to code for only about 25 amino acids. The difficulty of envisaging how such a small molecule could effect its own reproduction led Diener to the postulate that the necessary biosynthetic information preexists in susceptible hosts, and that PSTV RNA functions not as mRNA but as "an abnormal regulatory RNA" (Diener, 1971). In this context one notes that two of the nucleus-confined RNAs put forward by Britten and Davidson (1969) as possible candidates for activator RNA (e.g., the RNAs from HeLa cell nuclei and pea seedling nuclei) were only about 40 to 180 nucleotides in length.

The chances that the introduction of alien RNA into cells will result in gross malfunction are negligible, because virus RNA can act as activator RNA only if it possesses adequate base homology with (unpaired) receptor DNA.

It is especially easy to see how C-type RNA tumor viruses might act in this context. As Schlom et al. (1971) showed, these particles all contain the enzyme reverse transcriptase as part of the physical structure of their cores. Thus not only could they activate gene batteries, but the change could—if advantageous—become hereditary because the DNA transcript of the RNA could itself become integrator DNA from which modulated activator RNA might be produced. The theory predicts either that reverse transcriptase will be found in association with any RNA virus that fulfils the role of spreading gene variation, or that normal cells will be found to contain reverse transcriptase, especially during embryogenesis.

Since hereditary stabilization of any variation introduced by viruses seems to
require reverse transcriptase activity, it might at first sight seem more economical to introduce such variation in DNA form; on this basis most eukaryote viruses should contain DNA. Such DNA, however, if integrated into receptor or integrator gene sets, would still be switched off. The result would be an increment in the quantity of available information and a slight change in quality if the introduced sequences differed from the original, but no immediate change in biochemical patterns of activation. (This point is further discussed in Section XII.

The status of the function of reverse transcriptase at the moment is still ambiguous. Goodman and Spiegelman (1971) have defined criteria for distinguishing "true" reverse transcriptase from other cell polymerases. Fridlender et al. (1972) found a novel enzyme in human tissue cells which efficiently copies the ribo strand of synthetic oligonucleotide-homopolymer complexes but, unlike the reverse transcriptase in C-type viral capsids, this enzyme seems unable to utilize efficiently natural RNA as substrate. Temin (1972) has promulgated the view that reverse transcriptase plays an important role in normal embryogenesis. Todaro and Huebner (1972) have noted the occurrence of virus-specific gs antigen early in embryonic life, and the possibility must be entertained that this "viral" element may play a role in differentiation. In this context it is interesting to note that Stavrianopoulos et al. (1971) found a predominant enzymic activity in the developing (4-day) chick embryo, which prefers a DNA–RNA hybrid as template; the importance of this enzyme seems to decline in later stages of embryogenesis.

It is possible from the above arguments that erroneous activation of cell gene sets by RNA viruses, while unlikely, may sometimes occur; one such case is the activation of the gene set for DNA synthesis under conditions in which synthesis is not needed. This might result in a cancerous condition. The probability of tumor generation seems to be higher for the specifically regulatory RNA viruses than for a general DNA transducing virus such as polyoma, and this may account for the fact that RNA viruses cause cancer in nature, whereas lethal oncogenesis by polyoma is thought to be a laboratory artifact (Watson, 1970).

One fascinating extension of the theory is that activator RNA introduced into differentiated cells by viruses may activate repressed gene sets which are themselves of viral origin. This would complete the feedback circuit and may provide an explanation for the low-frequency stochastic release of C-type RNA virus particles from many vertebrate cells (see Weiss et al., 1971).

XII. Nongenetic Influence of Transducing Viruses

One of the most serious criticisms of the theory presented in this article is that viruses (apparently) infect predominantly somatic cells, hence any variation introduced by them would not be hereditary.

This contradiction may be more apparent than real. Bentvelsen et al. (1970)
found that murine oncogenes were transmitted vertically, and it is basic to the oncogene hypothesis that virus information is part of the vertically transmitted gene complement. The oncogene hypothesis thus presupposes that virus genes entered cellular germ lines at past points in evolutionary time [conversely, one can accept the postulate that such "viruses" arose (arise?) from normal cell chromosomes by acquiring independent replicative potential.] How far such processes operate in the lifetimes of individual organisms must be speculative until more data are available. C-Type viruses are known to occur in germinal cells. Virus budding was found by Dougherty and Di Stefano (1967) to take place in cells derived from all three embryonic germ layers. Avian leukemia virus multiplied well in the adult female reproductive system. Electron microscope data showed the presence of type-B viruses in the genital organs of R 111 and DBA male mice (Moore, 1963).

The propagation of a virus in the germinal cells is well documented in the case of of sigma virus of Drosophila. The carbon dioxide sensitivity caused by sigma is hereditary but is not transmitted according to Mendelian laws (Howatson, 1970). Berkaloff et al. (1965) found budding particles in sections of ovarian cysts of female Drosophila stabilized in their possession of the carbon dioxide-sensitive phenotype. Teninges (1968) saw rod-shaped particles budding from early spermatids but not from somatic cells.

In this context it may be significant that Szakal and Hanna (1968) found budding particles in the germinal centers of mouse spleens, compared to their relative absence from mature lymphocytes.

In point of fact it is not strictly necessary to postulate stabilization of variation in the germ cells to obtain the same overall result. Consider a simplified case. Organism X has associated with it 10 virus types. These interact with each other and with X such that continual but slight somatic variations exist between the individuals of the X population over and above those introduced by sexual transfer. Now selection acts not upon the genome of X per se but upon the "symbiotic" X-virus genetic interchange. If a particular virus (e.g., virus 5) confers upon an individual of X (or more probably an interbreeding group) a slight advantage such that X1 can reproduce more often and/or more effectively than the rest of the population, then there will be a slow selection for X1, provided the relevant virus continues to transduce advantageous information; the process will have a snowball effect, for the more rapidly X1 reproduces relative to the rest of the population, the greater the availability of the relevant virus 5 in the environment.

In one sense virus 5 is an environmental influence. Since it is a replicating genetic system, however, an evolutionary feedback is possible which is inconceivable with any other "nonhereditary" factor.
XIII. Noninfectious Viruslike Particles

If the chief postulate(s) of this article is correct, then there should exist in many cells at many times viruslike particles with no "infectious" character to which no pathological state can be attributed.

The existence of such "passenger" viruses has been documented for a very long time. It is exceedingly difficult, however, to prove that a virus which is a passenger in one species is not an infectious agent in another. The listing given below simply indicates that many reports are consistent with the postulate that viruslike particles transduce information without autonomous replicative potential.

The number of species in which such observations have been made is striking. Viruslike particles have been noted in the ameboflagellate Nagleria gruberi (Schuster and Dunnebacke, 1971); in Paramecium aurelia (Peer and Jurand, 1968); in Cephalosporium acremonium (Day and Ellis, 1971); in various strains of Penicillium (Banks et al., 1969); in Drosophila melanogaster (Philpott et al., 1969; Akai et al., 1967); in the wood ant (Steiger et al., 1969); in the beetle Tenebrio molitor (Zeikus and Steinhaus, 1969); in mice (Szakal and Hanna, 1968); and in guinea pigs (Ma et al., 1969). These are only a few of the many references that could be quoted.

Viruslike particles have often been noted in higher plants; Anton-Lamprecht (1965, 1966) observed in healthy Epilobium hybrids with the "irregular" plasma type large numbers of double-membrane particles with a core which was assumed to be RNA.

A large number of references describe the occasional appearance of particles resembling B- and C-type viruses in healthy animals (Dmochowski et al., 1963; Feldman and Gross, 1966; Feldman et al., 1967; Benedetti, 1957; among others).

XIV. History of the Theory

Several scientists have from time to time implicated viruses as positive agents in various aspects of evolution (e.g., Danielli, 1953). A short article embodying the central thesis of the present theory was presented by Anderson (1970). However, we disagree with the interpretation placed by Anderson on certain data, for example, the transducing ability of viruses between distantly related species. Anderson's views have also been criticized by West (1971). What is novel in this article is the unification of a considerable amount of data, much of it very recent, into what purports to be a coherent framework in which the existence of cancer viruses and the distribution of DNA and RNA viruses through taxonomy finds a logical basis.
**XV. Conclusion**

Viral transduction of both structural and regulatory genes provides a means for information to leave the body of an organism other than through the germ cells.

Thus if the theory is correct natural selection does not—and perhaps never has—act upon cell genomes as has commonly been believed. Natural selection acts upon the cell-virus nucleic acid coupling, and the rate and direction of the evolution of any species depends upon the number of associated viruses and the extent to which and speed with which they allow information to be cycled through the total gene pool of that population.

It is to be expected that nature has exploited this fundamental mechanism in a variety of ways, so that to look for a uniform process today may be unrealistic.

**Acknowledgments**

I am grateful to Mr. M. Allinson for help in compiling the Appendix and to Professor R. K. Ralph for critical discussion of the manuscript. I express my appreciation to the Lincoln College Council for supporting this work with the aid of a grant.

**Note Added in Proof**

A large amount of pertinent data has accumulated since acceptance of this article on November 3, 1972. Among the relevant papers, that by Koch deserves mention [J. Koch, *FEBS Lett.* 32, 22 (1973)]. Koch found (a) that in hamster cells, small DNA molecules (cDNAs) were migrating from nucleus to cytoplasm, (b) that such cDNA molecules appeared to contain unique base sequences, and (c) that the quantity of cDNA was greatest in embryo cells or in polyoma transformed cells. These observations are consistent with the notion that nuclear genes are regularly passaged from nucleus to environment: Koch's suggestion that polyoma activates a mechanism for nuclear gene amplification normally repressed in fully differentiated cells can be interpreted in terms of the role postulated for such viruses in this article.

If viral RNA does serve, in part, as regulatory RNA as suggested in this article, it may seem odd that about 99% of known plant viruses contain RNA since plants, which lack complex nervous and muscular systems, are generally considered less complex than animals. But to an extraordinary degree the variety of plant species can be explained on the basis of regulatory changes: modulations in overall size/shape/leaf and stem morphology, etc., do not usually require the introduction of novel proteins, rather alterations in rates and patterns of growth and differentiation. The existence of a pool of regulatory RNAs able to pass from individual to individual or species to species makes good sense in plants as it would maximize rapid adaptability to environmental changes. The essence of this argument is that it is precisely because the structure of higher plants is less inflexibly organized than that of higher animals that virus-transduced regulatory genes are more likely to be effective in producing adaptive change. For example, the introduction of a regulatory RNA that doubles the quantity of tissue produced at a specific stage of differentiation might matter little in a plant whereas to the finely coordinated biology of a vertebrate such a change would be intolerable.
Also, being sessile, many higher plants have to rely for fertilization on random processes (wind, passive carriage by insects)—the very processes which disseminate viruses! A final point is that in many plants the difficulty raised by the oncogene hypothesis of having to introduce virus information into the germ cells may not occur. An advantageous change stimulated in a local part of a plant by a viral RNA could be passed on to progeny by vegetative propagation of that section. If the viral RNA genes were transformed into DNA by reverse transcriptase, the vegetative product could regenerate a plant able to engage in sexual conjugation. It must be remembered that unlike the situation with animals an entire plant can often be regenerated from a differentiated cell.

We wish to take this opportunity to stress that the validity of the hypothesis proposed in this article does not depend too heavily on the existence or otherwise of activator RNA as such. As Britten and Davidson (1969) noted in their paper the structure of their model would not be changed if the regulatory function was carried out by some translation product of "activator" RNA.

REFERENCES

Aaronson, S. A. (1971a). Proc. Nat. Acad. Sci. U.S. 68, 3069.
Aaronson, S. A. (1971b). Nature (London) 230, 445.
Akai, H., Gateff, E., Davis, L. E., and Schneiderman, H. A. (1967). Science 157, 810.
Anderson, N. G. (1970). Nature (London) 227, 1346.
Anton-Lamprecht, I. (1965). J. Ultrastruct. Res. 12, 624.
Anton-Lamprecht, I. (1966). Z. Vererbungsfl. 98, 257.
Axelrod, D., Bolton, E. T., and Habel, K. (1964). Science 146, 1466.
Babel, F. J. (1962). Advan. Appl. Microbiol. 4, 51.
Baluda, M. A. (1972). Proc. Nat. Acad. Sci. U.S. 69, 576.
Banks, G. T., Buck, K. W., Chain, E. B., Darbyshire, J. E., and Himmelweit, F. (1969).
Nature (London) 222, 89.
Barnet, Y. M. (1972). J. Gen. Virol. 15, 1.
Benedetti, E. L. (1957). Bull. Cancer 44, 473.
Bendis, I., and Shapiro, L. (1970). J. Virol. 6, 847.
Ben-Porat, T., and Kaplan, A.S. (1967). Virology 32, 457.
Bentvelsen, P., Daams, J. H., Hageman, P., and Calafat, J. (1970). Proc. Nat. Acad. Sci.
U.S. 67, 377.
Berkaloff, A., Bregliano, J. C., and Ohanessian, A. (1965). C. R. Acad. Sci. 260, 5956.
Bradley, D. E. (1967). Bacteriol. Rev. 31, 230.
Bradley, D. E. (1971). In "Comparative Virology" (K. Maramorosch and E. Kurstak,
eds.), p. 208. Academic Press, New York.
Britten, R. J., and Davidson, E. H. (1969). Science 165, 349.
Britten, R. J., and Kohne, D. E. (1968). Science 161, 529.
Brunt, A. A. (1971). Ann. Appl. Biol. 67, 357.
Callan, H. G. (1967). J. Cell Sci. 2, 1.
Campbell, A. (1962). Advan. Genet. 11, 101.
Campbell, A. (1969). "Episomes." Harper and Row, New York.
Collins, E. B. (1952). J. Dairy Sci. 35, 381.
Collins, E. B. (1955). Appl. Microbiol. 3, 137.
Crick, F. H. C. (1970). Nature (London) 228, 613.
Crick, F. H. C. (1971). Nature (London) 234, 25.
Crill, P., Hagedorn, D. J., and Hanson, E. W. (1970). *Wis., Agr. Exp. Sta., Res. Bull.* No 280.

Danielli, J. F. (1953). *Symp. Soc. Exp. Biol.* 7, 440.

Darnell, J. E., Wall, R., and Tushinski, R. J. (1971). *Proc. Nat. Acad. Sci. U.S.* 68, 1321.

Day, L. E., and Ellis, L. F. (1971). *Appl. Microbiol.* 22, 919.

de Bokx, J. A., ed. (1972). "Viruses of Potatoes and Seed-Potato Production." Center for Agricultural Publishing and Documentation, Wageningen.

Diener, T. O. (1971). *Virology* 45, 411.

Dmochowski, L., Grey, C., Padgett, F., and Sykes, J. A. (1965). In "Viruses, Nucleic Acids and Cancer," Symp. Fundam. Cancer Res., Vol. 17, pp. 83 Williams Wilkins, Baltimore, Maryland.

Dougherty, R. M., and Di Stefano, H. S. (1967). *Cancer Res.* 27, 322.

Edelman, G. M., and Gall, W. E. (1969). *Annu. Rev. Biochem.* 38, 415.

Feldman, D. G., and Gross, L. (1966). *Cancer Res.* 26, 412.

Feldman, D. G., Dressyuss, Y., and Gross, L. (1967). *Cancer Res.* 27, 1792.

Fridlender, B., Fry, M., Bolden, A., and Weissbach, A. (1972). *Proc. Nat. Acad. Sci. U.S.* 69, 452.

Gerber, P. (1972). *Proc. Nat. Acad. Sci. U.S.* 69, 83.

Gershon, D., Hausen, P., Sachs, L., and Winocour, E. (1965). *Proc. Nat. Acad. Sci. U.S.* 54, 1584.

Gilden, R. V., and Oroszlan, S. (1972). *Proc. Nat. Acad. Sci. U.S.* 69, 1021.

Goodman, N. C., and Spiegelman, S. (1971). *Proc. Nat. Acad. Sci.* 68, 2203.

Gross, L. (1970). "Oncogenic Viruses." 2nd Ed. Pergamon, Oxford.

Hampar, B., Derge, J. G., Martos, L. M., and Walker, J. L. (1972). *Proc. Nat. Acad. Sci. U.S.* 69, 78.

Holmquist, R. (1972). *J. Mol. Evol.* 1, 115.

Howatson, A. F. (1970). *Advan. Virus Res.* 16, 195.

Huebner, R. J., and Todaro, G. J. (1969). *Proc. Nat. Acad. Sci. U.S.* 64, 1087.

Huebner, R. J., Kelloff, G. J., Sarma, P. S., Lane, W. T., Turner, H. C., Gilden, R. V., Oroszlan, S., Meier, H., Myers, D. D., and Peters, R. L. (1970). *Proc. Nat. Acad. Sci. U.S.* 67, 366.

Hunt, D., Saito, Y., and Watanabe, M. (1971). *J. Biol. Chem.* 246, 4151.

Jann, K., Schmidt, G., Wallenfels, B., and Freundmolbert, E. (1971). *J. Gen. Microbiol.* 67, 289.

Jawetz, E., Melnick, J. L., and Adelberg, E. A. (1970). "Review of Medical Microbiology," 9th Ed. Lange Med. Publ., Los Altos, California.

Kuff, E. L., Lueders, K. K., Ozer, H. L., and Wivel, N. A. (1972). *Proc. Nat. Acad. Sci. U.S.* 69, 218.

Lederberg, E. M. (1951). *Genetics* 36, 560.

Lwoff, A., and Tournier, P. (1971). In "Comparative Virology" (K. Maramorosch and E. Kurstak, eds.), p. 2. Academic Press, New York.

MacPhee, D. G., Sutherland, I. W., and Wilkinson, J. F. (1969). *Nature (London)* 221, 475.

Ma, B. I., Swartzendruber, D. C., and Murphy, W. H. (1969). *Proc. Soc. Exp. Biol. Med.* 130, 586.

Maramorosch, K., and E. Kurstak, eds. (1971). "Comparative Virology." Academic Press, New York.

Matthews, R. E. F. (1970). "Plant Virology." Academic Press, New York.
Miyake, T., Haruna, I., Shiba, T., Itoh, Y., Yamane, K., and Watanabe, I. (1971). Proc. Nat. Acad. Sci. U.S. 68, 2022.

Merril, C. R., Geier, M. R., and Petricciani, J. C. (1971). Nature (London) 233, 398.

Michel, M. R., Hirt, B., and Weil, R. (1967). Proc. Nat. Acad. Sci. U.S. 58, 1381.

Mise K. (1971). J. Virol. 7, 168.

Moore, D. H. (1963). Nature (London) 198, 429.

Nowinski, R., Edynak, E., and Sarkar, N. (1971). Proc. Nat. Acad. Sci. U.S. 68, 1608.

Ozeki, H., and Ikeda, I. (1968). Annu. Rev. Genet. 2, 245.

Philpott, D. E., Weibel, J., Atlan, H., and Miquel, J. (1969). J. Invert. Pathol. 14, 31.

Reaney, D. C., and Jurand, A. (1968). Genet. Res. 12, 331.

Rowe, W. P., Lowy, D. R., Teich, N., and Hartley, J. W. (1972). Proc. Nat. Acad. Sci. U.S. 69, 1033.

Rueckert, R. R. (1971). In "Comparative Virology" (K. Maramorosch and E. Kurstak, eds.), p. 256. Academic Press, New York.

Schlim, J., Harter, D. H., Burny, A., and Spiegelman, S. (1971). Proc. Nat. Acad. Sci. U.S. 68, 182.

Schuster, F. L., and Dunnbeacke, T. H. (1971). J. Ultrastruct. Res. 36, 659.

Shephard, R. J., Wakeman, R. J., and Romanoko, R. R. (1968). Virology 36, 150.

Sivolap, Y. M., and Bonner, J. (1971). Proc. Nat. Acad. Sci. U.S. 68, 387.

Smith, H. S., Gelb, L. D., and Martin, M. A. (1972). Proc. Nat. Acad. Sci. U.S. 69, 152.

Sober, H. A. (1968). "Handbook of Biochemistry," 2nd Ed. Chem. Rubber Publ. Co., Cleveland, Ohio.

Stavrianopoulos, J. G., Karkas, J. D., and Chargaff, E. (1971). Proc. Nat. Acad. Sci. U.S. 68, 2207.

Steiger, U., Lamparter, H. E., Sandri, C., and Akert, K. (1969). Arch. Gesamte Virusforsch. 26, 271.

Stent, G. (1963). "Molecular Biology of Bacterial Viruses," Freeman, San Francisco, California.

Szakal, A. K., and Hanna, M. G. (1968). Exp. Mol. Pathol. 8, 75.

Teh, P., and Reaney, D. C. (1973). Soil. Biol. Biochem. Submitted for publication.

Temin, H. M. (1972). Proc. Nat. Acad. Sci. U.S. 69, 1016.

Teninges, D. (1968). Arch. Gesamte Virusforsch. 23, 378.

Thomas, C. A. (1970). In "The Neurosciences. A Study Program." (F. O. Schmitt, ed), p. 973. Rockefeller Univ. Press, New York.

Thomas, C. A., Hamkalo, B. A., Misra, D. N., and Lee, C. S. (1970). J. Mol. Biol. 51, 621.

Todaro, G. J., and Huebner, R. G. (1972). Proc. Nat. Acad. Sci. U.S. 69, 1009.

Tomaz, A. (1969). Annu. Rev Genet. 3, 217.

Tsuchida, N., Noboyama, M., and Ikeda, Y. (1971). J. Gen. Appl. Microbiol. 17, 63.

Tsuei, D., Fujinaga, K., and Green, M. (1972). Proc. Nat. Acad. Sci. U.S. 69, 427.

Varmus, H. E., Weiss, R. A., Friis, R. R., Levinson, W., and Bishop, J. M. (1972). Proc. Nat. Acad. Sci. U.S. 69, 20.

Wall, R., and Darnell, J. (1971). Nature (London), New Biol. 232, 73.
Watson, J. D. (1970). "The Molecular Biology of the Gene." 2nd Ed. Benjamin, New York.
Weiss, R. A., Friis, R. R., Katz, E., and Vogt, P. K. (1971). *Virology* 46, 920.
Weppelman, R., and Brinton, C. (1971). *Virology* 44, 1.
West, D. A. (1971). *Nature (London)* 229, 637.
Wildy, P (1971). "Classification and Nomenclature of Viruses." Monogr. Virol. vol. 5.
Karger, Basel.
Winocour, E. (1968). *Virology* 34, 571.
Winocour, E. (1969). *Adv. Virus Res.* 14, 155.
Winocour, E., Kaye, A. M., and Stollar, V. (1965). *Virology* 27, 156.
Wolf, K. (1966). *Adv. Virus Res.* 12, 36.
Zeikus, R. D., and Steinhaus, E. A. (1969). *J. Invert. Pathol.* 14, 115.
Zur Hausen, H., Diehl, V., Wolf, H., Schulte-Holthausen, H., and Scheider, V. (1972).
*Nature (London), New Biol.* 237, 189.

**APPENDIX**

Part A. The Numbers of Different Viruses/Species

While phages are known for many bacterial species, in the majority of cases the numbers of characterized phages are gross underestimates of the "correct" figures. Hence only the known phages for two intensively researched bacteria, *E. coli* and *Bacillus subtilis*, are given here. There is no reason to doubt that the number of phages for other bacterial species will prove to be much less when the pertinent research is done.

**DNA-CONTAINING VIRUSES**

**FOR E. coli**

| Name | Reference | Name | Reference |
|------|-----------|------|-----------|
| T1   | Sober (1968) | T2   | Sober (1968) |
| T3   | Sober (1968) | T4   | Sober (1968) |
| T5   | Sober (1968) | T6   | Sober (1968) |
| T7   | Sober (1968) | λ    | Sober (1968) |
| Ω8   | Jann et al. (1971) | ΦX174 | Sober (1968) |
| WAK(2) | Bradley (1967) | ZG/3A | Bradley (1967) |
| P1   | Mise (1971) | D108 | Mise (1971) |
| N4   | Sober (1968) | M13  | Sober (1968) |
| fd   | Sober (1968) | E1   | Bradley (1967) |
|      |            | DD7  | Sober (1968) |
|      |            | Y2   | Bradley (1967) |
|      |            | Φ15  | Sober (1968) |
| P2   | Sober (1968) | α3   | Bradley (1971) |
| ΦR   | Sober (1968) | Φ80  | Sober (1968) |
| χ    | Sober (1968) | Sd   | Sober (1968) |
| C16  | Sober (1968) | fr   | Sober (1968) |
| AE2  | Sober (1968) | f1   | Sober (1968) |
| P2   | Sober (1968) | P1kc | Sober (1968) |
| 15   | Sober (1968) | Total | 34 |
VIRUSES AND EVOLUTION

DNA-CONTAINING VIRUSES
FOR B. subtilis

| Name | Name | Name |
|------|------|------|
| f2   | f    | NT   |
| 17   | sP10 | sP8  |
| 29   | PBS1 | sP82 |
| SP3  | PBS2 | sPO-1|
| pKc  | SP90 | sE   |
| SPo  | sP100| 25   |
| SPX  | sP70 | sP60 |
| SPso | sP80 | sP6  |
| 1    | sPT  | 7    |
| 2    | 6a   | 9    |
| 14   | 6b   | 13   |
| Vx   | 4P   | sPP-1|
|      |      | Total = 36 |

*From Sober (1968).*

Apart from the 18 phages listed below, all remaining characterized phages, to the best of our knowledge, contain DNA.

RNA-CONTAINING VIRUSES

| Name | Host         | Reference                |
|------|--------------|--------------------------|
| f2   | E. coli      | Mikaye et al. (1971)     |
| r17  | E. coli      | Mikaye et al. (1971)     |
| MS2  | E. coli      | Mikaye et al. (1971)     |
| ZR   | E. coli      | Mikaye et al. (1971)     |
| GA   | E. coli      | Mikaye et al. (1971)     |
| SD   | E. coli      | Mikaye et al. (1971)     |
| SP   | E. coli      | Mikaye et al. (1971)     |
| F1   | E. coli      | Mikaye et al. (1971)     |
| Qβ   | E. coli      | Mikaye et al. (1971)     |
| VK   | E. coli      | Mikaye et al. (1971)     |
| ST   | E. coli      | Mikaye et al. (1971)     |
| ZIK/1| E. coli      | Bradley (1971)           |
| ZJ/1 | E. coli      | Bradley (1971)           |
| R23  | E. coli      | Hunt et al. (1971)       |
| Y    | E. coli      | Tsuchida et al. (1971)   |
| Z    | E. coli      | Tsuchida et al. (1971)   |
|      |              | Total = 16               |

PP7     | *Pseudomonas aeruginosa* | Weppelman and Brinton (1971) |
| ΦC5    | *Candidobacter crescentus* | Bendis and Shapiro (1970) |

*It is not yet firmly established whether this organism possesses a sex factor analogous to the F factor of E. coli and the FP factor of P. aeruginosa.*
### Viruses Infecting Higher Animals—*Homo sapiens*

| Virus genus          | Number of viruses per genus that infect humans | Ether susceptibility | Budding |
|----------------------|-----------------------------------------------|----------------------|---------|
| **RNA-containing viruses** |                                               |                      |         |
| Rhinovirus           | 90                                            | -                    | -       |
| Enterovirus          | 64                                            | -                    | -       |
| Reovirus             | 3                                             | -                    | -       |
| Arbovirus            | 84                                            | +                    | +       |
| Rhabdovirus          | 3                                             | +                    | +       |
| Orthomyxovirus       | 3                                             | +                    | +       |
| Paramyxovirus        | 2                                             | +                    | +       |
| Leukovirus           | +                                             | +                    | +       |
| Coronavirus           | 1                                             | +                    | +       |
| Arenaviruses         | 3                                             | +                    | +       |
| **Total**            | 260                                           |                      |         |
| **DNA-containing viruses** |                                               |                      |         |
| Poxvirus             | 3                                             | -                    | -       |
| Adenovirus           | 32                                            | -                    | -       |
| Papillomavirus       | 2                                             | -                    | -       |
| Herpesvirus          | 6                                             | +                    | +       |
| **Total**            | 43                                            |                      |         |
| **Combined total**   | 303                                           |                      |         |

*a The classification recommended by the ICNV, 1971 has been adopted except in the case of the arboviruses.

*b From Jawetz et al. (1970) and Wildy (1971).*

### Viruses Infecting Higher Plants—*Alfalfa*

- Alfalfa dwarf virus
- Alfalfa mosaic virus
- Alfalfa witches broom virus
- Alsike clover mosaic virus
- Bean yellow mosaic virus
- Beet curley top virus
- Broad bean mottle virus
- Clover yellow mosaic virus
- Cranberry false-blossom virus
- Datura rugose leaf curl virus
- Little leaf disease virus
- Pea enation mosaic virus
- Pea leaf roll virus
- Pea streak virus
- Tobacco ringspot virus
- White clover mosaic virus

**Total = 16**

*a From Crill et al. (1970).*
A simple list of viruses pathogenic for a given organism, e.g. *H. sapiens*, cannot be taken as a statistically significant reflection of the distribution of viruses throughout a major taxonomic grouping. The list given below is not intended as a tabulation of all viruses known for various vertebrates, but rather as a sample of viruses which could be seen to exist in nature if sufficient data were available. It must be remembered that this tabulation probably only represents the tip of the iceberg with respect to the number of vertebrate viruses which actually exist. Possibly the largest group of viruses—those of a silent or temperate character—are those least represented in this tabulation (see text). Except in the case of the arboviruses, the classification used is that recommended by the ICNV, 1971. Hosts for any given virus represent those thought to be "natural" hosts. However, as viruses are often identified with the species from which they were originally isolated, the natural host range is extremely difficult to assess.
### RNA-Containing Viruses

| Common name of virus | Host(s)                  | Susceptible to ether | Budding |
|----------------------|--------------------------|----------------------|---------|
| **Mammalia and aves** |                          |                      |         |
| Genus *calicivirus*   |                          |                      |         |
| Feline *picornavirus* | Cat                      | No                   | No      |
| **Genus *rhinovirus***|                          |                      |         |
| Human, 90 serotypes  | Human                    | No                   | No      |
| Equine, 2 serotypes  | Horse                    | No                   | No      |
| Bovine, 1 serotype   | Cattle                   | No                   | No      |
| Foot and mouth disease, 7 serotypes | Cattle | No | No |
| **Genus *enterovirus***|                          |                      |         |
| Poliomyelitis, 3 serotypes | Human | No | No |
| Coxsackie, 29 serotypes | Human | No | No |
| Echo, 32 serotypes   | Human                    | No                   | No      |
| SA-1                 | Cattle                   | No                   | No      |
| Teschen              | Pig                      | No                   | No      |
| Mengo                | Chimpanzee               | No                   | No      |
|                      | Baboon                   |                      |         |
|                      | Monkey                   |                      |         |
|                      | Mongoose                 |                      |         |
|                      | Cotton rat               |                      |         |
| Murine encephalomyelitis | Mouse       | No | No |
| Duck hepatitis        | Birds                    | No                   | No      |
| **Genus *reovirus***  |                          |                      |         |
| Human reoviruses, 3 serotypes | Human | No | No |
| Colorado tick fever   | Human, rodents           | No                   | No      |
| Monkey reovirus       | Monkey                  | No                   | No      |
| Canine reovirus       | Dog                      | No                   | No      |
| **Avian reoviruses, 5 serotypes** | Birds | No | No |
| *African horse sickness, 9 serotypes* | Horse | No | No |
| Blue tongue, 12 serotypes | Sheep and other artiodactyls | No | No |
| *Epizootic hemorrhagic disease of deer* | Deer | No | No |
| *Epizootic diarrhea of mice* | Mouse | No | No |
| Arbovirus group<sup>b</sup> |                          |                      |         |
| *East equine encephalitis* | Human, horse, mule, Birds | Yes | Yes |
| *West equine encephalitis* | Human, horse, mule, Birds | Yes | Yes |
**RNA-Containing Viruses (Continued)**

| Common name of virus                  | Host(s)                          | Susceptible to ether | Budding |
|--------------------------------------|----------------------------------|----------------------|---------|
| Venezuelan equine encephalitis       | Rodents, human                   | Yes                  | Yes     |
| Tick-borne encephalitis              | Rodents, human                   | Yes                  | Yes     |
| Californian encephalitis             | Human, rabbit, squirrel          | Yes                  | Yes     |
| Yellow fever                         | Human, monkey                    | Yes                  | Yes     |
| Ross River                           | Human, horse, cat                | Yes                  | Yes     |
| Dengue, types 1 to 4                 | Human, monkey                    | Yes                  | Yes     |
| Phlebotomous fever                   | Human                            | Yes                  | Yes     |
| Kyasanur Forest                      | Human, monkey, rodents           | Yes                  | Yes     |
| Osmk hemorrhagic fever               | Human, musk rat, and other rodents | Yes            | Yes     |
| Tensaw                               | Human, rabbit, squirrel          | Yes                  | Yes     |
| Tahyna                               | Human, squirrel                  | Yes                  | Yes     |
| Louping ill                          | Sheep                            | Yes                  | Yes     |
| Bukalasa                             | Bat                              | Yes                  | Yes     |
| Daktar                               | Bat                              | Yes                  | Yes     |
| Entebbe bat salivary gland           | Bat                              | Yes                  | Yes     |
| Semliki                              | Birds                            | Yes                  | Yes     |
| Whataroa                             | Birds                            | Yes                  | Yes     |
| Japanese encephalitis                | Birds, pig                       | Yes                  | Yes     |
| St. Louis encephalitis               | Birds                            | Yes                  | Yes     |
| West Nile fever                      | Birds                            | Yes                  | Yes     |
| Quaranfil                            | Pigeon, cattle, egret            | Yes                  | Yes     |
| Genus arenavirus                     |                                  |                      |         |
| Junin                                | Human, rodent                    | Yes                  | Yes     |
| Tacaribe                             | Bats, rodent                     | Yes                  | Yes     |
| Machupo                              | Human, rodent                    | Yes                  | Yes     |
| Genus rhabdovirus                    |                                  |                      |         |
| Vesicular stomatitis                 | Mammals                          | Yes                  | Yes     |
| Rabies                               | Mammals                          | Yes                  | Yes     |
| Chandipura                           | Human                            | Yes                  | Yes     |
| Marburg                              | Shrew                            | Yes                  | Yes     |
| lbAn 27377                           | Monkey                           | Yes                  | Yes     |
| Bovine ephemeral fever               | Cattle                           | Yes                  | Yes     |
| M-1056                               | Rodents                          | Yes                  | Yes     |
| Mt. Eglon                            | Bat                              | Yes                  | Yes     |
| Lagos                                | Bat                              | Yes                  | Yes     |
| Kern Canyon                          | Bat                              | Yes                  | Yes     |
| Piry                                  | Opossum                          | Yes                  | Yes     |
| Flanders-Hart-Park                   | Birds                            | Yes                  | Yes     |
| Common name of virus                | Host(s)                              | Susceptible to ether | Budding |
|-----------------------------------|--------------------------------------|----------------------|---------|
| Genus orthomyxovirus              |                                       |                      |         |
| Influenza, Type A                 | Human, horse, pig, birds             | Yes                  | Yes     |
| Influenza, type B                 | Human                                | Yes                  | Yes     |
| Influenza, type C                 | Human                                | Yes                  | Yes     |
| Genus paramyxovirus               |                                       |                      |         |
| Parainfluenza, types 1 to 4       | Human, monkeys, cattle, mice          | Yes                  | Yes     |
| Mumps                             | Human                                | Yes                  | Yes     |
| Measles                           | Human                                | Yes                  | Yes     |
| SV5                               | Monkey, dog                          | Yes                  | Yes     |
| Rinderpest                        | Cattle, sheep, goat, water buffalo    | Yes                  | Yes     |
| Canine distemper                  | Dog                                  | Yes                  | Yes     |
| Pneumonia virus of mice           | Mouse                                | Yes                  | Yes     |
| Newcastle disease                 | Bird                                 | Yes                  | Yes     |
| Turkey virus                      | Turkey                               | Yes                  | Yes     |
| Genus coronavirus                 |                                       |                      |         |
| Human respiratory virus           | Human                                | Yes                  | Yes     |
| Transmissible gastroenteritis of pigs | Pig                             | Yes                  | Yes     |
| Mouse hepatitis                   | Mouse                                | Yes                  | Yes     |
| Avian infectious bronchitis       | Bird                                 | Yes                  | Yes     |
| Genus leukovirus                  |                                       |                      |         |
| Mason–Pfizer                      | Monkeys                              | Yes                  | Yes     |
| Feline leukemia                   | Cats                                 | Yes                  | Yes     |
| Feline sarcoma                    | Cats                                 | Yes                  | Yes     |
| Bittner factor                    | Mice                                 | Yes                  | Yes     |
| Murine leukemia                   | Mice                                 | Yes                  | Yes     |
| Rous sarcoma                      | Chickens                             | Yes                  | Yes     |
| Reptilia                          |                                       |                      |         |
| Arbovirus group                   |                                       |                      |         |
| Arbo encephalitis viruses         | Wild gopher snake                    | Yes                  | Yes     |
|                                   | Garter snake                         |                      |         |
|                                   | Blue racer snake                     |                      |         |
| Amphibia                          |                                       |                      |         |
| Arbovirus group                   |                                       |                      |         |
| West equine encephalitis          | Leopard frog                         | Yes                  | Yes     |
| Pisces                            |                                       |                      |         |
| Genus rhabdovirus                 |                                       |                      |         |
| Viral hemorrhagic septicemia      | Rainbow trout                        | Yes                  | Yes     |
| Infectious hemopoietic necrosis   | Salmon                               | Yes                  | Yes     |
### RNA-Containing Viruses (Continued)

| Common name of virus                        | Host(s)       | Susceptible to ether | Budding |
|-------------------------------------------|---------------|----------------------|---------|
| Oregon sockeye                            | Salmon        | Yes                  | Yes     |
| Sacramento River chinook disease          | Salmon        | Yes                  | Yes     |
| Genus reovirus                            |               |                      |         |
| Infectious pancreatic necrosis            | Trout         |                      |         |
| Unclassified                              |               |                      |         |
| Walleye sarcoma                           | Walley        | Not known            | Yes     |
| Walleye epidermal hyperplasia             | Walley        | Not known            | Yes     |
| IPN                                        | Trout         | Yes                  | Yes     |

### DNA-Containing Viruses

| Common name of virus                        | Host(s)       | Susceptible to ether | Budding |
|-------------------------------------------|---------------|----------------------|---------|
| Mammalia and aves                          |               |                      |         |
| Genus poxivirus                           |               |                      |         |
| Sparrow pox                               | Sparrow       | No                   | No      |
| Rabbit pox                                | Rabbit        | No                   | No      |
| Squirrel fibroma                          | Squirrel      | No                   | No      |
| Yaba monkey tumor                         | Monkey        | No                   | No      |
| Goat pox                                  | Goat          | No                   | No      |
| Variola                                   | Human         | No                   | No      |
| Genus iridovirus                          |               |                      |         |
| African swine fever                       | Pig           | No                   | No      |
| Genus adenovirus                          |               |                      |         |
| Human, 32 serotypes                       | Human         | No                   | No      |
| Simian, 23 serotypes                      | Monkey, apes  | No                   | No      |
| Bovine, 7 serotypes                       | Cattle        | No                   | No      |
| Porcine, 4 serotypes                      | Pig           | No                   | No      |
| Canine, 2 serotypes                       | Dog           | No                   | No      |
| Murine, 2 serotypes                       | Mice          | No                   | No      |
| Sheep adenovirus                          | Sheep         | No                   | No      |
| Avian, 9 serotypes                        | Chicken, goose| No                   | No      |
| Genus papillomavirus                      |               |                      |         |
| Warts                                     | Human         | No                   | No      |
| Rabbit oral papilloma                     | Rabbit        | No                   | No      |
| Deer fibroma                              | Deer          | No                   | No      |
| Genus polyomavirus                        |               |                      |         |
| SV 40                                     | Monkey        | No                   | No      |
| Polyoma                                   | Mouse         | No                   | No      |
| K                                         | Mouse         | No                   | No      |
| Rabbit vacuolating                        | Rabbit        | No                   | No      |
### DNA-Containing Viruses (Continued)

| Common name of virus          | Host(s)         | Susceptible to ether | Budding |
|-------------------------------|-----------------|----------------------|---------|
| Genus parvovirus              |                 |                      |         |
| Porcine parvovirus            | Pig             | No                   | No      |
| Feline panleucopena           | Cat             | No                   | No      |
| RV                            | Rat             | No                   | No      |
| Minute virus of mice          | Mouse           | No                   | No      |
| Genus herpesvirus<sup>c</sup> |                 |                      |         |
| Herpes simplex                | Human           | Yes                  | Yes     |
| Varicella                     | Human           | Yes                  | Yes     |
| Epstein–Barr                  | Human           | Yes                  | Yes     |
| B virus                       | Monkey          | Yes                  | Yes     |
| Herpesvirus T                 | Marmoset        | Yes                  | Yes     |
| Infectious bovine rhinitis    | Cattle          | Yes                  | Yes     |
| Malignant catarrh             | Cattle          | Yes                  | Yes     |
| Pseudorabies                  | Pig             | Yes                  | Yes     |
| Equine herpes                 | Horse           | Yes                  | Yes     |
| Herpesvirus cuniculi          | Rabbit          | Yes                  | Yes     |
| Mouse cytomegalovirus         | Mouse           | Yes                  | Yes     |
| Marek’s disease               | Fowl            | Yes                  | Yes     |
| Avian herpes                  | Pigeons, owls, parrots | Yes | Yes |

Reptilia

| Genus iridovirus              |                 |                      |         |
| Gecko virus                   | Gecko           | No                   | No      |
| Genus herpesvirus             |                 |                      |         |
| Snake herpes                  | Snakes          | Yes                  | Yes     |

Amphibia

| Genus iridovirus              |                 |                      |         |
| Iridovirus                    |                 |                      |         |
| Amphibian cytoplasmic virus   | Amphibians      | No                   | No      |
| Genus herpesvirus             |                 |                      |         |
| Lucké carcinoma               | Frogs           | Yes                  | Yes     |

Pisces

| Genus iridovirus              |                 |                      |         |
| Lymphocytic fish virus        | Sizostedion     | No                   | No      |

From Maramorosch and Kurstak (1971), Nowinski et al. (1971), Wildy (1971), and Wolf (1966).

<sup>a</sup> These have been grouped because many of the viruses listed infect both mammals and birds.

<sup>b</sup> Arthropod vectors are not listed.

<sup>c</sup> Oncogenic members are known for this genus.