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JAPANESE ENCEPHALITIS — A PLAGUE OF THE ORIENT

JAPANESE encephalitis has attracted attention recently in the United States, Europe, and Australia because of a small number of cases among travelers, but the epidemic proportions of the disease in Asia have compelled immunization of entire regional or national populations. Japanese encephalitis, which is caused by a flavivirus transmitted by mosquitoes, often strikes in unpredictable form. It affects principally school-age children and is greatly feared because of its high lethality and frequency of permanent neurologic sequelae.

The clinical disease was described as early as 1871 in Japan, but the causative agent (Japanese encephalitis virus) was not isolated until 1934. A major summertime epidemic problem in Japan until the late 1960s, Japanese encephalitis has subsequently caused fewer than 100 cases annually. The decline in incidence is due to changes in agricultural and pig-rearing practices, increased use of pesticides, and immunization. A similar trend has been observed in the Republic of Korea and in Taiwan. In China, Japanese encephalitis occurs in all but the two westernmost provinces and over 10,000 cases are reported annually, although morbidity and mortality have decreased since 1969.¹ In contrast, dramatic annual epidemics involving many thousands of cases have emerged in the northern part of the Indian subcontinent and Southeast Asia.² In some areas, such as Nepal and northeastern India, the increased incidence is due to developments in irrigated agriculture, with concomitant expansion of vector populations. As Hoke et al. point out in this issue of the *Journal*,³ the incidence in northern Thailand exceeds that of poliomyelitis at its peak in the United States. Japanese encephalitis also occurs in southern parts of tropical Asia, but in endemic form, with only sporadic cases. An unresolved question is whether the contrasting pattern is due to geographic differences in the

dynamics of virus transmission or to the intrinsic virulence of virus strains.

Could Japanese encephalitis be introduced and spread in the United States? Although indigenous mosquitoes, such as *Culex tarsalis*, are efficient vectors, the risk of introduction seems exceedingly remote. Nevertheless, the recent repeated importations of larvae of the Asian tiger mosquito (*Aedes albopictus*) in used tires has raised concern,⁴ since Japanese encephalitis virus is known to be vertically transmitted through the eggs of this species.⁵

Americans were first affected by Japanese encephalitis in Okinawa in 1945. Hundreds of clinical cases occurred in American soldiers during the Korean War, and nearly 50 percent of troops in the Pusan perimeter had serologic evidence of infection. In 1969, at least 10,000 Americans were infected in Vietnam and 57 encephalitic cases were recorded.⁶ This history underlies the military interest in Japanese encephalitis, but it also emphasizes the high ratio of subclinical to overt infection (200:1 to 300:1). Since 1981, when an American civilian acquired the disease in China, increasing attention has been paid to the risks associated with travel. Physicians in the United States should thus be aware of the clinical and epidemiologic features of the disease and of the characteristics of available vaccines.

The most important risk factor for infection of travelers is exposure to *Culex tritaeniorhynchus* mosquitoes, which is most likely in the late afternoon to early evening in areas of rice cultivation. Although principally rural, rice paddies are also commonly found on the outskirts of large Asian cities.

After an incubation period of 7 to 14 days, the clinical illness begins with rapid onset of fever, chills, malaise, headache, nausea, and vomiting. This prodromal phase lasts several days and is followed by symptoms and signs of generalized central nervous system infection, including nuchal rigidity, photophobia, confusion, delirium or stupor, generalized convulsions, tremors, muscular rigidity, masklike facies, and localized paresis, generally of the upper-motor-neuron type. A peripheral leukocytosis with relative lymphopenia is typical. The cerebrospinal fluid is under increased pressure and contains mildly elevated concentrations of protein and up to 500 lymphocytes per microliter.

No specific therapy is available. Approximately 10 percent of patients die despite optimal care; the higher fatality rates of 30 to 70 percent reported during epidemics reflect the lack of supportive therapy and recognition of only the most severe cases. Elderly persons are more prone to fatal infection. Neurologic sequelae, including intellectual and emotional changes and motor impairment, occur in up to 80 percent of survivors, especially children. Poor prognostic indicators include prolonged fever, a severely depressed sen-

sorium, Babinski's sign, and the presence of virus and low levels of specific IgG and IgM in the cerebrospinal fluid.⁷

The disease can be diagnosed by isolating the virus from cerebrospinal fluid or by serologic tests on cerebrospinal fluid and serum samples (available from the Centers for Disease Control through state health department laboratories). Transplacental infection followed by abortion has been documented in humans and is a correlate of stillbirth in infected swine — the principal viremic host in the transmission cycle.

Crude, formalinized mouse-brain vaccines were tested in humans in Japan in the late 1930s and were licensed in 1954. Partial purification with protamine sulfate was reported in 1958 and became a routine commercial procedure in 1962. Vaccine thus purified of myelin basic protein fails to induce allergic encephalomyelitis in guinea pigs. Since a large double-blind, placebo-controlled trial of protamine sulfate-purified vaccine in Taiwan demonstrated an efficacy of 81 percent in 1965,⁸ the vaccine has been routinely administered to millions of Japanese schoolchildren, without postvaccinal neurologic accidents.

Although the protamine sulfate-precipitated vaccine was further purified by ultracentrifugation in 1968, the efficacy of this more highly purified product, prepared by the Research Foundation for Microbial Diseases of Osaka University (Biken vaccine), was not studied critically until Hoke et al.³ conducted their extensive trial in Thailand. They reported an efficacy of 91 percent in children after two doses of vaccine. Others, including the Centers for Disease Control, have found that as many as 25 percent of persons receiving two doses do not seroconvert⁹; therefore, a three-dose schedule of primary immunization probably affords the best protection.

The Centers for Disease Control have published recommendations for the immunization of travelers.¹⁰ Although the supply of the Biken vaccine to the general population was interrupted in 1987 because of the manufacturer's concern over liability, efforts are under way to resolve this issue, and the Food and Drug Administration is currently reviewing applications for licensure of the vaccine. In developing countries of Asia, wide-scale immunization with purified mouse-brain vaccines is not likely because of its high cost (Biken vaccine costs approximately \$2.30 per dose). Less expensive vaccines — both inactivated and live, attenuated vaccines — produced in tissue culture have been used successfully in China. The best of the live vaccines (designated SA14-14-2) has been adapted to an approved cell-culture substrate and is undergoing molecular characterization in the United States. Indeed, the entire genome of Japanese encephalitis virus has been cloned and sequenced,¹¹ and immunogenic viral proteins have been expressed in yeast and bacteria. These approaches of-

fer the promise of future vaccines that are inexpensive as well as efficacious and safe.

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