Meetings

Cholera Research: United States–Japan Cooperative Medical Science Program

The United States–Japan Cooperative Medical Science Program was established in 1965, by agreement between President Johnson and Premier Sato, with the objective of stimulating cooperative medical research programs designed to improve the health of the peoples of Asia. As a part of this program, American and Japanese scientific panels were appointed in six areas including tuberculosis, leprosy, cholera, parasitic diseases, malnutrition, and viral diseases. The objectives of these panels have been to develop integrated research programs designed to solve major practical problems in their respective areas and to stimulate research.

At the initiation of the U.S.–Japan Program, the Joint Cholera Panel emphasized the following points. Despite the fact that a consistently effective regimen with intravenous fluids for cholera has been developed, the overall mortality rate during the current cholera pandemic has been greater than 20 percent. The continued cholera toll has resulted from the fact that a large proportion of cholera cases have occurred in impoverished rural areas, where adequate and appropriate therapy with intravenous fluids are not available. It is unlikely that prompt and adequate intravenous fluid therapy can be made available to a large proportion of affected patients in rural Asia in the near future. It is also unlikely that the sanitary measures essential to the ultimate eradication of cholera can be carried out in cholera endemic areas within the next two decades. In view of these considerations, the Cholera Panel adopted the following primary research goals: (i) the development of an effective means of conferring long-term immunity against cholera, and (ii) the precise delineation of pathophysiologic mechanisms in cholera, with the object of developing a pharmacologic means of rapidly reversing the gut physiologic alterations responsible for the disease.

A Symposium on Cholera Research, sponsored by the U.S.–Japan Cooperative Medical Science Program, was held in Palo Alto, California, in July 1967. At this time, recent advances in cholera research were reviewed, and current research needs, especially in the areas of immunology and pathophysiology, were emphasized.

In the area of immunology, H. W. Mosley (Pakistan-SEATO Cholera Research Laboratory) described recent field trials which indicated that available whole-cell and fractionated antigen cholera vaccines conferred only limited immunity for a relatively short period (3 to 6 months). In these field trials, a significant correlation was demonstrated, for the first time, between the vibriocidal antibody titer and immunity. A causal relation between vibriocidal antibody and immunity was not, however, established. In the ensuing discussion, both Japanese and American participants emphasized the dearth of knowledge of basic immunologic mechanisms in cholera, and the great need for further studies of antibodies directed against both *Vibrio cholerae* and the heat-labile exotoxin produced by this organism.

In the area of pathophysiology, investigators from Johns Hopkins reported that experimental cholera, duplicating the major clinical and physiologic features of the naturally occurring disease, can be produced in the dog by challenge with either virulent *V. cholerae* or sterile filtrates of broth cultures of *V. cholerae*. Studies on this experimental cholera model have indicated that (i) almost all the diarrheal fluid originates in the small bowel; (ii) the fluid secreted by each segment of small bowel after stimulation by exotoxin has the electrolyte pattern characteristic of spontaneous secretions from that segment of bowel; and (iii) the exotoxin-induced hypersecretion of fluid and electrolyte is not accompanied by evidence (on electron microscopy) of damage to either mucosal epithelial or capillary endothelial cells. It is felt that the dog may serve as an adequate model for defining the mechanism by which the cholera exotoxin causes hypersecretion of electrolyte by the small bowel mucosal cells.

Representatives of the SEATO Cholera Laboratory in Dacca and the Johns Hopkins University group in Calcutta reported independent studies which demonstrated that active gut absorption of glucose, and the sodium associated with it, remains essentially normal in actively purging cholera patients. The two groups of investigators further reported that glucose-associated sodium absorption can counterbalance the cholera-induced electrolyte secretion into the gut lumen. Thus, electrolyte balance can be maintained, during severe cholera, by oral administration of electrolyte solutions containing glucose. These observations lead to the hope that an effective oral therapy of cholera may prove a practical solution in the treatment of a large proportion of cholera patients in rural areas of developing countries.

At the conclusion of the symposium, it was pointed out that neither of the primary research goals of the Cholera Panel has been achieved. Several factors, however, make it possible that these goals may be attained in the foreseeable future.

1) Funds have been set aside for support of research directed toward development of an effective immunizing agent against cholera and for more precisely defining the pathophysiologic mechanisms in cholera.

2) Commercial production of crude cholera exotoxin has been initiated; limited amounts of the crude exotoxin will be made available to qualified investigators for cholera research.

3) The recently described canine model of cholera should facilitate pathophysiologic and long-term immunologic studies of this disease.

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Paleolimnology

Paleolimnologists aspire to interpret past conditions and processes in lakes by comparison with the present and thereby also to gain a better understanding of the present by knowing its genesis. The raw materials of paleolimnology are the accumulated sediments and the geomorphology of their basins. The kinds of primary materials deposited are controlled by regional geology, climate, and by an array