Papers and Originals

A New Trend in Cholera Epidemiology

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World Incidence of Cholera since 1961

A new phase in the epidemiology of cholera has become evident since 1961, when cholera El Tor, which was originally confined to a limited geographical area in the Celebes Island in Indonesia for several decades, emerged from its original home and spread extensively in the West Pacific region and South and South-east Asian countries. The world incidence of cholera, which had been progressively declining during the last few decades, is again showing a tendency to increase. Since 1923 classical cholera, caused by *Vibrio cholerae*, has been confined to a few countries in Asia, and from 1962 it has remained limited in India and Pakistan; whereas cholera El Tor, caused by El Tor vibrios, still continues its spread over wide areas in a pandemic form. The chronological order of spread of El Tor infection since 1961 is shown in the accompanying map.

Cholera El Tor appeared in Burma in 1963, and, spreading further westwards, reached Chittagong in East Pakistan by the end of 1963. Its entry into India was first detected in Calcutta in April 1964 (Mukerjee, 1964). Before the end of the year cholera El Tor was found to have spread to seven districts of East Pakistan and West Bengal. In Calcutta cases of El Tor infection soon outnumbered those of the already endemic classical cholera. From July 1964 scattered areas in Bihar state, from which only *V. cholerae* strains had been isolated during the first half of the year, showed cholera infections due exclusively to El Tor vibrios. During the middle of 1964 El Tor vibrios were isolated in almost equal proportion with *V. cholerae* from outbreaks in Surat and Baroda areas in Gujrat state on the western coast of India. In the first three months of 1965 only El Tor vibrios were isolated from cholera cases in Baroda. During the latter half of 1964 the city of Bombay was found to harbour cholera vibrios of both types, which were isolated from patients suffering from diarrhoea after the cholera epidemic of 1964 was over. In the Kottayam area in Kerala, on the other hand, El Tor cultures alone could be isolated from cases during the cholera outbreaks in 1965. A small epidemic of "acute gastro-enteritis" in Ujjain and other places around Indore, in

Madhya Pradesh, was reported in 1965. A single strain of agglutinable vibrio isolated from one of the patients proved to be El Tor. Thus in less than one year both the eastern and western states of India have become widely involved in El Tor outbreaks. Cholera El Tor has also spread beyond the western border of India, and caused epidemic in West Pakistan in 1964 (Felsendfeld, 1965).

A sporadic case of El Tor infection was known to have occurred also in a Middle East country in 1964. By courtesy of Dr. K. Patricia Carpenter, Director, International Shigella Centre, Central Public Health Laboratory, London, we were able to confirm the identification of one pathogenic type of El Tor strain, which was reported to have been isolated from a sporadic case of clinical cholera in a Bahraini National living within a mile of Bahrain National Airport on Muhrraq Island. He had never been outside the island, nor was he aware of contact with a recently returned traveller. The origin of infection of this patient remained untraceable.

It may thus be seen that cholera El Tor has for the first time been proved capable of speedy and extensive spread over much wider areas than classical cholera. It is also noticeable that cholera El Tor is for the first time spreading to areas where

Distribution of classical cholera and cholera El Tor since 1961. The years of incidence in respective areas are indicated.

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classical cholera is already endemic, and in several such areas cases due to cholera El Tor have displaced those of classical cholera.

Interaction of *V. cholerae* and *V. eltor*

In order to examine the possible effects of competition for survival between the two types of cholera vibrios, laboratory studies were carried out on the interaction of *V. eltor* and *V. cholerae* in mixed culture, *in vitro* and *in vivo*. It was found that in mixed culture in peptone-water and nutrient broth El Tor vibrios could eliminate *V. cholerae* within four to six hours. Similar results were also observed in *in vivo* tests: *V. cholerae* were eliminated in less than 24 hours when mixed cultures were injected into the ligated loops of intestine of adult rabbits (De and Chatterjee, 1953) and when intra-intestinally administered in infant rabbits (Dutta and Habbu, 1955). It is possible that reactions of a similar nature may take place when the two types of vibrios come into contact in environmental sources or in the human intestines. The mechanism of this interaction has been studied in detail, and the results will be reported in a separate paper.

Effect on Cholera Epidemiology

The biological effect of this interaction between the two types of vibrios on the epidemiology of classical cholera would appear to be far-reaching. Evidence of this has been observed in Calcutta, Bihar, and areas in East Pakistan, where cases of classical cholera are being rapidly outnumbered by those of cholera El Tor. In Calcutta, where classical cholera has been endemic for centuries, cholera El Tor made its first appearance in April 1964. Since then cases due to classical cholera are being progressively displaced by those of cholera El Tor. By the end of 1964 there was only one case of classical cholera for every 10 or more cases of cholera El Tor. The yearly incidence of cholera cases in Calcutta from 1960 to 1963 was 2,029, 3,639, 2,865, and 4,632 respectively. But in 1964 the total number of cholera cases in that city had fallen to 1,299, only a small proportion of which were due to classical cholera. Thus the incidence of classical cholera cases showed a sharp decline from previous years. Although it may not be possible to establish a direct correlation between interaction of *V. cholerae* and *V. eltor* and rapid change-over in the relative proportion of the two types of cholera cases, the laboratory findings about the effect of interaction of the vibrios in the mixed culture doubtless provide a possible explanation for the observed epidemiological phenomenon.

In Bihar state the change-over of cases of classical cholera to cholera El Tor took place within two months of the similar change in Calcutta epidemics. This also further confirmed our earlier observations that cholera infection spreads from Calcutta to Bihar state (Mukerjee, 1963a) and the time-lag between outbreaks in the two areas is within a limit of two months. It may be expected that one of the results of cholera El Tor gaining a foothold in India will be an altered pattern of distribution and density of cholera outbreaks in the country. Owing to the low case incidence in El Tor infections as compared with the higher carrier rates (of the order 1 to 10) the total number of clinical cholera cases in formerly endemic areas may decline, while the total area involved in epidemic outbreaks and the overall number of cholera cases in the country may actually increase. It also appears possible that if the present trend continues cases of classical cholera may substantially diminish in number (as in Calcutta) or may perhaps practically disappear.

Most of the areas where the cholera El Tor epidemic had spread in recent years still continue to remain endemic foci of El Tor infection, as is evident in Indonesia, the Philippines, Vietnam, Cambodia, Thailand, Burma, Pakistan, and India. This has been made possible because of the greater endemicity

of cholera El Tor. Taking into consideration the greater epidemic and endemic potentialities of El Tor infection and the speed with which the infection is known to spread, it is reasonable to suggest that the danger of cholera El Tor soon extending further westward to the Middle East countries, and perhaps also to southern Europe, may seem to be real.

Containment Measures

With the prospect of the appearance of cholera El Tor in areas so far free from it, there is need to organize special measures for diagnosis, treatment, and prophylaxis in the new areas on the line of spread. In view of this possibility of cholera El Tor spreading to areas lacking clinical experience of the disease, cases there may not be promptly diagnosed symptomatically. The difficulty of diagnosis may be further increased, because, unlike classical cholera, cholera El Tor tends to be sporadic in incidence and may often present atypical symptoms of mild gastro-enteritis. Such cases are those most likely to form reservoirs of infection and lead to widespread outbreaks, with the result that the disease becomes endemic. Bacteriological identification of cholera El Tor, therefore, is even more important than that of classical cholera. In order to conserve the available resources, centralized facilities for mobile bacteriological diagnostic units should be organized at the national level, the public health laboratories working in close co-operation with international bodies such as the World Health Organization.

Treatment would also present new problems, since facilities for prompt treatment and hospitalization might not be readily available in newly infected areas. A solution may be in the provision of a central transfusion service with stocks of fluid for rehydration of cholera patients in anticipation of expected outbreaks. Both medical and paramedical personnel should be alerted to the possibility of cholera outbreaks and be trained in the methods of management of cholera patients. Some consultant service may be available also from the W.H.O. Cholera Team (Cholera Information, 1964). As a containment measure all patients of cholera El Tor should be kept under observation until they cease to be carriers of vibrios. This is important, as the carrier state in cholera El Tor is of longer duration than in classical cholera.

The value of vigilance and prompt application of effective containment measures has in recent years been clearly proved in Japan, where cholera could not gain a foothold although a number of cholera cases and carriers were known to have made their entry since 1962.

Prophylactic Immunization

The prophylactic cholera vaccines used in most countries consist of injections of killed suspensions of *V. cholerae*, although in some areas, particularly the Philippines and Thailand, El Tor vaccines are used against El Tor infection. The preliminary reports of the recent controlled field trials of cholera vaccines so far available indicate that the protection obtained by injectable cholera vaccine is poor (Cholera Information, 1965). The degree of protection provided by the inoculation was only about 50 to 60% at the maximum, and the duration of immunity was only three to four months. El Tor vaccine has not been tried against infection due to *V. cholerae*. However, Basaca-Sevilla, Pesigan, and Finkelstein (1964) reported that, in comparison with *V. cholerae* vaccine, that prepared from El Tor vibrios was more antigenic in humans and more potent in protecting mice against challenge by both *V. cholerae* and *V. eltor*. We believe that in cholera the object of prophylactic immunization should be antigenic stimulation of the immunologically competent cells of the intestinal tract, which is difficult to achieve by the use of parenteral vaccine (Mukerjee, 1963b). However, if the present injectable vaccines

are used we would suggest that greater emphasis should now be placed on El Tor vaccines than on those prepared with *V. cholerae* (Mukerjee, 1964).¹

Summary

Since 1962 classical cholera has been limited to India and Pakistan; but cholera El Tor, which began to spread in pandemic form after 1961, is involving increasingly large areas in the West Pacific region and South and South-East Asian countries. It is rapidly extending to areas in India and Pakistan, where classical cholera was already endemic, and in many of these areas it has progressively displaced cases due to classical cholera. Laboratory experiments to study the interaction of *V. cholerae* and *V. eltor* have shown that in mixed cultures *V. eltor* is capable of eliminating *V. cholerae* within a short time both *in vitro* and *in vivo*. These findings provide a possible explanation of the observed alteration in the pattern of cholera outbreaks in the Indo-Pakistan subcontinent. Because of the greater epidemic and endemic potentialities and speed of dissemination of cholera El Tor there is a likelihood that in the near future El Tor infections may spread further westward to the Middle East countries and from there to Southern Europe. Consequently it is suggested that containment measures, particularly the organization of mobile diagnostic and treatment services, should be undertaken in the threatened areas in anticipation of possible outbreaks. As *V. eltor* is now the causative organism of cholera in most areas, and since a better degree of protection is obtainable with vaccines made of El Tor vibrios, it is suggested that more emphasis should be placed on El Tor vaccine than on the classical cholera vaccine.

Most of the observations relating to spread of El Tor infection in India and other countries were made during the course of phage-typing of vibrio strains referred to our Centre from various laboratories. Our grateful thanks are due to the workers and chiefs

¹ It has recently been reported that in the Philippine field trials El Tor vaccine conferred comparatively longer protection against the disease than *V. cholerae* vaccine (Azurin, 1965).

of these laboratories for their valued co-operation. We are particularly thankful to the World Health Organization and the Health Directorate of the Government of India. Owing to their sustained help we have been able to follow up regularly the progress of cholera infection in different areas. We are indebted to Dr. K. Patricia Carpenter, Director, International Shigella Centre, London, for opportunities of testing the El Tor strain isolated in Bahrain and for providing the relevant information concerning the patient. The annual incidence of cholera cases in Calcutta was supplied by the Office of the Director of Health Services, New Delhi. Dr. A. Narayanaswami, a colleague in the Institute, deserves our gratitude for his helpful suggestions.

ADDENDUM.—Since the above paper was prepared cholera outbreaks have been reported from Afghanistan, Nepal, and Iran during June, July, and August this year. The causative vibrios from the first two countries were received for test in our laboratory and found to comprise both classical and El Tor types. Cholera outbreaks with a high fatality rate due to El Tor vibrios were also reported from a number of provinces in Iran in July and August this year (*Wkly. Epidem. Rec.*, 1965a). Bahrain was also declared a cholera-infected area on 12 August 1965, after another case of cholera had been notified on 11 August (*Wkly. Epidem. Rec.*, 1965b). On 21 August localized outbreaks of cholera due to imported cases were reported from Uzbekistan, in U.S.S.R. (*Wkly. Epidem. Rec.*, 1965c).

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Abnormalities of Development Associated with Hypothalamic Calcification after Tuberculous Meningitis

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Any bacterial meningitis, including tuberculous meningitis (TBM), may be associated with neurological complications, such as epilepsy, hemiplegia, paraplegia, optic atrophy and blindness, deafness, mental retardation, and hydrocephalus. Attention to these complications has recently been drawn by the *British Medical Journal* (1964).

Diabetes insipidus may also follow TBM (Acheson and Smith, 1964; Lorber, 1958a; Hay, 1960). Infrequently sequelae have included other endocrine disorders, such as the so-called "Fröhlich syndrome" (obesity, hypogonadism, retarded growth), sexual precocity, and simple obesity (Lincoln *et al.*, 1960; Wasz-Höckert and Donner, 1963). These endocrine manifestations have been recorded mainly in the Continental literature (Allimant and Peiffert, 1952; Peruzzi, 1958; Lorenz, 1959).

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Intracranial calcification, presumably as a result of mineral deposition in small tuberculomata, may also follow tuberculous meningoencephalitis, but the occurrence of endocrinal dysfunction in association with intracranial calcification is apparently uncommon.

In this paper we describe three cases of endocrinal syndromes that followed tuberculous meningitis, two with obesity and hypogonadism, and one with precocious sexual development. All three were associated with radiological calcification in the suprasellar region, confirming the probability that damage to the hypothalamus was the cause of the disorder in each case.

Methods

Urinary 17-hydroxycorticosteroids (17-OHS) were determined by the procedure of Appleby *et al.* (1955), and 17-oxosteroids (17-OS) as described by the Medical Research Council