70 Newly Recognized Viruses in Man

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THE 1948 textbook, Virus and Rickettsial Diseases of Man (Rivers), listed approximately 60 viruses which were known to infect man. Two-thirds of these agents were animal or arthropod agents which involve man only secondarily. Truly human viruses (that is, parasites specific for man and dependent on him for maintenance of their parasitic cycle) recognized in 1948 numbered a mere 20, of which only 9 were established in the laboratory. Ten years later, in 1958, 70 additional, specifically human viruses have been established and studied in the laboratory.

The newly recognized agents are not only numerous but exceedingly prevalent, and in intensely populated urban areas it appears that most humans at one time or another experience most of them. Unlike the viral diseases of man transmitted from other species, these common viruses tend to be milder in their pathogenic activity and only very rarely fatal. This mildness is not unexpected, since they are dependent on man, their natural host, for the perpetuation of their parasitic existence. Many animal and arthropod viruses which quickly lay the human low produce extremely mild effects in their natural hosts.

The following is the current box score of newly recognized viruses (1958), including polioviruses. For purposes of discussion, the viruses are divided into the enteroviruses and the respiratory tract viruses. This is an arbitrary separation, based on the sites in which the viruses are commonly demonstrated. However, most of the enteroviruses can and do occur in the pharynx, at least during the brief, early stages of infection. Similarly, some of the respiratory tract viruses, particularly the adenoviruses, can be demonstrated in the intestinal tract. One might consider as newly recognized the newer influenzal strains of type A and type B. Influenza C, measles, chickenpox, and herpes zoster have only recently been established in laboratory systems.

Enteroviruses

	Number
Coxsackie:	
Group A	19
Group B	5
ECHO	20

Respiratory tract viruses

Adenoviruses	18
New myxoviruses (Sendai, croup associated, hemadsorption, types 1 and 2)	4
Other viruses (salivary gland virus, JH, 2060, respiratory syncytial	4
	70

The first representatives of the Coxsackie viruses were reported by Dalldorf and Sickles in 1948. Subsequently, agents isolated in tissue culture, called orphan viruses by Melnick, and enteric viruses by Sabin, Hammond, and En-

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ders, were gathered together in 1955 into a group now known as the ECHO viruses. The first adenoviruses were reported toward the end of 1953 and early 1954 by Rowe and his co-workers and by Hilleman and his co-workers. The Sendai virus, or the hemagglutinating virus of Japan, recently named influenza D, was first reported by Kuroya and associates in 1953. Other new myxoviruses, the croup-associated (CA) virus, the hemadsorption viruses (HA), the respiratory syncytial virus, or chimpanzee coryza agent (CCA), the salivary gland virus (SGV), and JH and 2060 viruses, have all been reported since 1955 by Chanock, Smith, Rowe, Weller, Price, Pelon, Mogabgab, and their co-workers. The HA viruses were reported by our laboratory only this year.

Clinical Illnesses

Fifteen clinically and epidemiologically distinguishable entities attributable to the newly recognized viruses are listed in the tabulations that follow. When the more specific signs and symptoms are not produced, the illnesses are generally lumped under such nonspecific terms as "common cold," "virus infection," "fever of undetermined origin," and "acute respiratory illness." In the warm months they might be called "summer grippe"; in the cold months "febrile colds."

Enteroviruses

Five clinically distinct entities, namely, herpangina, epidemic pleurodynia, aseptic meningitis, epidemic exanthemata, and myocarditis neonatorum, now well established as Coxsackie and ECHO viral diseases, are listed below together with acute summer respiratory illnesses.

Disease	*Viral serotypes incriminated, 1958*
Herpangina (vesicular pharyngitis)	Coxsackie group A 2, 4, 5, 6, 8, 10 (probably 3)
Epidemic pleurodynia (Bornholm disease)	Coxsackie group B 1, 2, 3, 4, 5
Aseptic meningitis (nonbacterial meningitis)[1]	Coxsackie group A 7, 9; group B 1, 2, 3, 4, 5; ECHO 4, 6, 9, (14)
Epidemic exanthemata ("Boston exanthem") ("meningoencephalitis with rash")	ECHO 9, 16
Myocarditis neonatorum (acute aseptic myocarditis)	Coxsackie group B 3, 4
Acute febrile respiratory illnesses ("summer grippe")[1]	Many of the new viruses.

[1] These diseases are caused also by other enteroviruses including polioviruses types 1, 2, and 3.

Not only can certain virus types cause different clinical illnesses, but it is also apparent that the same clinical illness, such as aseptic meningitis, can be caused by a number of distinct virus types. Double and even triple simultaneous virus infections add to the complexity of the clinical aspects of these viruses.

Adenoviruses

At least six distinct entities are currently attributable to adenovirus infections. They are the following:

Disease	*Adenovirus types implicated*	
	Most commonly	*Less commonly*
Acute respiratory disease	4, 7	3, 14
Pharyngoconjunctival fever	3, 7a	1, 2, 5, 6, 14
Acute febrile pharyngitis	1, 2, 3, 5	
Follicular conjunctivitis	3, 7a	2, 6, 9, 10
Epidemic keratoconjunctivitis	[1] 8	[2] 3, [2] 7a
Virus pneumonia:		
Infants	7a	1, 3
Adults	4, 7	3

[1] Classic cases.
[2] Mild cases.

The first clinical illness shown to be caused by adenoviruses was acute respiratory disease (ARD). This common epidemic disease of military recruits is caused most frequently by types 4 and 7. These serotypes rarely occur in children in the United States. Most adults eventually develop antibodies to types 4 and 7.

Pharyngoconjunctival fever (PCF) occurs in children in any month. It is frequently associated with swimming pools and camps. Attributed chiefly to serotypes 3 and 7a, it occurs only sporadically in adults. Many if not most adults have antibodies to these serotypes.

The most common manifestation of adenoviruses is acute febrile pharyngitis due to types 1, 2, 3, and 5 in infants and young children.

Most are infected with types 1 and 2, it would appear, prior to entering grade school. These febrile illnesses are much more common in cold seasons. They are quite similar to pharyngoconjunctival fever, except that conjunctival inflammation is rare. Common follicular conjunctivitis without fever, due to adenoviruses, is seldom epidemic. It is observed most often in adults, since in children adenoviruses tend to produce fever, in which case the illness would more properly be called pharyngoconjunctival fever.

Epidemic keratoconjunctivitis (EKC) appears to be most commonly caused by type 8 adenovirus. It occurred chiefly in industrial areas during World War II. EKC is prevalent in Japan and has recently been observed in Scotland and in continental Europe. When type 8 infections are observed in children, as in Japan, the illness tends to resemble pharyngoconjunctival fever; in adults, the infection usually results in classic afebrile keratoconjunctivitis.

Other adenoviruses (types 3 and 7a) can also on occasion cause mild keratitis expressed as subepithelial opacities which, according to Thygeson, are distinguishable from the severe and prolonged classic EKC, which not infrequently is followed by permanent corneal damage.

Primary atypical pneumonia without cold agglutinins was found associated with adenovirus infections, chiefly type 4, by Hilleman and Werner. This illness is invariably associated with outbreaks of ARD. Virus pneumonia in infancy is the most recent illness shown to be caused by adenoviruses. Type 7a was demonstrated repeatedly during an epidemic of virus pneumonia in infants in Paris, 1955–56. The findings in fatal cases resembled very closely an unusual pneumonia described by Goodpasture in 1938, which featured intranuclear inclusions quite similar to those produced by adenoviruses in cells grown in tissue culture. Types 1 and 3 have also been found in the tissues of infants dying from pneumonia in this country.

As illustrated in the tabulation, certain adenoviruses can also cause clinically different illnesses, and the same illness may have multiple adenovirus causes.

Myxoviruses

The myxoviruses, particularly influenza, mumps, and Newcastle, are probably the most intensively studied of the animal viruses. In recent years, however, new human myxoviruses have been found, with properties differentiating them from the older varieties. In 1955, outbreaks of infant pneumonitis were associated with a new myxovirus called Sendai virus, isolated so far, only in Sendai, Japan, and in Vladivostok, Russia. However, serologic reactions to Sendai virus in this country, England, and elsewhere, suggest that Sendai virus or an immunologically related virus was causing prevalent infections.

In 1954, Chanock reported a croup-associated virus. When propagated in monkey kidney tissue culture, CA virus revealed minor serologic relationships to mumps and to Sendai virus. The hemadsorption myxoviruses types 1 and 2, discovered not many months ago by Chanock and others of my associates at the National Institutes of Health, in collaboration with Dr. Robert Parrott, physician-in-chief, Children's Hospital, Washington, D. C., are also isolated in monkey kidney tissue cultures, but they require the new hemadsorption technique, described by Vogel and Shelokov, for their demonstration. These agents appear to be responsible for a significant amount of acute febrile respiratory illness in children in urban areas.

Our recent hospital clinic studies, done in collaboration with Children's Hospital, Washington, D. C., and the District of Columbia Welfare Department, indicate that types 1 and 2 hemadsorption viruses were responsible for as much as 25 percent of the influenza-like illnesses observed during recent months in children. Retrospective studies indicate that the hemadsorption viruses may have been responsible for a relatively high proportion of respiratory illnesses in children, at least since 1953, and may have caused in military recruits a proportion of acute respiratory disease not accounted for by the streptococci, influenza virus, or the adenoviruses. The following shows the illnesses associated with newly recognized myxoviruses and other respiratory tract diseases:

Acute laryngo-tracheobronchitis (croup)	CA, HA type 2

Pneumonitis in infants and children	Sendai (influenza D), CCA, HA type 1
Mild respiratory illness (common cold, coryza, nasopharyngitis)	JH, 2060, CCA
Acute febrile respiratory illnesses	Sendai, CA, HA types 1 and 2
Cytomegalic inclusion disease	Salivary gland virus

Chanock and associates showed a temporal association of the new respiratory syncytial virus with such pneumonitis in infants and children. This virus was shown to be identical with the chimpanzee coryza agent (CCA) reported earlier by Morris and associates. This virus, like the croup-associated virus, appears to occur in sharply localized epidemics.

Two viruses with similar properties, JH virus and 2060 virus, were reported almost simultaneously from two separate laboratories, in association with mild respiratory illnesses with very low-grade fever. Subsequently, Price has reported protection against an outbreak of mild respiratory disease in children with a vaccine prepared against the JH strain.

The virus causing cytomegalic inclusion disease, so termed because of the distinctive giant intranuclear inclusions produced, is, in a sense, an old virus in that it was recognized as a pathological entity many years ago. This virus, however, was not isolated and established in the laboratory until 1956, when Smith reported its recovery in human uterine fibroblasts. Shortly afterwards, Rowe, Hartley, and I, as well as Weller, reported in some detail on the occurrence of this virus in man. It would appear that the salivary gland virus, as it is also known, is an extremely common and ubiquitous agent in man. Related but species-specific representatives occur in many other mammals. The mouse and guinea pig varieties have also been established in tissue culture.

This group of viruses occasionally causes disseminated disease with lesions observed in nearly all the critical organs in the species in which they occur. The human agent in its active form in newborn infants, called cytomegalic inclusion disease, is frequently fatal. Weller and Rowe recently showed that the virus can be demonstrated for long periods in salivary secretions and in urine of infected children. Like adenoviruses, the human agent has been unmasked from long-term cultures of tonsils and adenoids.

The search for human viruses has demonstrated previously unrecognized viruses in other species as well. At least 20 newly recognized viruses have been demonstrated in tissue cultures of monkey kidneys. Some are biologically and immunologically related to human adenoviruses, others to human ECHO viruses, and others to the newer hemadsorption myxoviruses.

Implications

Recognition of so many new viruses and their effects cannot fail to provoke a reexamination of current concepts. It is a familiar observation that the usefulness of hypotheses concerning the etiology of disease depend in great part upon whether or not they can be tested. When they are based on a microbial theory, this necessary and desirable circumstance usually obtains. But such testing is not always easily accomplished.

One of the most important implications of so many new, different, and prevalent viruses is the complexity of the business of trying to find out what they are doing in their hosts. Simultaneous infections with multiple viruses are commonplace, particularly in young infants. We have observed as many as four acute viral infections in the same child during the same week. Since, in very young children, these new viruses most often cause clinical entities that are difficult to distinguish from one another, attributing the illness to the proper agent can be quite difficult. The elucidation of significant etiological associations of prevalent viruses which only rarely cause fatal infections becomes, as a consequence, almost a problem in logistics, requiring carefully planned, extensive, and controlled epidemiological and laboratory studies. One of the more proximate and important implications of modern research on virus diseases, therefore, is that it will cost significantly more money than microbiological studies have in the past.

Clinical Importance of New Viruses

Specific clinical illnesses attributable to viruses may represent only a small proportion

of the total amount of illness they produce. Our studies, as well as those of Dingle's group at Western Reserve University and the Newcastle-on-Tyne studies in England, show that the common respiratory and other undifferentiated illnesses tend to occur most frequently in the young child. In this age group, it is difficult even for a pediatrician to distinguish among the illnesses most commonly caused by the adenoviruses, Coxsackie, ECHO, and even polioviruses.

The 6-year longitudinal study of suburban communities, by Bell and my other associates at the National Institutes of Health, showed that respiratory illnesses characterized by mild fever of more than 1 day's duration occurred approximately 5 times more often in children under 6 years of age than in persons over 17. The intermediate age group showed an intermediate experience. For this reason, our recent studies of these illnesses have been focused on the childhood illnesses in three different population groups: (*a*) in the suburban community, (*b*) in pediatric hospital wards and clinics, and (*c*) in infants and young children confined to an orphanage nursery. By longitudinal and cross-sectional observations, we hope to determine more precisely the roles of viruses, and other pathogens as well, in producing the common acute and undifferentiated illnesses in children.

Already these studies have led to interesting findings. For instance, in collaboration with Dr. Robert Parrott, our group is now engaged in studying the relative contributions of Asian influenza, the brand-new hemadsorption viruses, and the adenoviruses to current pediatric respiratory illnesses in local pediatric clinics and hospital wards. During October and November 1957, approximately 60 percent of the acute respiratory illnesses could be attributed to Asian influenza and approximately 25 percent to types 1 and 2 hemadsorption viruses. The adenoviruses, the croup-associated virus, the respiratory syncytial virus, as well as Coxsackie and ECHO viruses, known to be prevalent at other times and places, were not prevalent during this period. Because of technical difficulties, we have been unable thus far to assay the contributions of JH and 2060 viruses.

During October and November, we were able to account for the majority of the respiratory illnesses on the basis of Asian influenza and the new hemadsorption viruses. In December 1957, when the Asian influenza virus disappeared entirely from the clinic and hospital wards, approximately 25 percent of respiratory illnesses could still be attributed to the hemadsorption viruses. The adenoviruses appeared in December and were held responsible for approximately 5 percent. Of the respiratory illnesses observed for about 60 days, these two agents produced 30 percent.

Asian influenza reappeared in February, but only a small percentage of illnesses were attributable to this virus. In late February, type 1 hemadsorption virus disappeared. At this time, we were able to account for probably less than 15 percent of the acute respiratory and undifferentiated illnesses. Subsequently the hemadsorption virus reappeared and adenoviruses became more common, but large segments of respiratory disease remained unexplained. Since bacteriological studies have provided no explanation for the vast majority of unexplained illnesses, additional, presumably new, viruses will have to be sought.

Longitudinal studies in an orphanage nursery have provided us with observations on thousands of respiratory and undifferentiated illnesses. Thousands of virus isolates were obtained and, for the most part, identified. (The data are being prepared for publication.) At least 35 to 40 different prevalent viruses occur regularly in this population, and substantial amounts of illnesses can be attributed to the adenoviruses, some of the enteroviruses, and myxoviruses. During nearly 3 years of observation since 1955, many of these viruses have made periodic, almost predictable, reappearances at appropriate seasons. However, even under intensive scrutiny, many illnesses still cannot be identified as viral or bacterial infections.

Prophylactic Vaccines

Even though there are still many common respiratory and other undifferentiated diseases with no known agent, serious consideration should be given to the development of prophylactic viral vaccines.

At the National Institutes of Health, we are engaged in preliminary tests of properly constituted viral vaccines. Our studies of the high prevalence of viral illnesses in children suggest that a properly constituted, safe, and effective vaccine would probaby be incorporated in pediatric immunization schedules. Such a vaccine would require perhaps as many as 25 separate viral antigens.

Speculation concerning the eventual utilization of this hypothetical "virus cocktail" is premature. Too many questions remain to be answered. Some may feel that such a vaccine would be fraught with unexpected hazards either immediately or later in life. Others may assume that such a vaccine would be of immediate great value. Generally speaking, the first vaccines for any disease are poorer than the modifications that come later. However, it is important to take the initial steps, carefully, of course, and then to answer questions as they become real rather than merely hypothetical.

The justification for study and eventual use of an all-purpose virus vaccine ought not to be put purely on an economic basis. I believe that a multivalent vaccine capable of preventing as much as 25–30 percent of undifferentiated respiratory disease, particularly in early childhood, would be desirable for the good and simple reason that this is, in any vocabulary, an enormous mass of illness, probably much more illness than is now prevented by all currently available vaccines.

New Viruses and Noninfectious Disease

It has been only a few years since our chief infectious diseases were pneumonia, smallpox, diphtheria, and the great plagues, the latter mostly transmitted from other animal species to man. Although vigilance is still required to keep them in check, they are no longer regarded as important, at least in this country.

This remarkable success story has led to an unfortunate myth that infectious disease research is now a comparatively dead science. Nevertheless, numerically speaking, it would appear that most of Western man's microbial experiences, as exemplified in large part by the newly recognized virus flora, still remain to be defined, if not eliminated.

Many chronic and degenerative diseases also remain largely a riddle as to ultimate causes. Among the various hypotheses, those which postulate viral etiology deserve consideration. As viral infections are most frequent precisely during the formative periods, they frequently affect organs that are critically necessary for healthy growth. Despite the fact that the newly recognized and numerous human viruses are almost never fatal, the astronomic number of illnesses they cause seems to me to imply a great deal. Our knowledge of the pathogenic behavior of these viruses rests on comparatively few autopsies. But from studies of these few fatal cases, it is quite clear that many representatives of the new and common viruses cause pathology in critical organs, including the central nervous system, lungs, heart, liver, adrenals, kidneys, and the reticuloendothelial system. It is almost impossible to think that these pathological effects are not duplicated, to a lesser extent, in many nonfatal infections.

The well-known virus diseases of early childhood, measles, mumps, chickenpox, herpes, and poliomyelitis, also cause pathology in central organs with uncomfortable frequency. No fewer than 14 Coxsackie and ECHO viruses have now been shown to affect the central nervous system. Certain enteroviruses also cause myocarditis and pericarditis in children. It is quite possible that repeated infections in childhood with specifically human viruses which affect the central nervous system represent far greater contemporary threats to human health than all the viral encephalitides transmitted from nature combined.

Consider also the salivary gland virus, a notorious cause of neonatal death, and, as recently demonstrated by Weller and Rowe, a potential cause of chronic cerebral disease in infants who survive the early perinatal infection. In fatal cases, this virus causes lesions in virtually all the critical organs; it has been shown to be excreted by as many as 10 percent of infants under the age of 3; and serologic surveys show that it eventually succeeds in producing infectious processes in perhaps as many as 80 percent of all persons by the time they reach 35 or 40. Furthermore, the infection is persistent and has been reported occasionally as a generalized recrudescent disease in fatal illnesses, usually attributed to other chronic maladies. It is un-

reasonable to think that the giant intranuclear inclusions produced by the generalized disease are confined to fatal cases. This and other latent viruses may have outstanding importance for those suffering from a lack of testable hypotheses concerning ultimate causes in certain chronic diseases.

Viruses in Etiology of Human Cancer

It has become clear that the viruses responsible for animal tumors are not altogether strange microbes. Recent studies have shown that the animal tumor viruses grow to high titer, that they produce antibodies, and that some of them grow in tissue cultures. Their manifestations are generally hyperplastic rather than cytolytic and the viruses frequently remain latent for many months; but these are not unusual properties. Only their oncogenic activities set them apart. The methods for working with them appear to be slightly more difficult than those for some of the ordinary, nontumor viruses, yet they seem to present no more severe technical problems than, for example, the salivary gland viruses.

The delineation of certain viruses in one species has frequently been based upon studies of similar viral experiences in other species. When representatives of various families of human viruses turn up in animal species other than man, it is merely taken for granted. In the same way, it is not uncommon for the first representatives of a virus family to be found in an animal species, then, subsequently, related representatives to be found in man. It is hardly possible for a virologist to think that family relatives of the numerous tumor viruses of animals will find no expression in the human species. To say that such a virus has never been demonstrated is quite correct. It is equally correct to say, however, that the critical experiments which have been necessary for the demonstration of animal cancer agents in man have not yet been performed. In fact, the question "Do viruses cause human cancer?" has not yet been effectively asked. One of the major implications of modern virus research, therefore, is based on the likelihood of an early answer to this most important medical question.

Regular Corps Examinations

The Public Health Service announces competitive examinations for appointment of physicians, dentists, sanitary engineers, clinical psychologists, biochemists, and veterinarians to its commissioned corps as Regular Corps officers.

The examinations will be held throughout the country on March 31 to April 3, 1959, for the veterinarians and on April 21–24, 1959, for the other categories.

Appointments will be made in the ranks of assistant and senior assistant grades, equivalent to Navy ranks of lieutenant (j.g.) and lieutenant, respectively. Active duty as a Public Health Service officer fulfills the obligations of Selective Service.

Only United States citizens need apply and applicants must be at least 21 years old. The entrance pay is $4,817 per year for an assistant grade officer with dependents and $6,270 for a senior assistant grade officer with dependents. Physicians, dentists, and veterinarians receive an extra $1,200 to $3,000 a year incentive pay.

Applications for the veterinarian's examination must be received by the Surgeon General no later than February 20, and March 6 for the other categories. Forms may be obtained by writing to the Surgeon General, Public Health Service (P), Washington 25, D. C., or to the nearest field station of the Service.