Two effects would tend to round off or otherwise modify these steps: (i) when there is a breakdown of local adiabaticity for the vibrational motion near the TS during the motion of the system along q, and (ii) when there is sufficient nuclear tunneling (*16*) through the energy barrier along q in the TS region. Examples of (ii) are seen in quantum mechanical calculations for reactions involving the transfer of an H atom, reactions where nuclear tunneling is expected because of the lightness of the H atom. In the reaction studied by Lovejoy *et al.* (*7*), the dissociation of the triplet state of ketene, $CH_2CO \rightarrow CH_2 + CO$, the motion along q is that of nuclei substantially heavier than H, so the reaction would be less prone to a tunneling through the potential energy barrier.

The report of Lovejoy *et al.* (*7*) provides evidence for stepwise increases in k_{EJ}, which indicates that quantization is maintained. The question of "what next" naturally arises. Two ingredients are present in RRKM theory: (i) a statistical treatment which samples all parts of the "phase space" of the molecule and which leads to the underlying monotonic increase of the rate constant k_{EJ} as a function of energy; and (ii) a quantization of the TS, which leads to steps in k_{EJ} of size $1/h\rho_{EJ}$ imposed by the quantization of the TS upon this monotonic increase. When the statistical assumption (i) breaks down (a search for "non-RRKM" behavior is actively pursued in the literature) one expects an underlying behavior of k_{EJ} versus E to be more highly structured, that is, one would obtain nonmonotonic behavior of k_{EJ} versus E, as was found in the dissociation of CH_2O under extremely high resolution (Stark level-crossing spectroscopy) conditions (*17*). If there is sufficient averaging over an energy range in the ensemble prepared, such local structure would disappear in the averaging (*18*). Regardless of whether or not this averaging has occurred in the experiments of Lovejoy *et al.* (*7*), a question which remains concerns the size of the steps and how closely they match the expected value of $1/h\rho_{EJ}$. Estimates of ρ_{EJ} have been made, but as Lovejoy *et al.* (*7*) point out, more accurate values would be useful.

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Epidemic Cholera in the Americas

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In January 1991, cholera, the most feared epidemic disease of the 19th century, characterized by severe, often fatal diarrhea, made a dramatic and unexpected reappearance in the Americas after a 100-year absence (*1*). The first confirmed cases occurred in Peru, and by mid-February more than 10,000 patients were being treated weekly. The epidemic spread to involve a new country almost every month, and by year's end 391,000 cases and nearly 4,000 deaths had been reported to the Pan American Health Organization, more cases than reported worldwide during the previous 5 years.

Much of our knowledge of epidemic cholera comes from experience with the six previous pandemics of the 1800s and early 1900s (*2*). Each pandemic began in Asia, swept through Europe, and some went on to the Americas. All went away within a few years for reasons still unknown. During the epidemic in London in the 1850s, John Snow laid the groundwork for control by linking the transmission of disease with consumption of fecally contaminated water. By 1883, when Robert Koch discovered the causative organism, *Vibrio cholerae* 01, cholera was on the decline in Europe. In the 1900s, cholera persisted as a seasonal endemic disease in many areas of Asia until 1961 when a new pandemic began in the Celebes Islands heralded by the novel El Tor biotype of *V. cholerae* 01 (*3*). This seventh pandemic spread in Asia and the Middle East and reached Africa in 1970 where it invaded 29 countries in 2 years. Unlike previous pandemics, this pandemic has not gone away.

The extension of the seventh pandemic to the Americas has raised many questions: How was *Vibrio cholerae* 01 introduced? Why did it spread so rapidly? What can be done in each country to control the epidemic? Its reemergence has breathed new life into issues both of public health—the need to provide quality water and sewage treatment and address food hygiene—and of science—the need to apply epidemiologic and molecular techniques to examine disease transmission, identify environmental reservoirs, and develop improved vaccines.

We may never know how *V. cholerae* 01, El Tor, was introduced into the Americas, but characterization of early isolates with new techniques such as ribotyping or se-

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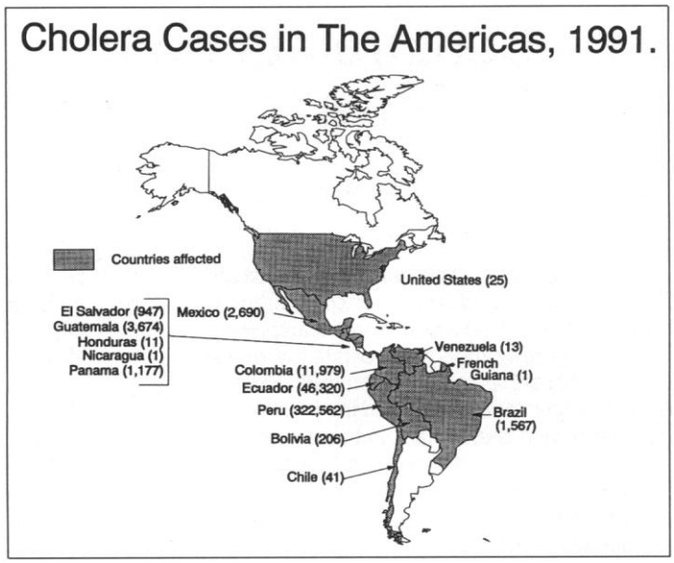
quencing could provide clues to the origin of the epidemic strains (4). Once introduced, fecal contamination of the municipal water supplies serving several large urban areas became an efficient means to amplify the organism while producing a massive epidemic. In Peru, the epidemic was recognized rapidly and the public was informed early, but delays in providing pure drinking water allowed the disease to spread.

Water has not been the only vehicle of transmission. In Chile, cholera was believed to be spread by the consumption of vegetables irrigated with raw sewage containing cholera vibrios and eaten uncooked. Public health measures prohibiting the sale of affected produce and educating the public to cook all vegetables may be responsible for a decrease in the incidence of both cholera and typhoid fever. In Ecuador, contaminated shellfish were linked to the spread of disease. Foods and beverages sold by street vendors and foods eaten without reheating have also been incriminated, consistent with observations that vibrios multiply well in some foods (5). In the United States, cases have occurred among travelers infected in epidemic areas, aboard the flight home, or from contaminated seafood transported in their luggage.



Cholera in the Americas. Map indicates the number of cholera cases reported throughout the Americas, by country, to the Pan American Health Organization during 1991.

Although identifying the mode of transmission can be straightforward, the ability to implement effective control measures is often limited. The basic problem lies in deficiencies in providing safe drinking water and adequate sewage disposal to large segments of the population. The investment in water, sanitation, and health services needed to eliminate the risk of cholera throughout the region has been estimated to exceed $200 billion over the next 12 years. However, many short-term solutions, such as the repair of existing water distribution systems and chlorination of water supplies, would be a cost-effective place to begin. Because some water becomes contaminated in the home, interventions to put small-mouthed containers into homes or to encourage people to boil or chlorinate household water could ensure water quality rapidly and at less expense. Programs to educate people about the fecal-oral spread of cholera and the need to drink clean water, to cook foods that might be contaminated, and to avoid foods and drinks prepared by street vendors might significantly decrease the risk of disease.

Considering the magnitude of the epidemic, the likelihood that cholera will remain endemic for years, the high cost of major sanitary interventions, and difficulties inherent in changing peoples' behavior concerning water use and hygiene, the accelerated development of a cholera vaccine has become a long-term goal. Several oral vaccines are under development which could prove to be more effective than the current parenteral vaccine (6). The most extensively tested, a killed whole-cell vaccine prepared with B subunit, the binding portion of cholera toxin, was more than 70% protective for 3 years in studies in Bangladesh. Two genetically engineered vaccines containing deletions in the toxin gene have been developed, one (CVD 103-HgR) uses a classical biotype of *V. cholerae* 01 and the other uses an El Tor parent. Several years of field testing are required to assess whether these vaccines have a role in cholera control.

The future of cholera in the Americas can be suggested from the situation in areas of Asia and Africa. (i) The epidemic will likely spread to new areas in the Carribean, the Amazon Basin, and the Atlantic coast and remain for years to come as it has in Asia and Africa. This persistence may be due to the establishment of reservoirs of cholera vibrios in the environment—in plankton, shellfish, water, and humans—all interacting in ways not clearly understood. (ii) Endemic cholera is seasonal, so declines in the number of cases after a peak or their reappearance this year may represent the natural seasonality of disease rather than the success or failure of control measures. (iii) Cholera may spare or behave differently in temperate areas such as Argentina, Uruguay, and Chile and in populations partially protected by virtue of their access to safe water and sewage treatment. (iv) Among people infected with *V. cholerae* 01, the proportion developing severe diarrhea in the Americas may be much greater than in Asia because the population has no prior immunity to cholera and has a high prevalence of O blood group genes, a predisposing factor for severe disease.

Although attempts to stop the spread of cholera have not been extremely successful, efforts to decrease mortality represent one success story of the current epidemic. Severe cholera used to be associated with a mortality in excess of 20%. Advances in understanding glucose-mediated transport of electrolytes in the gut led to the development of inexpensive oral rehydration therapy (ORT) allowing treatment of patients even in remote areas. The application of ORT has reduced the fatality rate for cholera to about 1%. Although we may not be able to contain the epidemic in the near future, deaths from cholera could be reduced even further through cheap, effective, and timely treatment.

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