Given present knowledge of Echo and Coxsackie viruses, what may be the trend of infection with these agents in tropical areas? Based on the characteristics of tropical environments, viral attributes, and related factors, an attempt is made to answer this question. He predicts a long-term increase.

EPIDEMIOLOGICAL ASPECTS OF COXSACKIE AND ECHO VIRUS INFECTIONS IN TROPICAL AREAS

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MY INTENT is not to review the existing very fragmentary information concerning the occurrence of infection with and disease produced by Coxsackie and Echo viruses. This task has been well done in the relatively recent past by others.[1-3] Rather, I propose to speculate concerning the present situation and reasonably anticipated future developments in tropical areas, basing such speculation on viral attributes of epidemiologic significance, on pertinent features of tropical environments, on analogy with the polioviruses, and on selected data for infection and disease in tropical and temperate areas.

Virus Characteristics

We are presently concerned with 56 distinct viruses which fall into three enterovirus subgroups, Coxsackie viruses (CV) A, CV-B, and Echo viruses (EV) with 23, 6, and 27 members, respectively.[3,4] In general, these viruses are known or presumed to share the following attributes of epidemiologic significance: (1) relative stability in the free state (a factor favoring indirect transmission via environmental contamination); (2) a natural host range chiefly restricted to man; and (3) ability to induce transient infection of the human alimentary tract with both pharyngeal and fecal excretion of virus. The viruses differ with respect to antigenic character (important to identification and specific immunity) and experimental host range (limitation to newborn mice has severely restricted study of many CV-A viruses). Also of interest but incompletely defined are possible differences in such human-host related properties as ability to induce long-lasting antibody response (crucial to serodiagnosis and to serosurveys for past infections) and pathogenicity (clinically silent infections are likely to go undetected).

Environmental Factors

The inherent features of a tropical environment are a relatively constant, warm, and humid climate and the flora and fauna determined by such a climate. These features probably exert little direct influence on the spread of enteroviruses since these agents are very stable in the free state, and we know of no essential extrahuman phases in their life cycles. Nor do we know that man's susceptibility to disease produced

by these agents is influenced by climate. However, there are other important environmental factors which, although not exclusive features of the tropics, prevail widely in tropical areas. These include nutritional deficiencies which, as with measles and tuberculosis, may enhance host susceptibility, and overcrowded habitations and poor personal and community sanitation which favor ready dissemination of enteric infectious agents by direct and indirect means.

The Poliovirus Model

Let me turn briefly now to infection and disease caused by the polioviruses in the prevaccination era. Except in isolated populations, polioviruses have been completely ubiquitous. However, the frequency and patterns of disease occurrence have varied greatly from tropical to temperate zones and, indeed, in both zones have undergone significant change.

Ubiquity reflects ability to persist in large population groups which in turn depends upon an unbroken chain of direct or indirect transmission. In temperate zones, but not in the tropics, transmission slows down greatly in winter and early spring, only to burst forth anew in the summer and fall in areas where sufficient numbers of susceptibles have accumulated. In Louisiana, a periodicity of from three to five years for a given poliovirus type was indicated.[5-7] Pharyngeal excretion as exemplified by vaccine strains[8] is relatively brief (10-16 days) and at best can provide only a short link in the chain of transmission. Fecal excretion, in contrast, endures 50 days on the average and may continue for 120 days or more.[6] The ubiquity of polioviruses probably depends chiefly on two facts: (1) this long period of fecal excretion, and (2) virus stability sufficient to permit a wide diversity of indirect and perhaps prolonged paths of transmission.

With respect to disease occurrence, we are confronted with a paradox. Poliovirus infections occur most abundantly in those areas, including the tropics, and those population segments in which disease is least often observed (isolated population groups excepted). The most important single factor influencing the frequency of disease occurrence is probably the age at which primary infection is acquired. Although silent infections probably predominate at all ages, the proportion resulting in overt and serious disease is believed to increase markedly with age. Hence, where poor sanitation facilitates virus spread, as in many tropical areas, infection occurs early in life and disease is infrequent. Improvement in living standards and sanitation, now under way in many tropical populations, interposes a partial barrier to virus spread which serves to delay the usual occurrence of infection. Paul[9] has pointed out that infant mortality rates provide an index of sanitation and that, when the rates fall to about 75 per 1,000 live births, the frequency of paralytic disease increases.

Coxsackie and Echo Virus Infection and Disease

Before considering infection and disease due to CV and EV, it is important to remember that most of our knowledge represents a by-product of investigations done in the name of poliomyelitis. This fact often dictated the nature of the specimens collected and the means by which they were screened for viruses. It also led, in disease-oriented studies, to concentration on central nervous system (CNS) disease.

As Gelfand's excellent review[1] makes clear, these viruses as a class are ubiquitous and, during the appropriate season, can be detected frequently in the feces of children, in sewage and, in poorly sanitated areas, in privy speci-

Table 1—Enterovirus Excretion in Feces, Toluca, Mexico, Before Feeding Trivalent Sabin Oral Poliovaccine (August, 1959) and Three Months Later*

Time	Age Group	Number of Specimens	Per cent Virus Positive		
			Polio	Nonpolio†	Total
August 1959— Pre-vaccine feeding	<1 mo	78	0	10.2	10.2
	1–5 "	230	8.2	37.8	46.0
	6–11 "	135	11.1	43.0	54.1
	1–5 yrs	719	11.0	50.8	61.8
	6–10 "	369	4.4	30.6	35.0
	Mothers	361	5.0	16.0	21.0
	All	1,892	7.9	36.2	44.1
Three months post-vaccination	1–5 yrs	417	0.7	50.6	51.3

* Adapted from Sabin, et al., 1960.[10]
† Nonpolio includes all agents causing CPE in MK or HEP-2 cell cultures or detected in newborn mice.

mens, and filth flies. While some individual viruses may be as ubiquitous as polioviruses, we do not have in any instance extensive information concerning age-immunity patterns and the frequency of viral excretion in many different populations. For most of the viruses we also lack information as to duration of pharyngeal and fecal excretion.

Toluca, Mexico, in August, 1959, just prior to mass feeding of vaccine polioviruses, illustrates what may be an extreme in enterovirus prevalence.[10] Although rectal swabs rather than fecal specimens were collected, all were screened in three systems, monkey kidney and HEp-2 cell cultures and newborn mice. Only polioviruses were type identified. Relevant data are summarized in Table 1. Points of interest are the high over-all enterovirus burden (44.1 per cent), the early age at which it begins (10 per cent in the first month, 46 per cent from one to five months) and the relatively high prevalence of infection among school-age children and mothers (35 per cent and 21 per cent, respectively). Since the Toluca population was not kept under long continuing observation, no seasonal pattern could be defined. However, the one-to-five-year-age group was followed for three months after vaccination with no basic change except for the sharp reduction in poliovirus prevalence.

Enteroviruses in general resemble polioviruses with respect to patterns of seasonal variation.[1] Only in the true tropics does no consistent variation occur, the amplitude of the variation and the duration of the "season" elsewhere being roughly related to latitude. These and certain other points are illustrated in Table 2 in which I have summarized data from four studies of the longitudinal type. Leopoldville in the Congo[11] represents the true tropics, and one notes that the over-all enterovirus burden (based on 12 months' observation) in infants less than one year old was slightly less (31 per cent) than that recorded in a single month for the same age group in Toluca, Mexico (42 per cent, including those under one month). In June of 1958, Vandeputte also screened 101 children (aged two to six) and 99 adults, recording enteroviruses present in 48 per cent and 6 per cent, respectively. The other three study areas, Louisiana,[12] West Virginia,[13] and New York, lie progressively further from the tropics. The data for metropolitan New York are heretofore

Table 2—Summary of Data from Four Selected Continuing Studies of Enterovirus Occurrence

Populations Studied	Methods for Virus Detection	Virus Group	Per cent of Specimens Virus Positive			"Season"§ (Months Included, Peak Underlined)
			Over-all	Low Month	High Month	
Leopoldville (Congo) sample of 100 healthy infants studied each month, Oct., 1957-Sept., 1958*	Human amnion and Hela cell cultures, newborn mice	All entero	31.0	14.0	48.0	1–12
		Poliovirus	8.1	2.0	18.0	1–12
		Coxsackie virus	14.3	6.0	36.0	1–12
		Echo virus	8.7	5.0	16.0	1–12
Southern Louisiana, 115 index children followed monthly from birth, Jan., 1954-Dec., 1956†	Monkey kidney cell cultures	All entero	15.7	5.4	27.7	5, 6, 7, 8, 9, 10
		Poliovirus	5.0	1.8	10.9	6, 7, 8, 9, 10
		Coxsackie virus	2.5	0	8.2	5, 6, 7, 8, 9, 10
		Echo virus	7.4	1.8	16.6	6, 7, 8, 9, 10, 11
Charleston, W. Va., 136 children aged 2 wks to 4 yrs contributed average of 53 specimens/month, June, 1951-Oct., 1953‡	Monkey kidney cell cultures	All entero	5.0	0	18.6	7, 8, 9, 10
		Poliovirus	1.0	0	4.0	7, 8, 9, 10
		Coxsackie virus	1.9	0	8.5	7, 8, 9
		Echo virus	2.1	0	9.3	7, 8, 9, 10
Metropolitan New York, Virus Watch Program, families with young children contributed average of 250 fecal specimens/month, Jan., 1961-Mar., 1963¶	HEP-2 and monkey kidney cell cultures	All entero	2.4	0	9.7	8, 9, 10, 11
		Poliovirus	0	0	0	—
		Coxsackie virus	1.7	0	7.1	8, 9, 10, 11
		Echo virus	0.7	0	2.6	8, 9, 10, 11, 12, 1

* Vandeputte, 1960.[11]
† Gelfand, et al., 1959.[12]
‡ Honig, et al., 1956.[13]
¶ Fox, J. P.; Elveback, L.; and Spigland, I. Unpublished data.
§ "Season"—defined as months with per cent positive specimens at or above mean or over-all per cent.

Table 3—Observations on Enterovirus Excretion in Southern Louisiana Children, 1958 and 1959*

Viruses Included	Age of Children (Years)	Total Number Excreting	Number Excreting for Indicated Days			Estimated Mean Days Duration of Excretion‡
			1–4	5–14	15+†	
Coxsackie, types A9, B2, 3, and 5	10+	28	16	5	7	—
	5–9	46	22	8	16	
	2–4	48	26	9	13	17.3
	0–1	31	10	6	15	
	All	153	74	28	51	16.5
Echo-types 1, 3, 6, 7, 9, 11, 14, and 19	10+	10	9	1	0	—
	5–9	28	10	6	12	
	2–4	18	8	4	6	14.5
	0–1	11	6	2	3	
	All	67	33	13	21	12.8

* Children observed were members of New Orleans households,[8] or residents in two lower class neighborhoods[17] being observed for spread of Sabin oral vaccine strains.
† Maximum observed excretion was 73 days for C viruses and 31 days for E viruses.
‡ Based on mean observed excretion plus estimated average interval (3 days) between collection of specimens.

unpublished, preliminary figures from the continuing observation of families with young children residing in two lower middle income communities, a program known as the Virus Watch. Comparison of the three sets of data reveals that, as one progresses northward, the over-all enterovirus burden declines and the "season" is delayed, shorter, and more sharply defined. Also, as previously noted by Gelfand,[1] the EV season appears to be both late and lingering.

Determination of age-immunity patterns by serosurvey has been done systematically for selected viruses in relatively few areas.[12,14,15] Although neutralizing antibody to any given virus usually could be found in some members of each population studied, the age-immunity patterns varied substantially with specific viruses and from one population to another. As compared with polio, the patterns often showed a slow accumulation of immunes with age and, in some instances, a decline in older age groups. These differences indicate either that antibody responses are weaker and less permanent than to polioviruses or that the viruses are significantly less able to spread. Occasionally, a particular virus appears to have been long absent from populations well able to maintain enteroviruses. Thus, in Osaka, Japan, as of 1959, CV-B Type 5 appeared to have been absent for nearly 30 years, a fact that set the stage for a major outbreak of viral meningitis in 1960 with many infants as well as older persons attacked.[15]

The ability of viruses to spread depends in part on the mode and duration of their excretion. Existing data for nonpolio enteroviruses indicates that they are excreted in the feces and probably in the pharynx for much shorter periods than are polioviruses. Perhaps the best data for a single virus were collected in Louisiana in 1956 during an epidemic of silent E7 infections in which bi-weekly observation of households provided data on 96 infected chil-

dren.[16] The maximum observed fecal excretion was 105 days, and the estimated mean was 24 days. Additional data, shown in Table 3, describe observations of CV and EV fecal excretion made during studies of the spread of vaccine polioviruses in Louisiana in 1958 and 1959.[8,17] Of special interest are the high proportions (48 per cent for CV and 51 per cent for EV) of abortive infections (duration 1-4 days) encountered despite very frequent specimen collection, the maximum observed excretion (73 and 31 days for CV and EV, respectively), and the short estimated mean excretion (17.3 and 14.5 days, respectively, for infections in children below age 10). In Table 4, similar data for the New York Virus Watch study indicate that the maximum observed and estimated mean periods of fecal excretion were very close to the corresponding Louisiana figures. Also, pharyngeal shedding was studied. In only about 40 per cent of infections was pharyngeal virus detected and then, most often, on but a single occasion.

We now come to the role of CV and EV in causing disease. Clearly, as with polioviruses, most infections are silent. All of 119 E7 infections detected in Louisiana,[16] all of 220 miscellaneous Louisiana infections included in Table 3, and more than half of the 118 New York infections included in Table 4 were definitely silent; also clearly, for no individual member of the CV or EV groups has the pathogenic potential been fully defined, either qualitatively or quantitatively.

In general, acceptance of etiologic relations has followed in the wake of outbreaks of relatively homogeneous disease of sufficient severity to come to medical attention, such as aseptic meningitis and pleurodynia[18] or neonatal myocarditis[19] associated with CV-B infections, herpangina with CV-A,[20] and both exanthems and aseptic meningitis associated with EV.[21-25] This approach to etiologic association obviously may result in failure to include less severe or atypical syndromes in the spectrum of clinical response.

Finally, it should be noted that etiologic association of these viruses with disease has been basically a temperate zone phenomenon to date, a fact for which two relevant explanations may be considered. The first is that, as with polioviruses, infection in temperate zones may more often result in disease be-

Table 4—Observations on Enterovirus Excretion in Virus Watch Families, Metropolitan New York City, 1961 and 1962

		Coxsackie Viruses Types A9, B1-5	Echo Viruses, Types 2, 3, 6, 11, 18, 25, and 27
Number of index infections observed*		79	39
Pharyngeal virus	Per cent excreting	40%	38%
	Days excreting—range	1–14	1
Days total duration of excretion	Observed range	1–69	1–28
	Estimated mean†	18.6	13.9

* Paired pharyngeal and fecal specimens collected bi-weekly and in relation to reported intervening illness; index persons usually preschool children, one per family.

† Based on mean observed days plus estimated average interval between collection of specimens (10 days).

Table 5—Enterovirus Isolations Among Patients with "Nonpolio" CNS Disease in Charity Hospital, New Orleans, and a Matching Control Group of Surgical Patients, 1956-1957*

Virus Isolated	CNS Disease Patients	Control Patients
None†	79	92
Polio Type 3	0	1
Coxsackie A9	1	1
B1	1	1
B2	3	0
B4	5	0
B5	4	3
Echo Type 4	3	0
6	1	1
7	2	8
9	4	0
10	1	0
14	0	2
Untyped‡	8	5
All	112	114

* Unpublished data—Carey, D. E., and Fox, J. P.
† Includes 26 of 29 patients considered to have paralytic disease, but from whom polioviruses were not isolated (serology did not exclude poliovirus infection).
‡ Antisera available to Coxsackie A9, B1-5, and Echo 1-14.

cause it is delayed to older ages or because, as with CV-B myocarditis in newborns, maternal antibody may be lacking. The second reason is that, when disease occurs sporadically in populations with the heavy and multitypic burden of enteroviruses characteristic of tropical areas, it may be impossible to establish the fact of etiologic association even when it exists. Data presented in Table 5 illustrate the variety of enterovirus isolates made in Louisiana in 1956 and 1957 from 112 "nonpolio" CNS disease patients and 114 matching controls. Some 12 identified viral species plus untyped agents were isolated, but no single agent predominated in the CNS disease group.

Discussion

In temperate zones where virus spread through the community probably is mediated largely through intimate personal contact, polioviruses may enjoy an advantage over CV and EV agents because of their longer period of fecal excretion. However, this advantage should decrease substantially where, as in much of the tropics, indirect mechanisms for spread appear to predominate. In any event, as Gelfand[1] concludes, the available data concerning CV and EV infections "strongly suggest that the level of endemicity increases with the mean annual temperature." However, it should be clear that temperature per se is not a major factor since, with adequate insanitation, respectable endemicity may occur in Arctic populations.[26]

As would be expected, infections are highly prevalent in very young children under conditions of high endemicity, e.g., Toluca[10] and Leopoldville.[11] However, particularly in Toluca, a surprising number of school-age children and adults were excreting virus. It seems probable that in most instances these were re-infections in partially immune persons. In any event, these data coupled with those from Louisiana[12] make it clear that in tropical and subtropical areas CV and EV infections are commonplace among healthy persons. This very fact undoubtedly would operate to obscure the relation of these viruses to the probably infrequent, sporadic disease they may be causing at present.

For the future, the poliovirus model is our chief guide. Outbreaks of significant disease occurred first in temperate zone populations[27] and have appeared in warmer climates only as substantial declines in infant mortality (reflecting improved sanitation) have been achieved.[9] A similar cycle appears under way with the CV and EV subgroups since it is unlikely that the increase in recognized temperate zone outbreaks of CV and EV disease, especially aseptic meningitis, is entirely an arti-

fact due solely to the control of poliomyelitis. While increase in CV and EV disease in tropical areas seems inevitable, the time and form are hard to predict, the latter because the spectrum of clinical response to infection is in no case fully defined and for many viruses, e.g., E7, completely unknown.

Summary

Analogy with poliomyelitis, knowledge of virus properties and environmental factors of epidemiologic importance, and selected available data from tropical and temperate areas have served as the basis for speculation as to the present situation and future developments with regard to Coxsackie viruses (CV) and Echo viruses (EV) in the tropics. Speculation concerning the present is necessary because CV and EV are so numerous (56 viruses at present) that for no single virus does adequate information exist concerning the occurrence of infection and disease.

The level of endemicity of EV and CV, as a class, like polioviruses, increases with the mean annual temperature, a phenomenon not due to temperature per se but to insanitation. With polioviruses, and probably with EV and CV, significant disease is least common where infection is most prevalent—a paradox chiefly explained by the usual occurrence of infection in highly endemic areas at an early age when little disease results. In any event, well defined outbreaks of CV and EV disease so far have been chiefly limited to temperate zone populations, and the spectrum of clinical response to infection is in no case fully defined and for many viruses completely unknown. Because of this, while one can safely predict a long-term increase in CV and EV disease in tropical areas similar to that now occurring with poliomyelitis, one cannot predict what forms of disease will emerge.

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This paper was read before the Seventh International Congresses on Tropical Medicine and Malaria at Rio de Janeiro, Brazil, on Sept. 5, 1963.

Original observations included were aided by Grant AI-3340, Division of Research Grants, National Institutes of Health, U. S. Public Health Service.
