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Enterovirus Infections:

Etiologic, Epidemiologic and Clinical Aspects

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■ *The term* enteroviruses *was introduced in 1957 to bring together in one large family the polioviruses, Coxsackie A and B and echoviruses, all agents for which the human alimentary tract is the natural habitat. At present more than 60 distinct members are recognized: three polioviruses, 24 Coxsackie A, six Coxsackie B and 30 echoviruses. The list of new members, particularly in the* ECHO-group, *grows regularly. The viruses are frequently widely disseminated in the summer and fall of the year, circulating chiefly among young children, causing both apparent and inapparent infection. The enteroviruses are responsible for a wide spectrum of clinical manifestations, including non-specific febrile illness, sometimes with rash, aseptic meningitis, paralytic disease, respiratory infections, pericarditis and myocarditis. There is considerable overlap in biologic behavior, and the same syndrome can be induced by many different agents.*

In a few instances the clinical pattern is distinct enough to suggest the group of agents involved. Thus, herpangina is associated with the Coxsackie A viruses and epidemic myalgia (devil's grip) with the Coxsackie B group. Paralytic disease is caused primarily by the polioviruses, but recently it has been found that other members, particularly the Coxsackie B viruses and Coxsackie A7 can also cause "paralytic poliomyelitis."

The ultimate potential of enteroviruses in terms of central nervous system disease and other manifestations is unpredictable. Great variety in terms of clinical and epidemiologic behavior of known and "new" viruses has been the pattern in the past, and is likely to continue.

THE ENTEROVIRUSES are an extraordinarily versatile family of viruses. Although illnesses which they cause are more often of concern to pediatricians than to internists, the many discoveries over the past 15 years relating to this group of agents have general interest and application in virology and in clinical medicine. In the following discussion, I shall review briefly something about the enteroviruses themselves, the epidemiology of infections caused by them and some of the clinical problems which they present.

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Etiology

The term *enteroviruses* was introduced in 1957 to bring together in one family the polioviruses, Coxsackie A and B, and echoviruses, all agents for which the alimentary tract is the natural habitat.[4] The characteristics which these agents have in common are summarized in Table 1. Unlike the

bacterial flora, they are transient inhabitants of the alimentary tract—that is, they cause acute infection, are excreted for a period of weeks, and disappear, leaving the host relatively immune to reinfection with the homologous virus type. All are small (15 to 30 mμ) ribonucleic acid (RNA) viruses which exist in multiple antigenic types. They lack essential lipids and are therefore resistant to ether and other organic solvents. On the basis of shared physical and biochemical properties, the enteroviruses, along with the rhinoviruses (the chief agents causing the common cold in adults) are now classified together as the *Picornaviruses* (Table 2) The *pico* in the name refers to their very small size, and the RNA indicates their nucleic acid type. In addition to picornaviruses of human origin, there are a number of similar agents which have been isolated from lower animals. These include the virus of hoof and mouth disease, Teschen disease of swine, Theilers virus, enteroviruses of monkeys, cattle and swine, as well as bovine and equine rhinoviruses.

The story of the enteroviruses is a good illustration of the crucial role of methodology in scientific research, for each burst of discovery in this field has depended upon the development of a new technique. It is astonishing to reflect that before 1948 when the monkey was the major test system used for isolation of viruses from patients with central nervous system (CNS) disease, polioviruses were the only known members of the enterovirus group. In 1948 the use of suckling mice for testing fecal specimens led Dalldorf and Sickles[5] to their discovery of the Coxsackie viruses, of which 24 group A and 6 group B are now known. Subsequently, the introduction of tissue culture methods resulted in the discovery of the continually growing family of echoviruses (the ECHO stands for enteric cytopathogenic human orphans) so named because in the beginning it was not known whether or not they were associated with human illness. Some 30 echovirus types are now recognized. By and large, they do not induce disease when inoculated into animals, and their *sine qua non* is cytopathogenicity for primate cells in tissue culture. The discovery of the echoviruses is a direct result of the introduction of practical tissue culture techniques in 1948 by Enders, Weller and Robbins.

The diagnosis of the specific etiologic agent of enterovirus infections can be accomplished only in the laboratory. Virus isolation is the most satisfactory means, and the agents are recovered readily from throat swabs and fecal specimens by inoculation into tissue cultures of primate cells, or in the case of most Coxsackie A viruses, by inoculation of suckling mice. Infections induce neutralizing and complement-fixing antibody responses, but because of the multiplicity of antigenic types, serologic diagnosis in the absence of virus isolation is rarely feasible.

TABLE 1.—*Characteristics of Enteroviruses (Poliovirus, Coxsackie,* ECHO

1. Transient inhabitants of the alimentary tract.
2. Multiple antigenic types.
3. Small particle size—15 to 30 mμ.
4. Ribonucleic acid (RNA) core.
5. Lack essential lipids and are therefore resistant to ether and other organic solvents.
6. Stabilized against thermal inactivation by divalent cations (Mg^{++}, Ca^{++}).

TABLE 2.—*Picornaviruses (Pico-RNA)*

	Serotypes
A. *Picornaviruses of human origin:*	
1. Enteroviruses	
(a) Polioviruses	3
(b) Coxsackie A	24
(c) Coxsackie B	6
(d) ECHO	32 (−2)*
2. Rhinoviruses	53 (+)
3. Unclassified	Many
B. *Picornaviruses of lower animals:*	
Foot and mouth disease virus	
Enteroviruses (of cattle, swine, monkeys, mice)	
Rhinoviruses (of cattle, horses, etc.)	

*Two echoviruses have been removed from the group and reclassified, ECHO-10 as reovirus type 1, and ECHO-28 as rhinovirus type 1.

Epidemiology

In addition to sharing the same physical and biochemical properties, the enteroviruses behave similarly epidemiologically (Table 3). In temperate zones they have a sharp seasonal incidence with a peak in the summer and fall. In the tropics and in semi-tropical areas, however, they are endemic the year round, often to an extraordinary degree. The seasonal incidence in temperate climates is similar to the pattern for other enteric infections, but the reasons for this behavior are poorly understood. The viruses are often widely disseminated in a community during a given period; frequently more than one agent is active at the same time, the types of illnesses induced being similar whatever the agent. In spite of wide prevalence, however, there may be relatively little clinical disease, for in general the majority of enterovirus infections are inapparent, and only occasionally do they induce clinical symptoms and

TABLE 3.—*Enterovirus Infections—Epidemiologic Features*

1. Seasonal incidence: summer-fall in temperate climates; prevalent the year round in tropical and subtropical areas.
2. Inapparent infections commoner than clinical disease.
3. Modes of virus dissemination: fecal-oral, and pharyngeal-oropharyngeal.
4. Virus dissemination influenced by sanitary environment.
5. Age incidence: primarily in young children; older children and adults often immune as a result of previous inapparent infection.

signs. Thus for poliovirus infections, the most thoroughly studied of the group, there is evidence that even during severe epidemics there are at least a hundred inapparent infections for every paralytic case. There is some variation depending upon the agent involved, but the clinically ill segment of the population usually represents only the visible part of the iceberg; beneath the surface is a far larger segment in which the viruses circulate silently, chiefly among young children.

Whether an individual experiences an apparent or an inapparent infection, however, he seems to be an equally good source of enterovirus spread. These infections are highly contagious, particularly in the family setting. The incubation period is short, and several days after exposure and as long as a week before onset of symptoms, virus is often present in the blood, throat and feces (Chart 1). Excretion from the throat continues for seven to ten days, and from the feces for several weeks or more. The period of greatest infectiousness appears to be around the time of onset, when virus is shed from the throat, and is excreted in the feces in maximum quantities. There is some question as to whether transmission is primarily from the pharynx of one person to the oropharynx of another, or whether the fecal-oral route is the main one. At present, based on evidence accumulated as a result of widespread use of inactivated Salk-type poliovirus vaccine, it appears that one or the other of these routes may dominate, depending upon certain environmental factors.[2] Thus in populations with high standards of hygiene and sanitation, pharyngeal-oropharyngeal transmission seems to be the more important, while in populations living in poor sanitary environments, major dissemination occurs by the fecal-oral route.

Socio-economic factors and environmental sanitation have a decided influence on the degree of dissemination as well as on the mode of spread of enteroviruses. Surveys of populations living under crowded conditions in poor sanitary environments indicate that as high as 60 per cent of normal children under 2 or 3 years of age are infected with and excreting one or more enteroviruses at any given time.[22] Excretion rates among children of the same age living in a more favorable environment are much lower, even during periods of epidemic prevalence.[7] Age has a pronounced effect on ability to spread enteroviruses: young children under 2 years are the most effective dis-

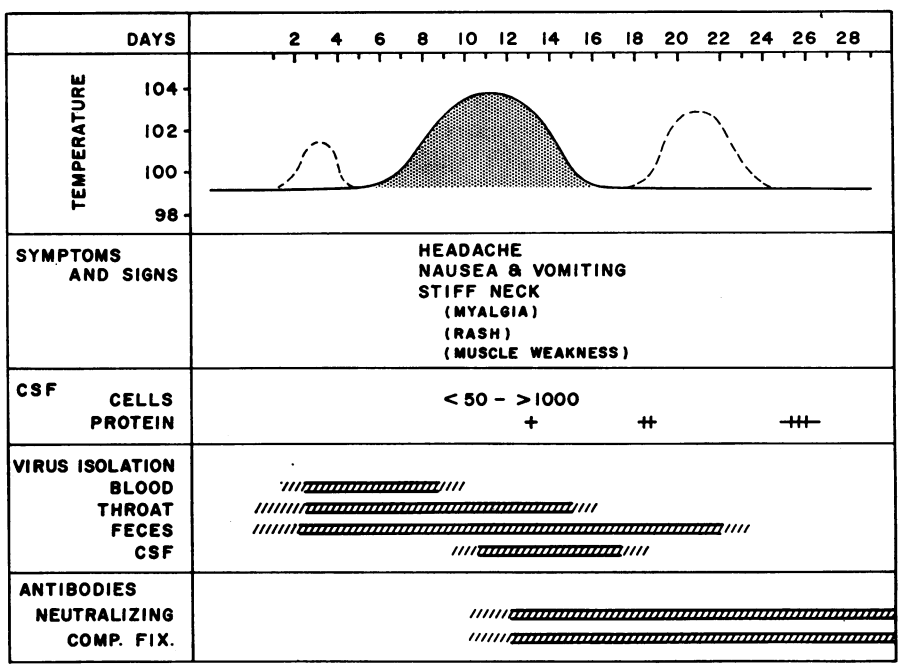

Chart 1.—Schematic diagram of the course of enterovirus infections of the central nervous system. Whether the clinical response is mild or severe, patterns of virus excretion and antibody rises are similar. Temperature curves with interrupted lines indicate that: (1) a "minor illness" followed by several days of well-being may precede the onset of CNS symptoms and signs; and (2) in certain epidemics (e.g. with ECHO 9 virus) recurrence of fever and meningeal signs may occasionally be observed after apparent recovery.

TABLE 4.—*Clinical Syndromes (Other Than Neurologic) Associated with Enterovirus Infections*

Syndrome	*Associated Agents*
Minor febrile illness (nonspecific)	Polioviruses Coxsackie A Coxsackie B Echoviruses
Herpangina	Coxsackie A1, 2-4, 6, 8, 19
Hand, foot, and mouth disease	Coxsackie A5, 16
Acute lymphonodular pharyngitis	Coxsackie A10
Neonatal myocarditis	Coxsackie B1-5
Myocarditis and pericarditis in children and adults	Coxsackie B1-5
Pleurodynia	Coxsackie B1-5 Echovirus 6, 8, 9
Acute respiratory tract infections URI (upper respiratory illness)	Coxsackie A21, 24 Coxsackie B1-5 Echovirus 11, 20
Bronchopneumonia	Coxsackie A9 Coxsackie B4, 5
Enteritis (diarrheal disease)	Echovirus 11, 14, 17, 18, and ? others; ? Coxsackie viruses

seminators, probably because of their unhygienic habits whatever the external sanitary environment. As with polioviruses, widespread infection early in life results in a solidly immune older population in which epidemics of clinical disease do not occur. In populations living under optimum conditions of sanitation and hygiene, however, young children are protected from immunizing infections in early life, and the resulting build-up of a susceptible older population provides fertile soil in which epidemics may start when virulent strains are introduced.

Age has a good deal to do with both susceptibility to infection and to the type and severity of clinical manifestations. As with so many viral infections, the young adult experiences a more severe disease than does the young child. With poliomyelitis, this became increasingly apparent in the United States between the years 1930 and 1955, during which there was a shift in the pattern of age distribution of paralytic cases toward an ever increasing incidence in older children and young adults. Whether this same shift will occur with other enterovirus infections is not known, but there are indications that it is not an unlikely possibility. Thus in the large epidemics of ECHO-9 virus infections which swept the United States in 1957-58, as high as 50 per cent of adults were susceptible and many became ill when exposed in the family setting.[26] In the 1960 epidemic of aseptic meningitis in Minnesota, associated with echovirus type 30, the highest attack rate was in the 20 to 24 age group, which suggests that this agent was new to the area, or at least had not been circulating for many years.[15]

Clinical Aspects

Turning to the clinical features of infections with enteroviruses, these are as complex, diverse and ever-changing as other aspects. Discovery of new techniques, "new" viruses and "new" clinical syndromes has been—and is likely to continue to be—the pattern. By and large there are few specific *diseases* associated with enteroviruses, but instead, a variety of *syndromes* (Table 4, 6). Any one syndrome can be caused by a number of different agents, and any one agent is capable of inducing a variety of clinical syndromes. The specific etiologic diagnosis of an illness can be made only in the laboratory, and here too there are difficulties, for recovery of an agent does not necessarily mean that the agent caused the patient's illness since inapparent infections with enteroviruses are so common. Controlled studies and the accumulated experience over the past 15 years, however, have established the role of these agents in causing certain syndromes. These will be reviewed briefly.

Nonspecific febrile illness; enterovirus exanthems

The commonest syndrome associated with enteroviruses is the non-specific febrile illness. Probably all 63 of the known enteroviruses can cause this. The "minor illness" or abortive form of poliovirus infection[23] is the classic example: a 24 to 48 hour illness with low grade fever, anorexia, sometimes sore throat and vomiting. The other agents commonly induce a similar clinical response. Many, or even most such infections are so mild that the physician is not called. But in recent

years it has become apparent that enterovirus infections may be associated with skin eruptions,[1,19] and if the minor illness is accompanied by a rash, the patient is more likely to be seen by a physician. Table 5 indicates the enterovirus infections so far associated with rash, either commonly or occasionally. There are doubtless others, and as the list grows steadily it would seem likely that skin lesions can occur with most enterovirus infections under certain circumstances. The appearance of the rash is similar, no matter which agent is involved. The most common form is a maculopapular (rubelliform) eruption which is non-pruritic and does not desquamate. Sometimes petechial, vesicular, scarlatiniform or mixed forms appear. A given virus type may be associated with different eruptions even during the same epidemic, and there is also variation from epidemic to epidemic, as has been reported with type 4 echovirus infections: in one outbreak rash was frequently seen,[16] while in another, this was not one of the clinical features.[12] On a few occasions virus has been isolated from vesicular skin lesions associated with type 4 echovirus, and Coxsackie A5 infections.[1] Both Coxsackie A5 and A16 viruses induce a vesicular eruption of characteristic distribution, leading to the designation "hand, foot, and mouth disease."[25] In this syndrome, the oral lesions occur chiefly on the buccal mucosa and tongue, less frequently on the palate, gums and lips. The lesions on the extremities are interdigital, on the dorsum of the hands and feet, and involve palms and soles.

Rash has also been a prominent feature of certain echovirus infections, particularly those caused by types 9 and 16. In "Boston exanthem" (type 16) the eruption appears as fever and other systemic symptoms subside.[21] Echo 9 infections, epidemic in Europe and the U.S.A. during 1956-1959, were often accompanied by a dramatic eruption, most prominent and persistent on the face. As with most enterovirus rashes, the lesions were present chiefly in children under five years, and were seen in relatively few over 15 years.[26]

Herpangina; hand, foot and mouth disease and lymphonodular pharyngitis

The most distinctive disease induced by the Coxsackie A viruses is *herpangina*. This syndrome was reported first by Zahorsky in 1924 and his description of the clinical manifestations has not been surpassed. Herpangina is not often seen by internists, for it is primarily an infection of young children who present with fever and typical oral lesions, not more than 15 or 20, in the posterior pharynx and on the tonsillar pillars. These are tiny vesicles which go on to become punched out ulcers surrounded by bright red areolae. Other Coxsackie A syndromes include the previously mentioned hand, foot and mouth disease, and the recently described clinical entity, *acute lymphonodular pharyngitis*.[30] So far only Coxsackie A10 has been isolated from patients with this syndrome in which the diagnostic lesions are nonulcerating nodules in the posterior pharynx and occasionally on the conjunctivae.

Aseptic meningitis

Neurologic syndromes associated with enteroviruses cover the spectrum from mild aseptic meningitis to fatal encephalomyelitis. Whatever the clinical response, however, the pattern of virus excretion and the development of antibodies is similar (Chart 1). Aseptic meningitis, the commonest neurologic manifestation, has been associated with many different virus types both in epidemics and as probable etiologic agents in sporadic cases (Table 6). The types responsible for large epidemics have been relatively few: Coxsackie A7 and 9; Coxsackie B1-5; and echoviruses 4, 6 and 9. An etiologic diagnosis is made most readily by virus isolation from the stool or pharyngeal secretions. Spinal fluid is also a good source of virus when the infection is due to Coxsackie A or B or a number of echoviruses,[18] but the agent is rarely recovered from the spinal fluid in cases of poliomyelitis.[28] Diagnosis based on serologic tests alone—that is, by screening acute and convalescent sera to demonstrate an antibody rise against a specific enterovirus—is not often attempted because of the multiple serotypes (more than 60) which might be involved.

As with other enterovirus syndromes, more cases of aseptic meningitis are seen in children than in adults, but in some recent outbreaks as high as 50 per cent of patients have been adults.[15] This trend is significant, for the severity and duration of the clinical course tends to increase with age. Often, as in mumps meningitis, there is also a difference in the incidence of the disease in the two sexes, the ratio of cases in males to females being at least 2:1 in those under 20 years.[18,20] Over the age of 20, cases in women predominate, presumably because of their greater exposure to young children, the chief virus disseminators.

TABLE 5.—*Enterovirus Infections Associated with Rash*

Commonly
Echovirus 4, 9, 16
Coxsackie A 9, 16
Occasionally
Echovirus 1-3, 5, 6, 11, 14, 18, 19
Coxsackie A 2, 4, 5
Coxsackie B 1, 3-5

There are few clinical features of aseptic meningitis which suggest the etiologic agent responsible. Some of the viruses are among those commonly associated with rash, such as Coxsackie A9 and ECHO-9, and this may be a helpful diagnostic point (Table 5). With ECHO-9 virus infections there is a tendency to unusually high spinal fluid cell counts, even up to several thousands, with 40 to 60 per cent or more polymorphonuclear cells persisting for a number of days.[10] If there is a petechial rash, as may occur in infections with ECHO-9, it may be difficult to distinguish between aseptic and meningococcal meningitis. The possibility of inadequately treated bacterial meningitis also comes up when the patient has received antimicrobial therapy which may have been sufficient to modify the clinical manifestations without having eradicated the agent. In general, however, the viral nature of the infection is indicated by the milder course, the normal or modestly elevated leukocyte count in peripheral blood, and the cerebral spinal fluid findings early in the illness: cell counts commonly in the range of 50 to 300 per cu mm with a predominance of lymphocytes, normal glucose levels and normal or slightly increased protein content.

Encephalomyelitis

It seems likely that any agent which can invade the central nervous system and induce aseptic meningitis may also under certain circumstances result in paralytic or encephalitic disease.[8,29] Some ECHO and Coxsackie viruses have already demonstrated their capacity to do this, and even to result in fatal infections, particularly in very young children. For the world as a whole, however, polioviruses still account for more than 95 per cent of cases of paralytic poliomyelitis. But as this disease has declined in the United States and elsewhere, it has become increasingly apparent that diseases indistinguishable from it clinically can result from infection with other enteroviruses. These agents have been recovered from spinal fluid and cord or brain of some of the fatal cases.[8] The pathologic findings are similar to those of poliovirus infections in type, although often with some differences in distribution in the central nervous system. Coxsackie A-7 virus has been more frequently associated with definite paralysis than have the other non-polio enteroviruses. It has caused outbreaks of aseptic meningitis, with a number of cases of paralysis in the U.S.S.R. and in Scotland,[6] and several fatal cases have been reported. Our Russian colleagues have been so impressed with the paralytogenic potential of Coxsackie A-7 virus that they have suggested that it be called Type IV poliovirus.[3]

Among the echoviruses, types 6 and 9 have been responsible for many cases of mild muscle weakness which persists for several months and then disappears. Residual paralysis or fatal disease has been rare with these two types as with echoviruses generally.[8]

Other clinical manifestations which have been reported as due to various enteroviruses include encephalitis and paralysis with sensory loss, diagnosed clinically as the Guillain-Barré syndrome,[8] and encephalomyocarditis in the neonatal period, which deserves special mention.

TABLE 6.—*Neurologic Disease Syndromes Associated with Enterovirus Infections*

Syndrome	*Associated Agents*
Aseptic meningitis	Poliovirus 1-3 Coxsackie A 2, 4-11, 16-18, 22-24 Coxsackie B 1-6 Echovirus 1-9, 11-14, 16-19, 20-25, 30, 31
Paralysis	Poliovirus *1*, 2, 3* Coxsackie B *1, 2, 3, 4, 5* Coxsackie A *2, 4, 7, 9* Echovirus *1, 2,* 4, *6, 9, 11,* 13, 16, *30*
Encephalitis	Coxsackie B *5* Coxsackie A 2, 4, 5, 6, 8, 9, 18 Echovirus *9,* 14, 19
Encephalomyocarditis (neonatal)	Coxsackie B *1, 2, 3, 4, 5*

*Types which have been associated with fatal illness or residual paralysis are in italics.

Encephalomyocarditis, myocarditis and pericarditis

The syndrome of encephalomyocarditis in newborns has been prominently associated with the Coxsackie B group of viruses. Newborn nursery epidemics have been reported in many parts of the world, always associated with a high mortality rate.[11,14] Virus has been recovered frequently from heart, brain and viscera. Because of the potential danger when Coxsackie B viruses are introduced on an obstetrical service, the woman who at the time of delivery has fever and other evidence of an acute viral infection—no matter how mild—is suspect, and should be isolated.

As to myocarditis and pericarditis in older children and adults, the Coxsackie B viruses have been implicated in some 15 reported cases, and there have been rare cases attributed to Coxsackie A viruses. Coxsackie B4 virus has been recovered from the pericardial fluid of a 13-year-old girl, the only fatal case recorded in a patient over two years of age.[27] In 14 others (aged 2½ to 36 years) with the characteristic clinical features, the diagnosis has been made on the basis of virus isolation from the feces and/or antibody rises. All of these patients recovered without apparent residual effect. There is at present no virologic evidence to link sporadic cases of chronic progressive myocarditis in children or adults to infection with Coxsackie viruses, although this possibility cannot be completely ruled out.

Pleurodynia (Epidemic myalgia; Bornholm disease)

Pleurodynia is not a common disease but it is one of the most typical manifestations of Coxsackie B virus infections. It usually occurs in epidemic form; sometimes there is an associated myocarditis or pericarditis or, more frequently, aseptic meningitis. Orchitis has been reported as a complication in some outbreaks,[31] and more rarely pneumonitis. In adults the characteristic onset is with sudden severe chest pain (devil's grip) similar to pleuritic pain, while in children abdominal pain is more frequent. In both, the problem is acute myositis involving chest, diaphragm and abdominal muscles. A few cases have been linked with echoviruses, but to date these are very rare and pleurodynia is essentially a Coxsackie B virus syndrome.

Acute respiratory illness

Only in the past few years has it been appreciated that enteroviruses are sometimes associated with respiratory illnesses.[13] Lennette and his colleagues established Coxsackie A21 as the etiologic agent in an epidemic of upper respiratory infections in a military population.[17] ECHO 11 and 20 have also been incriminated in naturally occurring infection, and ECHO 11 has induced the common cold in volunteers. Pneumonia and other lower respiratory tract disease are less common, but have been reported with Coxsackie B virus infections.

Enteritis-diarrheal disease

Finally, we come to what one might logically expect to be first—enteritis caused by enteroviruses. Paradoxically there is little firm evidence to implicate these agents except in a few epidemics, chiefly in infants, in which echoviruses type 14 and 18 were demonstrated to be the etiologic agents. There is a less definite association between diarrheal disease and other enteroviruses except perhaps in semi-tropical environments.[24] In the familiar clinical situation of acute gastroenteritis occurring as a family or institutional outbreak, frequent efforts to isolate enteroviruses have been fruitless. It appears that in general the currently known enteroviruses are not important causes of enteritis.

Comment

This brief review of a large and diverse subject has emphasized the similarities between the clinical manifestations caused by a number of different agents, and the impossibility of making a specific etiologic diagnosis except by laboratory means. Nevertheless, recognition of these syndromes and an appreciation of their diverse etiology should aid the clinician in dealing with acute febrile illnesses. Basically, the problem when one sees a patient with fever and other evidences of acute infection, is whether the infecting organism is bacterial or viral. On the basis of epidemiologic features—season of the year, age of the patient, prevalence of similar illnesses in the community—together with the particular clinical manifestations, an educated guess as to an enterovirus etiology is often possible. Recognition of the viral nature of such illnesses is of importance in terms of management, not because specific drugs are available (although the day is sure to come when they will be) but so that antibiotic agents and other antimicrobials will not be used unnecessarily. In this day of ever increasing incidence of iatrogenic drug-induced diseases, this consideration is a serious one.

With the virtual disappearance of poliomyelitis in the United States and other countries with a well vaccinated population, the other enteroviruses are assuming greater relative importance, particularly in the etiology of central nervous system disease. So far there is no evidence that these agents are becoming more widespread or more virulent as a result of the departure of wild polioviruses. But the appearance of "new" agents and the factors governing the epidemic rise and fall of both new and old enteroviruses are as poorly understood as ever. Changing epidemiologic patterns have been such a characteristic feature of poliomyelitis, it would be surprising if infections due to other enteroviruses did not also exhibit similar behavior. It seems safe to predict that these agents will have a lively future, and that "new" members and "new" clinical syndromes will be added, probably when we least expect them.

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