Pediatric Virology

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■ *Pediatric virology is not an isolated discipline. Rather, the syndromes associated with viral infection are modified by the unique characteristics of infancy and childhood. Fortunately for the pediatrician, and certainly for children, viral infections in childhood are rarely fatal, and are almost never serious. Future efforts of the pediatrician and virologist should be directed toward increased fetal salvage as with rubella and the prevention of severe, viral lower respiratory tract disease.*

"Christopher Robin
Had wheezles
And sneezles . . ."

FROM "SNEEZLES" BY A. A. MILNE[44]

So BEGINS Mr. Milne's delightful chronicle of a case of mild respiratory infection in a child. In his own inimitable way, Mr. Milne discusses the differential diagnosis, prognosis and treatment for the most common type of disease known to man. He approaches the subject in an appropriately lighthearted vein, for viral disease, and specifically viral respiratory disease in childhood, is usually not a serious malady. Although Mr. Milne did not plan these lines as an introduction to a tome on pediatric virology, they are appropriate for that purpose. Viral respiratory disease is usually the first disease experienced by the newborn infant, and as such it deserves first consideration in the discussions that follow.

Before proceeding, however, it should be emphasized that pediatric virology is not an isolated discipline, for there are few viral infections that are peculiar to pediatrics. Those agents important in pediatrics and the syndromes associated with them as modified by the unique characteristics of infancy and childhood will be stressed. Further, this review will be limited to viral disease as it appears in the Northwest temperate regions of the world, as the global ecology of human viruses is quite diverse.

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Respiratory Disease of Viral Etiology

Infection with the respiratory viruses is characterized by a heterogeneity of expression varying from the subclinical and mild upper respiratory infection (URI) to fatal pneumonia. As the clinical syndromes produced by these agents overlap greatly, Table 1 is provided to avoid unnecessary repetition.

Influenza

The influenza viruses are perhaps the best known of the respiroviruses responsible for respiratory disease in man. They are divided into three major groups designated types A, B and C, with a number of sub-types. Classically, influenza occurs in either wide-spread or local epidemics which peak in about three to four weeks and then wane. Sporadic cases also occur, although this epidemiological pattern has not been studied extensively.[28] Epidemics occur when one of two elements are present: (1) When "herd" immunity falls below a critical level, agents previously endemic in that same population, or their close antigenic relatives, can cause disease of epidemic proportions. This epidemiological pattern was observed in the years following the appearance of A-2 (Asian) virus in 1957. (2) If a major antigenic shift occurs, pandemics follow due to low levels or

absence of antibody in most of the world population, as was the case in 1957 when A-2 influenza first appeared. The antigenic shifts of influenza virus since 1934 can be seen in Table 2.

Epidemics of type A influenza occur every two to three years while type B influenza epidemics have a four to five year, but less predictable, periodicity. Disease produced by the type C virus is sporadic, rarely reaching epidemic proportions.

The clinical spectrum of illness produced by the influenza viruses is delineated in Table 1. An incubation period of one and a half to two days is characteristic—this followed by sudden onset of symptoms, whose expression is modified by age. The older child may have the clinical syndrome of chills, fever, myalgia, headache and nonproductive cough, but the younger child or infant, because of a limited vocabulary, may first come to medical attention merely with nonproductive cough and fever or simply fever of unknown origin. Vomiting or diarrhea should be looked upon as nonspecific reactions of the child to infection and not as a result of viral invasion of enteric mucosa. The term "intestinal flu," which is probably derived from this reaction, has been used to describe nonbacterial diarrhea of any type. It should be eschewed. Barring complications, influenza lasts from three to four days, and after a short convalescence the child is usually ready to resume normal activities. Infection with the influenza viruses is probably subclinical in one-third of all cases; and secondary bacterial infection, when it does occur, usually is seen in children with chronic pulmonary or cardiac disease.

TABLE 1.—*Respiratory Disease of Viral Etiology*

Clinical Syndromes	*Associated Viruses*
Upper respiratory infection (URI) (including common cold, coryza, nasopharyngitis, non-exudative tonsillopharyngitis)	Adenoviruses Echoviruses Parainfluenza Eaton's agent (PPLO) Respiratory syncytial Rhinoviruses Coxsackievirus A-21 Reoviruses ?
Exudative tonsillopharyngitis	Adenoviruses Infectious mononucleosis* (possibly others)
Vesicular or ulcerative tonsillopharyngitis	Group A Coxsackievirus Herpesvirus hominis (simplex)
Acute lymphonodular pharyngitis	Coxsackievirus A-10
Laryngotracheobronchitis (croup)	Parainfluenza viruses Influenza Adenoviruses Respiratory syncytial Rhinoviruses ? Eaton's agent (PPLO)
Acute epiglottitis	?
Bronchiolitis	Respiratory syncytial Adenoviruses Parainfluenza Eaton's agent (PPLO) Influenza
Pneumonia	Respiratory syncytial Adenoviruses Parainfluenza Eaton's agent (PPLO) Influenza Herpesvirus varicellae Psittacosis Rubeola
Influenza-like illness	Influenza Parainfluenza Adenoviruses Group A coxsackievirus Group B coxsackievirus Lymphocytic choriomeningitis

*Viral etiology not established.

Diagnosis. As influenza is usually epidemic, diagnosis can most often be made clinically. Although usually unnecessary in the individual case, laboratory confirmation has important prognostic and epidemiological implications. The cooperation of the clinician and local public health authorities in establishing the cause of respiratory disease at the outset of an epidemic is invaluable, and adequate liaison between the two is characteristic of most communities. A guide to the intelligent use of the viral diagnostic laboratory is presented in Table 3.

Treatment and prophylaxis. Treatment is entirely symptomatic in uncomplicated cases. For secondary bacterial infections, appropriate antibiotic drugs should be used.

Vaccine. When properly constituted, influenza vaccines may be expected to provide 75 to 90 per cent protection. Exceptions to this occur with major antigenic shifts. For maximum effectiveness, the vaccine should contain the strain currently responsible for disease in the community or one closely related to it. For specific immunization procedures and recommendations, the reader is referred to the report of the advisory committee on immunization practice of the U.S. Public Health Service.[30] In general, immunization is not recommended for a healthy child, but it should be considered for children with chronic pulmonary and cardiac disease.

Adenoviruses

The first member of the adenovirus group was isolated in 1953 from normal adenoid tissue.[65] First designated APC, ARD or RI viruses, these agents now make up a group of 28 different serotypes. Although they are responsible for predictable epidemics of acute respiratory disease in military recruits, they

TABLE 2.—*Antigenic Shifts of A & B Influenza Viruses**

Type	*Subgroup*	*Family*	*Era When Prevalent*
A	Swine		? — 1928 — ?
A	PR-8		1934 - 1946
A	A-1		1946 - Present (?)
		FMI 1947	1946 - 1951
		Scandinavian 1953	1952 - 1955
		Haw/303/56	1956 - Present
A	A-2	Japan/305/57	1957 - 1962
		D.C./301/63	1963 - Present
B	Lee		? — 1940 - 1942
B	BON (Warner)		1943 - 1953
B	Great Lakes 1954		1954 - 1961
B	Md/1/59		1959 - Present
B	TW/1/62		1962 - Present

*Adapted from Hilleman, M. R., Flatley, F. J., Anderson, S. A., Luecking, M. L., and Levinson, D. J.: Distribution and significance of Asian and other influenza antibodies in the human population, New Eng. J. Med., 258:969-974, May 15, 1958.

probably account for no more than 6 per cent of viral infections during the childhood period. Types 1, 2, 3 and 5 are the serotypes most often encountered in pediatrics.

Syndromes vary, from those clinically indistinguishable from that caused by Group A beta hemolytic streptococci, to pneumonia,[29] conjunctivitis and keratoconjunctivitis.[15] Additional clinical syndromes associated with the adenoviruses are listed in Table 1.

Recently, Trenton and his colleagues reported that adenoviruses types 12 and 18 can produce malignant tumors when inoculated into laboratory hamsters,[69] the first implication of a human virus in the production of tumors. There is no information available at present which would relate these agents to tumors in man.

Treatment and prophylaxis. Treatment is entirely symptomatic and secondary bacterial infections are infrequent. Prophylaxis for adenovirus infections is indicated only in military recruits in whom disease due to types 3, 4 and 7 occurs predictably. Because of this predictability, a divalent, inactivated vaccine containing types 4 and 7 is used in the military (types 3 and 7 cross serologically). The use of vaccine in childhood is probably not indicated as the type of adenovirus responsible for disease at any particular period cannot be predicted and the vaccine-induced immunity is transient.

Parainfluenza Viruses

The four known parainfluenza viruses were uncovered between 1956 and 1958. These agents are myxoviruses but are immunologically distinct from influenza. They exhibit intratypic antigen variation, although not as extreme as that noted with the influenza viruses.[9] Parainfluenza I and III are the only two that have been consistently associated with significant outbreaks of disease although types II and IV have definitely been associated with respiratory disease.[47] Original infection with these agents occurs early in life, and by young adulthood most persons have antibodies to types I and III. Reinfection can, and does, occur. Community outbreaks occur in the preschool segment of the population but probably do not come to widespread attention because they are not reflected in increased pneumonia deaths or school and industrial absenteeism.

Although the spectrum of disease associated with the parainfluenza viruses is wide (Table 1), these agents are the principal viruses responsible for croup. They account for approximately 44 per cent of the cases of croup studied at the Los Angeles County General Hospital. This figure is in close agreement with the 39 per cent reported in other series.[51]

Treatment and prophylaxis. As with all of the respiratory viruses treatment is entirely symptomatic. There are no commercially available vaccines, but work is presently proceeding in this direction.

Respiratory Syncytial (RS) Virus

Originally called Chimp Coryza Agent (CCA), respiratory syncytial virus was given its present name because of its characteristic cytopathogenic effect in tissue culture. This virus has the unique distinction of being the agent most commonly implicated in bronchiolitis and pneumonia in infancy. Primary infection usually occurs in infancy; and reinfection, characterized by milder cold-like symptoms, may occur throughout childhood and adult life. Antibody levels appear to be inversely associated with severity of disease. As with the other respiroviruses, subclinical infection is exceedingly common. An exanthem has been recently associated with RS virus infection.[6]

Respiratory syncytial virus infection in young children is present throughout the year, peaks coinciding with the peaks of pneumonia and bronchiolitis. Maxima are fairly predictable, with alternating

TABLE 3.—*Recommended Diagnostic Procedures*

Virus	*Isolation Specimen*									*Recommended Serologic Test (Paired Sera)*							
	CSF	*STL*	*TS*	*BLD*	*V.F.*	*TIS*	*URINE*	*SAL*	*SPU*	*HIST*	*NEUT*	*HAI*	*CF*	*FA*	*CA*	*ST-MG*	*HDI*
Adenovirus		X	X			Tonsil, lung					X	X	X				
Arbovirus	X			X		CNS					X	X	X				
Cytomegalovirus						Misc.	X§	X		X	X						
Eaton's Agent (PPLO)			X			Lung			X				X	X	X	X	
Enterovirus— (ECHO, Cox, Polio)	X	X	X			CNS					X		X*				
Exanthems—																	
Rubeola			X	X		Lung					X	X	X				
Rubella		X	X	X							X						
H. varicellae					X	Misc.				X			X				
H. hominis	X		X		X	Misc.				X	X		X				
Vaccinia			X		X					X	X	X	X				
Variola				X	X			X		X	X	X	X				
Inclusion conjunct.										X							
Lymphocytic choriomeningitis (LCM)	X			X							X**		X				
Myxovirus:																	
Influenza			X			Lung						X	X				X
Parainfluenza			X			Lung						X	X				X
Mumps	X		X			Misc.	X	X				X	X				X
Psittacosis				X		Misc.			X	X			X†				
Rabies‡						CNS		X		X				X			
Reovirus (ECHO-10)		X	X									X					
Respiratory syncytial			X			Lung				X	X		X				
Rhinovirus			X								X						

Key for Table 3—
CSF—Cerebrospinal fluid
STL—Stool (or rectal swab)
TS—Throat swab
BLD—Whole, clotted blood
V.F.—Vesicular fluid
TIS—Tissue
SAL—Saliva
SPU—Sputum
HIST—Histologic procedures
NEUT—Neutralization
HAI—Hemagglutination inhibition
CF—Complement fixation
CA—Cold agglutinins
ST-MG—Strep-MG
HDI—Hemadsorption inhibition
*Not useful for all enteroviruses
**Late convalescent serum necessary
†Crosses with LGV
‡Animal diagnostic procedures
§Fresh, refrigerated; do not freeze

13 to 15-month and 9 to 10-month intervals between peaks.[52] There does not appear to be a unique geographical concentration of cases in the United States.

Treatment and prophylaxis. Treatment for RS virus infection is symptomatic. Of all the agents implicated in the causation of lower respiratory disease in children, this one is perhaps the most important one to consider for incorporation in a vaccine. Although a killed virus vaccine is under investigation, no prediction as to its availability can be made at this time.

Picornaviruses

Picornavirus is a new designation for the group of viruses which include the enteroviruses (ECHO, poliomyelitis, Coxsackie) and the rhinoviruses. The name is derived from pico, meaning very small, and RNA for their nucleic acid cores.

Enteroviruses. Heterogeneity of clinical expression is perhaps best demonstrated in this group. The etiologic role of enteroviruses in central nervous system (CNS) disease will be discussed in another section. Perhaps the best known respiratory manifestation of these agents is herpangina, or summer sore throat, associated with certain members of the Group A Coxsackie viruses. More recently, Coxsackie A-21 has been associated with epidemic, upper respiratory illness in military recruits,[31] but its etiologic role in respiratory illness in childhood is as yet unknown. Coxsackie A-10 was recently described as the etiologic agent in lymphonodular pharyngitis, a syndrome similar to herpangina.[68] Miscellaneous ECHO viruses (types 11, 20 and 28, among others) have also been associated with sporadic, upper respiratory illnesses resembling the common cold; ECHO-28 belongs in the rhinovirus category.

Although they are not strictly classified as enteroviruses, the reoviruses (respiratory, enteric, orphans) will be described in this section. These agents, which formerly had the collective designation of ECHO-10, are divided into three types. Although probably important in disease in animals, the role of the reoviruses in human disease is not well defined.

Rhinoviruses. The group of viruses variously referred to as "common cold virus," coryzaviruses, salisbury strains, ERC viruses or muriviruses is made up of entero-like viruses recently shown to be significantly associated with upper respiratory disease in children and adults. Studies of children in hospital with *lower* respiratory tract disease did not implicate these agents as significant causes of these syndromes.[56] To date, 53 separate serotypes[26] have been described, and this is probably only the beginning. Reinfection can, and does, occur.

Treatment and prophylaxis. Treatment for disease associated with the picornaviruses is symptomatic. Vaccines do not appear to hold much promise because of the large number of viruses involved.

Eaton's Agent (mycoplasma pneumoniae)

Eaton's Agent (mycoplasma pneumoniae), now characterized as a PPLO (for pleuropneumonia-like organism) was originally (in 1944) isolated from a patient with primary atypical pneumonia (PAP).[16] Eaton's Agent is included in this discussion because originally it was believed to be a virus, and it produces disease closely resembling those produced by some viruses.

The ecologic features of this agent have been well studied in the Marine recruit population at Parris Island.[11] It spread slowly but disseminated widely. About 45 per cent of initially seronegative recruits showed serologic evidence of infection by the end of the 12-week training period, and one out of thirty with serologic evidence of infection had PAP. Nonspecific upper respiratory illness and subclinical cases were also associated with infection.[11] Recent findings suggest that infection with Eaton's Agent is associated with approximately 10 per cent of lower respiratory tract disease in children.[10]

Human volunteer studies have shown that reinfection can occur, although the presence of antibody is associated with mild or subclinical disease. Recently, similar studies[63] demonstrated that bullous myringitis can be a manifestation of disease due to this agent.

About 50 per cent of cases of Eaton's Agent pneumonia are associated with cold agglutinins, while cold agglutinin titers rarely rise in Eaton-negative pneumonia (less than 10 per cent). Retrospective studies have shown that about 80 per cent of cases of cold agglutinin-positive pneumonias are associated with Eaton's Agent.

Clinical and radiological response to the tetracyclines has been demonstrated.

General Comments on the Diagnosis of Viral Respiratory Disease in Children

The advances made during the last decade have not enabled us to make an etiological diagnosis based on clinical findings. As is the case with most viral diseases, all that is possible is a clinical "educated guess." The diagnosis of influenza during an epidemic or of adenovirus disease in a recruit camp is about the closest one can come to an etiological association based on clinical findings. There are, at present, no rapid laboratory tests available. All the syndromes produced by the agents described are interchangeable and, with the exception of Eaton's Agent pneumonia and herpangina, there are no associated pathognomonic (herpangina) signs or special clinical laboratory data (cold agglutinins). For

the other agents, viral etiology can only be determined in retrospect. Fortunately, most of the diseases produced by these agents are self-limited and not mortal.

Except for the presence of cold agglutinins toward the end of the second week of Eaton's Agent pneumonia, there is nothing new to add in the differentiation of viral and bacterial respiratory disease. Probably more than 90 per cent of upper respiratory disease in children and adults is viral and can be treated symptomatically. Cold agglutinin-positive pneumonia and bullous myringitis should be treated with one of the tetracyclines. The presence of tonsillar exudate would suggest antibiotic therapy for beta hemolytic streptococci.

Lower respiratory tract diseases (laryngotracheobronchitis, bronchiolitis, pneumonia) present problems not as yet amenable to "playing the odds." A high leukocyte content in peripheral blood does not always indicate bacterial infection. The median leukocyte count has been 17,000 in a group of children with lower respiratory tract illness currently being studied at Los Angeles County General Hospital.[57] The presence of a pleural effusion accompanying pneumonia is more frequent with bacterial disease, but effusions can accompany nonbacterial pneumonia. In adults, a smear and culture of sputum are still of great value. Unfortunately, since children usually swallow such material, it is not often available for study.

The frequency of secondary or concurrent bacterial infection is probably greatly overestimated, except possibly at the extremes of life and health. In normal children, antibiotic therapy probably functions more as a placebo and to bolster the physician's security in the absence of a precise diagnosis than as a defense against "secondary invaders"; and it may actually make superinfection more likely. We are thus left with new names for old diseases which are accompanied by the same problems.

The Exanthems of Viral Etiology

Of all the viral illnesses, the exanthems of childhood are perhaps the most distinctively pediatric. In this section, rather than repeating what is already well known, I will discuss the recent advances and the future prospects concerning the exanthems of childhood.

Rubeola (regular measles—Sarampión). Rubeola has been known as a disease entity for centuries. Our ancient forebears regarded it a disease serious enough to merit the descriptive name *morbilli,* the diminutive of *morbus,* which referred to the major disease *bubonic plague.* Thus, the ancients considered rubeola a minor plague, second only to disease produced by *pasturella pestis.*

American physicians consider regular measles a normal childhood disease, and rightly so. On the other hand, our colleagues in less affluent countries consider rubeola a severe and often fatal disease which deserves a great deal of attention. This is the case in Mexico where rubeola is the fourth most common cause of death in the age group 1 to 4 years.[41] In one Nigerian hospital, the mortality rate for measles and its complications is 20 to 25 per cent.[13] Less well known is the fact that even in the United States in the year immediately before the introduction of live vaccine for measles, rubeola caused more deaths than did poliomyelitis.[72] In the main, these deaths were due to complications, encephalitis being the most severe.

The use of antimicrobial agents, which has decreased the severity and importance of the bacterial complications, has not in any way reduced the incidence of measles encephalitis which occurs in about one case in a thousand. Approximately 15 per cent of patients with encephalitis die, 60 per cent recover completely and 25 per cent show permanent mental or motor residua. The recent introduction of live and killed measles vaccine has provided a means of attacking the problem of encephalitis.

The immunity that follows the administration of live measles vaccine is probably life-long, but a definite statement to this effect awaits long-term follow-up. To date, there have been no instances of severe CNS reactions to the live vaccine. A "further attenuated" live vaccine is now available. This vaccine is associated with significantly fewer side-effects. With the advent and widespread use of these newer vaccines, we can look forward to an era in which measles will be removed as a serious public health problem.

The recommendations for use of these vaccines have recently been reviewed in this journal.[72] The use of human gamma globulin for the prevention or modification of rubeola is familiar to all practitioners and will not be further elaborated.

Rubella (German measles). The isolation of rubella virus in tissue culture by Parkman and coworkers[49] and Weller and Neva[75] has provided the background for one of the most exciting advances in the field of pediatric virology in the last ten years. Utilizing human subjects, Green and coworkers[23] elegantly described the dynamics of virus infection and excretion. Rubella virus could be isolated from the pharynx for seven days before and for two weeks after the rash appeared. It was also present in serum for a week before, and as long as two days after, the appearance of rash. An unexpected finding was the isolation of virus from stool six days before and eight days after the rash developed. Virus was also present in the intervening periods. In Green's series, at least 25 per cent of children infected with

rubella virus were asymptomatic. Parkman and Buescher recently reported that the ratio of the number of persons infected to the number with disease may be as high as five or six to one among army recruits.[8]

The role of rubella virus in the production of congenital anomalies is well known. It is in this realm that these new findings provide the most stimulating prospects. The malformations which make up the so-called rubella syndrome include ocular defects (cataracts and microophthalmia), deafness, cardiac malformations and CNS anomalies. Green and coworkers[23] detected virus in fetal tissue obtained from seven of eight therapeutic abortions. Rubella virus has been isolated from fetal tissue obtained as long as one to eighteen weeks after onset of rash in a pregnant woman. Alford and Weller[73] detected virus in the pharynx and urine of a two and a half month old infant with the so-called rubella syndrome. The finding of prolonged viral infection in the fetus was unexpected and would add rubella to the herpesviruses as an agent capable of continued infection. Although rubella virus is not physically related to the herpesviruses, one might say that it is ecologically related.

As rubella is a mild disease and its complications rare, treatment is entirely symptomatic. Although arthritis and a post-rubella encephalitis have been described, these complications are uncommon. Prevention of this disease in the first trimester of pregnancy is most important. The efficacy of gamma globulin in the prevention of rubella has not been clearly established. Recent work by Green[23] has shown that gamma globulin will prevent clinical, but not subclinical, rubella. As virus can be detected in subclinical cases, the value of gamma globulin is questionable.

An ideal rubella vaccine would be one which, when given in childhood, would provide immunity through the child-bearing age. Further, the attenuated strain should not be communicated from the recently vaccinated child to the "potentially pregnant woman" unless the attenuated virus could be proven to be one which did not infect and subsequently cause malformations in the fetus. Work on such a vaccine is currently progressing rather rapidly.

Varicella (chicken pox). Although the advances in the study of *herpesvirus varicellae* have not been as dramatic as those with rubella and rubeola virus, Weller and his group[76,77] have produced outstanding results in the study of this agent, and have laid the foundation for a better understanding of the disease as well as for the development of a vaccine. Thus, the isolation and characterization of *herpesvirus varicellae* has made it possible to definitely establish that herpes zoster (shingles) is due to the same agent. Apparently, along with *herpesvirus hominis* and the cytomegalovirus, this agent is capable of remaining in a latent stage and manifesting its presence when body defense mechanisms are compromised. The dynamics of these manifestations had been previously elucidated epidemiologically, but virologic proof was lacking. Although vaccines are being tested, prophylaxis for varicella is in its infancy. Ross[64] showed that gamma globulin in large doses cannot prevent but does modify the disease.

Exanthem subitum (roseola infantum). Although roseola is probably a disease of viral etiology, no single virus has been implicated. Kempe and associates in 1950[34] transmitted the disease from one infant to another by the intravenous injection of bacteria-free serum. Neva and Enders (1954)[48] isolated an agent from a patient with an illness that resembled roseola, but these results have not been confirmed. We have isolated an ECHO-14 virus and an adenovirus respectively from the stools of two different children with roseola and demonstrated a subsequent increase in homologous, neutralizing antibody.

The incubation period of roseola is difficult to determine, as the contacts are rarely known, but it probably is about 10 to 21 days.[5] The most striking clinical feature and the hallmark of the disease is the relationship of the fever to the rash. There is a paucity of physical signs, although pharyngeal and tympanic inflammation are often described.

The age incidence of roseola is quite distinctive. More than 95 per cent of the cases occur in infants between six months and three years of age. As there is rarely more than one case within a family, roseola probably has a high subclinical attack rate. It is unlike other infectious diseases in that both sexes are equally susceptible. It occurs the year around but, as with the other exanthems of childhood, the highest incidence is in the spring. Although epidemics have been described, the etiologic agent apparently does not spread as easily as do the agents of rubeola, rubella and varicella.

Treatment is symptomatic. Febrile seizures are the most significant, albeit a nonspecific complication of the illness.

Erythema infectiosum (fifth disease). Erythema infectiosum is classically described as a mildly contagious disease of childhood characterized by a typical eruption and usually no fever or other constitutional symptoms. This disease is presumably viral, but no definite etiologic agent has been isolated. Evidence that it is caused by a virus was reported by Werner and his associates (1957)[78] but has not been confirmed.

Krugman and Ward[35] divided the progression of the rash into three stages: first appearing on the face is a bright red erythema with circumoral pallor; second is a symmetrical rose-red macular-papular eruption of the extremities beginning proximally and then spreading to involve the trunk and distal extremities with lesions assuming a lace-like appearance due to central fading; and finally in the third stage, a evanescent rash which tends to recur if the skin is irritated or traumatized, or if there are wide swings in ambient temperature.

The diagnosis is entirely clinical and the only difficulties in this regard have to do with differential diagnosis and the unpredictability of the duration of the disease. As with roseola, a great deal of work is needed to further clarify etiologic and epidemiologic questions and the course of this illness.

Vaccinia and variola (smallpox). As variola is a disease not endemic or epidemic in the United States, my comments will be limited to vaccine and chemoprophylaxis.

In the field of the chemoprophylaxis of variola, Bauer and his associates[3] have reported significant results with a compound called n-methylisatin-β thiosemicarbazone. They found that among more than 1,000 persons who were given the drug after contacts with variola, there was a significant decrease in the number of secondary cases. This occurred in vaccinated and unvaccinated persons even when the drug was given late in the incubation period. No data are available at present as to the value of this drug if given after disease has appeared.

Experience in the recent outbreaks of smallpox in Sweden, Great Britain and Poland, attests the value and the importance of universal vaccination. The virus used for the vaccination is referred to as vaccinia virus, and although this virus probably is a passage from the original cowpox virus of Jenner, the passage history has been lost and the vaccinia virus should be considered a laboratory strain. This prophylactic agent, the first live virus vaccine for humans, has been in use since the time of Jenner and has proven to be of great value. The problems involved in vaccination have been recently reviewed in this journal by Wehrle[72] and I will merely summarize the review.

The most common problem encountered in vaccination is the so-called "no-take" reaction. The known reasons for "no-takes" are as follows: (1) Improper storage and subsequent inactivation of the live vaccine. (2) Improper skin preparation. Alcohol should not be used. Rather, the vaccination site should be cleansed with a rapidly evaporating fluid such as acetone or ether. (3) Improper inoculation. Vaccination is essentially the intracutaneous introduction of vaccinia virus into the prickle cell layer of the skin. If this is not accomplished, replication will not occur. The multiple pressure method, utilizing lateral placement of the needle over the skin, is recommended.

Although a recent report[55] indicates that immunity may develop in the absence of a primary "take" a primary reaction should be the only one accepted as indication of a "take" in any person who has no history of smallpox or who has not been previously vaccinated. If the person has had previous vaccination, revaccination should be attempted with a batch of vaccine which is known to have produced primary responses in previously unvaccinated persons until a satisfactory immune reaction or accelerated "take" is observed. This precaution is very important, as inactivated vaccine can produce the accelerated skin reaction in persons who have previously experienced a successful vaccination.[4] This reaction is one of delayed hypersensitivity and immunity does not follow.

The most serious complication of vaccination is encephalitis. The frequency of this complication is probably very low. In the large New York City experience of 1947, the rate was approximately one in 100,000.[24] The most severe non-CNS complication of vaccination is eczema vaccinatum. No one, child or adult, with active eczema or any other dermatitis should be vaccinated. It is also recommended that even a person who does not have eczema not be vaccinated if there is an opportunity for him to have contact with anyone at home who has eczema or dermatitis of another type.

Generalized vaccinia occurs in about one out of 100,000 vaccinations and usually is not severe. Vesicles usually appear about the ninth day after vaccination and go through the stages of the primary vaccination but much more rapidly.

A generalized erythema multiforme type of reaction has been described also occurring on about the ninth day of a primary "take."

Booster doses. Revaccination is advocated for everyone at approximately four to five-year intervals. To his dying day, Jenner believed that the use of cowpox virus provided life-long immunity. Recent work has shown that this is not true.

Treatment. When mild, generalized vaccinia should be treated symptomatically. When secondary infections occur, appropriate antibiotics should be chosen and used wisely. In cases of severe eczema vaccinatum, or generalized vaccinia, the use of hyperimmune, human, vaccinia gamma globulin is indicated. There is no specific treatment for reaction of erythema multiforme type, but steroids have been used with equivocal results.

Miscellaneous Viral Infections of Childhood

Herpesvirus Hominis (Herpes Simplex)

Whereas 85 to 95 per cent of infections with rubeola virus result in disease, the situation is reversed in infections due to herpes simplex. By the age of four, most children have been infected with this virus, but infection is inapparent in about 99 per cent of patients. Whether the primary infection is subclinical or manifest, the herpes virus can remain in a latent state to reappear in the form of fever blisters or coldsores when the individual is under stress.

Clinical Manifestations of Primary Herpes Simplex Infections

Gingivostomatitis. This is the most common clinical manifestation of primary herpes simplex infection. It usually begins abruptly with the onset of fever. Painful vesicular involvement of the gums, tongue and buccal mucous membrane is concurrent with, or soon follows, the fever. Involvement of the soft palate is not uncommon and extension to the oropharynx is sometimes seen. The gums are usually swollen and friable, bleeding quite easily with light trauma. The child with gingivostomatitis is extremely uncomfortable and is a pathetic, drooling soul. Even mild liquids produce pain, either by direct contact or on the act of swallowing. The disease usually runs a course of five to seven days and the treatment is symptomatic. The most serious complication is dehydration resulting from decreased intake of fluids. Healing usually occurs without scarring.

Vulvovaginitis. This is a rare manifestation of primary herpes. The onset and course of herpetic involvement of the vulva is similar to that seen in gingivostomatitis. The pain is just as severe and the pathologic changes similar to those seen with gingivostomatitis. Due to the proximity of the urethra, dysuria is not uncommon. Deep scarring is usually absent.

Eczema herpeticum (Kaposi's varicelliform eruption). This syndrome is a manifestation of primary herpes superimposed upon eczema. The lesions appear in crops, giving the appearance of varicella. Thus, the name. The systemic signs are severe, with pronounced fever lasting seven to nine days. When large weeping and oozy skin surface areas are present, complications of fluid loss and superimposed bacterial infection should always be anticipated. Unless there is severe secondary infection, deep scarring usually does not result.

Traumatic herpes. Physically traumatized areas of the skin may be the site of primary herpetic involvement. The trauma may be in the form of an abrasion, burn or other damage compromising skin integrity. Although the source of the virus may be overt (coldsore in a member of the family), the latency of herpesvirus infection makes any close contact a potential vector. Fever and constitutional signs accompany the vesicular lesions.

Keratoconjunctivitis. Although herpetic keratoconjunctivitis may be associated with fever and constitutional symptoms, the most important complication of this syndrome is permanent scarring of the cornea. The use of (IDU) 5-iodo-2-deoxyuridine (Stoxil®), the first commercially available antiviral drug, has been shown by Kaufman[33] to be efficacious. Thus far, this drug has been shown to be active against herpesvirus infection only when used locally in the conjunctival sac. There is no evidence that it is useful in systemic involvement.

Meningoencephalitis. Acute herpetic meningoencephalitis is a primary although a rare manifestation of primary herpesvirus infection. This syndrome has been associated with a high morbidity and mortality rate.[43]

Disseminated visceral herpetic infection. This is almost exclusively confined to the premature and newborn period and will be discussed in a later section.

Recurrent herpes infection. Recurrent herpes infection is more common than the primary type and usually takes the form of so-called fever blisters or coldsores. However, any other area of the skin or mucous membranes may become involved. Constitutional symptoms and fever are usually not associated with infection of the recurrent type. Treatment is entirely symptomatic. There is no experimental evidence that vaccination with vaccinia virus is useful in recurrent herpes labialis. Although both agents produce vesicular lesions, there is no antigenic relationship between the two.

Diagnosis of herpes infection can usually be made clinically. When the differential diagnosis includes generalized vaccinia, varicella or variola, the virus laboratory may be necessary. The laboratory methods used, and the specimens necessary for confirmation of herpetic cause, can be seen in Table 3.

Mumps (Epidemic Parotitis)

Mumps may be considered the disease of childhood with the most protean manifestations. Although best known for involvement of the salivary glands, mumps has definitely been implicated in the etiology of carditis,[79] pericarditis,[32] orchitis, oophoritis and meningoencephalitis.

Pancreatitis, a severe but uncommon manifestation of mumps infection, is manifested by severe, epigastric pain and tenderness often associated with fever, chills, weakness, nausea, and vomiting. Recovery is usually complete.

Orchitis, probably the most widely discussed complication of mumps, appears in about 20 to 30 per cent of post-pubertal boys who have the disease. It is unilateral in approximately 98 per cent of cases. The fear that mumps orchitis may result in sterility is unwarranted. Males who are threatened by the spectre of sterility may take assurance from the fact that rarely are both testes affected and even when they are the involvement is of a spotty nature.

Treatment. Treatment of uncomplicated mumps is entirely symptomatic, most persons requiring merely antipyretic and analgesic drugs. The treatment of orchitis is more complicated. The efficacy of diethylstilbestrol and surgical incision of the tunica albuginea has not been confirmed by well controlled studies. Many physicians believe that corticosteroids reduce testicular swelling, but this also lacks well controlled documentation. Convalescent gamma globulin in doses of 20 ml intramuscularly has been reported by Gellis and coworkers[21] to significantly reduce the incidence of orchitis. Convalescent mumps *serum* should not be used, for the agent of serum hepatitis or infectious hepatitis may be carried in it.

Question often arises as to what course of action should be followed when an adult without a previous history of mumps is exposed to a child with the disease. First, the adult should be assured that there is a 50 per cent probability that he has already had subclinical mumps. Provided the person tested does not have sensitivity to egg, a positive reaction to a skin test for mumps may be indicative of previous subclinical infection. In persons who have a negative skin test result, the use of hyperimmune mumps gamma globulin is indicated when an economic hardship would result from disease. The use of mumps vaccine (killed) in adults exposed to mumps has not received adequate and controlled testing. There are indications, however, that the vaccine may be effective when given to children immediately before exposure (two weeks). Immunity following mumps vaccine appears to be temporary.

Nonbacterial Diarrhea

With the exceptions of the common cold and other upper respiratory tract infections, the so-called nonbacterial diarrheas perhaps have been associated with a larger body of folklore, misinformation and misnomers than any other group of illnesses in childhood. Variously referred to as gastroenteritis, summer diarrhea or infant diarrhea, this large group of diseases is poorly understood. Viruses were etiologically implicated as far back as 1943 when Light and Hodes[40] published the results of their studies. This was followed in 1944 by the studies of Budding and Dodd[7] and Gordon and coworkers in 1947.[22]

The etiologic role of the enteroviruses in these syndromes has not been well defined. Confusion has resulted because of the prefixing of the epithet "entero" to this group of agents, many persons assuming that enteric disease, and thus, diarrhea, is caused by these viruses. Although this is true in a few cases, it is certain that many of the nonbacterial diarrheas are not due to these agents. Other misnomers that have been applied to this group of diseases are intestinal flu and intestinal grippe. The term diarrhea, or diarrhea and vomiting, is sufficient and is not confused with influenza, which is a true respiratory tract disease entity known to be due to a specific group of etiologic agents. Specific nomenclature will have to await isolation of specific agents and proof that these agents do in fact cause the disease.

The problem in ascribing a specific diarrhea episode to agents isolated from the gastrointestinal tract are great. These difficulties result from the fact that at any particular point in time, multiple types of microorganisms—viruses as well as bacteria and protozoa—can be isolated from the gastrointestinal tract of healthy children, as well as the sick. Studies must be designed which include the serologic response of the host to any agent isolated from the gastrointestinal tract. Concurrent, similar studies among healthy children in the same community are essential to establish a statistically, excessive prevalence of the suspected viruses among sick children. Such work has been conducted by Ramos-Alvarez and Sabin[61] and Ramos-Alvarez and Olarte.[60] These investigators demonstrated that enteroviruses, as well as adenoviruses, can be associated with diarrheal disease. However, these studies are few compared to the number of cases of diarrhea seen throughout the United States; and until concerted effort similar to that now being expended on the respiratory viruses is begun, our knowledge of the disease potential of these various agents will be incomplete.

Viral Infections of the Fetus and Newborn

Cytomegalic inclusion disease (CID). (Inclusion disease, generalized salivary gland infection, salivary gland virus inclusion disease and generalized cytomegalic inclusion disease.) Until the propagation of the CID virus in tissue culture by Smith in 1956,[67] diagnosis of this disease was retrospective and rested on pathological descriptions of diseased tissue. Since 1956 our knowledge of the virus, and subsequently of the pathogenesis of CID, has increased greatly. The physiochemical properties, and the fact that the agent produces a type A intranu-

clear inclusion, argue in favor of including the cytomegalovirus in the herpes group of viruses. Inclusion-bearing cells have been found in salivary glands, kidney, liver, lung, brain, pancreas, thyroid, adrenal gland, gastrointestinal tract, spleen, thymus, lymph nodes, parathyroid gland, pituitary gland, testis, epididymis, ovary, heart, eye, muscle, bone marrow, skin and blood vessels. The description of large intranuclear inclusions in cells found in urinary sediment by Fetterman[19] in 1952 was a significant advance in the diagnosis of CID.

The clinical features of congenital CID are not unique and include jaundice, hepatosplenomegaly and thrombocytopenic purpura. Patients may be jaundiced from one to several weeks after birth; less often, jaundice appears at some time within the first two months and may persist as long as four months.[27] Microcephaly is found in most infants with CID and it is not unusual for an infected infant to excrete cytomegalovirus in the urine for two to three years after birth. This persistence of virus shedding is similar to that seen with *herpesvirus hominis*, although the rate and quantity of virus excretion appears to be greater with the cytomegalovirus.

The role of cytomegalovirus in the postnatal period is not well understood. The virus has been isolated from infants presenting with interstitial pneumonitis, and its association with *pneumocystis carinii* has been described. It is not known whether infants infected with cytomegalovirus after birth are affected neurologically. Although cytomegalovirus is a definite cause for neonatal hepatitis, it has not been recovered from most infants and young children with unexplained hepatitis. The role of cytomegalovirus during childhood is also poorly understood. It is probable that severe generalized infection is limited to newborn and premature infants. In older children, asymptomatic infection is relatively common.

Inclusion bodies have been observed in the salivary gland of 10 to 30 per cent of pediatric patients at autopsy, suggesting wide virus dissemination, and it would seem reasonable to postulate that most persons acquire the disease in an inapparent form. Rowe and coworkers, and Weller and his associates demonstrated an increasing incidence of complement fixation and neutralizing antibody with age, and also observed the presence of these antibodies in gamma globulin. The virus has been isolated from a child with leukemia and pneumonia and from the urine of children with unexplained hepatosplenomegaly. On the other hand virus has been isolated from the urine and mouth swabs of normal children. Thus, the relationship of this virus to childhood disease is still unknown. Hanshaw[27] has recently summarized these findings.

Infants surviving cytomegalic inclusion disease usually have severe neurologic sequelae. Microcephaly, motor dysfunction and mental retardation probably result from brain damage secondary to generalized infection. All but two of 16 patients observed by Weller[74] had residual damage.

Differential diagnosis includes congenital toxoplasmosis, erythroblastosis fetalis, disseminated herpes simplex, sepsis of the newborn and congenital syphilis. Diagnosis is based upon the clinical findings and the isolation of virus from the urine or diseased tissue along with demonstration of the characteristic inclusion in cells found in the urinary sediment. Intracranial calcification is seen in approximately 20 per cent of patients.

Disseminated herpes simplex infection. Unlike the pattern of infection in the older child in which the subclinical variety is the "norm," infection in the premature and term newborn infant usually results in disseminated disease. The virus can be acquired by the newborn in one of three ways: (1) From lesions in the mother's genital tract, (2) from lesions in a nursery attendant and (3) possibly by transplacental transfer of virus.[46] Unlike a patient with erythroblastosis fetalis, the child usually appears well until about the fifth to ninth day of life. Infection during the newborn period is usually fatal, although there are occasional cases in which the only manifestation may be skin vesicles. An infant with severe, generalized infection usually comes to medical attention because of hepatosplenomegaly, jaundice, lethargy and, sometimes, convulsions. The virus has been isolated from all organs, tissues and fluids studied, including the liver, spleen, brain and spinal fluid.

Diagnosis in the newborn period is based upon demonstration of typical intranuclear inclusions and/or isolation of virus from diseased tissue. Differential diagnosis includes cytomegalic inclusion disease, erythroblastosis fetalis, sepsis of the newborn, toxoplasmosis and syphilis.

Group B Coxsackie virus infection of the newborn. Group B Coxsackie virus infection in the newborn manifests itself in a manner quite different from that seen in older children and adults. With the report of van Creveld and de Jager[70] it became apparent that myocarditis seen in the first ten days of life may be due to these agents. In addition to infection of the myocardium, other organs have been involved. Rapmund and coworkers[62] isolated Group B type 4 Coxsackie virus from the heart, brain and kidneys of a child who died of myocarditis in the second week of life. The child's mother in this case had aseptic meningitis and made an uneventful recovery. Here, then, is another instance in which newborn infants respond to infection differently than adults or older children. Newborn in-

fants with Coxsackie virus infections resemble those with disseminated herpesvirus, and they have been described by some investigators as "sacks of virus." Recently, Wright and his associates[80] isolated a Group A type 16 Coxsackie virus from the myocardium of a seven-week-old infant who died of myocarditis. The diagnosis of Coxsackie virus infection of the newborn may be confirmed by the isolation of virus from the stool as well as from diseased tissue.

Inclusion body conjunctivitis (Inclusion blennorrhea). Inclusion body conjunctivitis is caused by a virus of the trachoma group. Infection is probably acquired during the birth process, as inclusion-bearing cells have been described in the cervical epithelium in many adult females. The disease usually appears after the fifth day of life with a purulent conjunctivitis which is clinically indistinguishable from that due to chemicals or Neisseria gonorrhoea. The diagnosis is confirmed by appropriate staining of conjunctival scrappings and the demonstration of the characteristic intracytoplasmic inclusion bodies. Because this infection does not appear until about the fifth day of life and most infants are discharged from the nursery before that time, many instances of the infection go unnoticed. Treatment with sulfonamides or tetracycline ointments is usually successful. There is usually no scarring.

Other Viral Diseases

Because the scope of pediatric virology essentially encompasses all of human virology, only those agents of particular importance to pediatricians have been stressed. For readers with special interests in specific disease syndromes, the following references are suggested:

(1) Central Nervous System Disease of Viral Etiology, reference numbers 1, 2, 12, 17, 18, 20, 37-39, 42, 43, 53, 54, 58, 59, 71, 72.
(2) Rabies, reference numbers 14, 25, 50.
(3) Hepatitis, reference numbers 36 and 45.

Comment

The usual format for a review article consists of an introduction, in which the importance of the subject is stressed, a detailed historical review, followed by a larger section of factual material, and finally predictions by the reviewer as to what might be expected in the future. However, feeling that such a formal presentation discourages conceptual synthesis, I have not attempted to review the entire field of pediatric virology. However, certain concepts that can never become outdated can be formulated from the mass of new data. In fact, future information can only serve to reinforce them. These concepts, which are not new to the field of virology, are those of the pantropism of infectious agents and the variability of specific host response.

The concept of pantropism is well illustrated in the wide spectrum of disease caused by the enteroviruses. Thus, members of the Group B Coxsackie viruses have been associated with, or proven to be etiologic agents in, aseptic meningitis, pleurodynia, neonatal myocarditis and acute benign pericarditis. Various ECHO viruses have been shown to cause aseptic meningitis as well as many exanthematous syndromes which may be clinically indistinguishable from rubella or roseola. However, exanthems have also been observed in disease due to the Group A Coxsackie viruses. The polioviruses continue to be the principal causes of severe paralytic CNS disease but, as is the case with the other enteroviruses, they have also been implicated in the causation of gastroenteritis.

All of this information merely emphasizes the second concept which has been minimized or even overlooked in the mad scramble for new viral agents. That is, the clinical picture produced by infection with any one agent depends not only on the biological characteristics of that agent but also on the biological characteristics of the host. Here again enteroviral disease may be used as an example. Several of the Group B Coxsackie viruses have been proven to be etiologic agents of neonatal myocarditis but the very person from whom the neonate acquired the infection, its mother, may manifest a clinical picture of aseptic meningitis, a syndrome quite different from that in the newborn. Here, perhaps, the differences in host response stands out in their boldest relief—a self-limited infection as opposed to a fatal one. The ECHO viruses, especially ECHO-9, are frequently implicated in exanthematous disease, but manifestations of this kind are more often seen in children than in adults. Such differences in host response are less obvious in the field of viral disease of the respiratory tract, and yet we are all familiar with family outbreaks of respiratory disease which produce croup or bronchiolitis in a 12-month-old child and pharyngitis in his 10-year-old sibling.

The concept of the variability of host response is again well illustrated by the phenomena of subclinical and latent infections. Infection with *herpesvirus hominis* is perhaps the best known example of latent infection in man, while a related agent, *herpesvirus simiae* ("Monkey B") produces similar manifestations in certain monkeys, but fatal encephalitis in man. The adenoviruses can produce both clinical and subclinical disease in man, but that they can remain in a "latent" stage is less appreciated. Rabbits inoculated with the adenoviruses merely respond with the formation of antibody, while newborn hamsters infected with either type

12 or 18 adenovirus can, and do, develop transmissible tumors. Similarly, Simian Virus 40 (SV-40) infection in monkeys is characteristically latent but produces sarcomas in newborn hamsters while humans inadvertently inoculated with this agent respond, as far as is known at present, with the formation of antibody alone. The factors governing the phenomena of subclinical and latent infection have deservedly assumed increasing importance in the fields of virology, epidemiology and immunology. They straddle the variables of age, sex, heredity, climate and animal species to become the common denominator in the host's response to infection.

The pediatrician, in particular, is concerned with that age group in which the biological differences in the host are most outstanding, for he is dealing with a group of susceptibles that are continually in that state of change which we call growth. In the confines of no other specialty can the spectrum of disease due to a single agent be viewed more succinctly. In the past, the pediatrician, being, cognizant of this basic fact, became aware early in his training that if he were to understand and treat infectious disease effectively, he would have to think in terms of broad diagnostic categories when considering an individual patient's illness. In recent years, however, there has been a trend toward making more specific etiological diagnosis of clinical viral disease. Although the direction of this trend is understandable, the clinician is cautioned to avoid the use of tubular vision in the diagnosis of a particular infectious disease. For instance, during an epidemic of ECHO virus disease it is very tempting to ascribe a particular exanthem to this agent. However, the exanthem in question may very well be scarlet fever, or meningococcemia, *diseases which can be treated,* rather than the more ethereal ECHO-9 which *cannot be treated.* The myocarditis or pericarditis seen in a 10-year-old is more likely to be rheumatic in origin than due to the more "modern" Group B Coxsackie viruses.

There is no need other than the personal security and self-satisfaction of the physician to assign a specific etiological diagnosis to an acute illness which, from a clinical point of view, is presumably of viral origin. Rather, a broad etiological diagnosis is all that is possible—and all that is necessary—during the acute phase of such an illness. Is it really important whether one says that the cause of a case of aseptic meningitis is "one of the enteroviruses" rather than being specific and ascribing the disease to a Group B Coxsackie, type 2? It should not be inferred from this that a more specific diagnosis should not be sought. However, the main value of specific diagnosis lies not in the particular acute phase treatment of an individual patient, but in the prognosis of his illness and in the epidemiological repercussions it may have on the community.

Fortunately for the pediatrician, and certainly for children, viral infections in childhood are rarely fatal, indeed are almost never serious. In the future, the efforts of the pediatrician and the virologist, should be directed mainly toward those areas in which fetal and infant salvage are possible. In the area of fetal salvage, the development of an effective and safe rubella vaccine is most pressing. Further, efforts should be made in the prevention of severe viral lower respiratory tract disease and diseases in which permanent residua may be a problem. As to the milder viral respiratory tract diseases of childhood, I feel that the attitude of Christopher Robin should be followed.

Christopher Robin
Got up in the morning,
The sneezles had vanished away.
And the look in his eye
Seemed to say to the sky,
"Now, how to amuse them today?"

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