

A PERSPECTIVE ON THE GLOBAL PROBLEM OF ENTERIC DISEASES^{1, 2}

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Experience has shown that neither drugs nor vaccines can hope to solve the world's enteric disease problems. But oral-fluid therapy, which has sharply reduced cholera mortality, is proving effective in treating other enteric diseases as well. And most developing countries are making real progress in providing the safe water supplies and sanitary conditions that deny enteric pathogens an opportunity to flourish and spread.

In keeping with the theme "Past achievements which have resulted in better health,"¹ I, as a student for the past two decades of the infectious enteric diseases, would like to give you my perspective on the major achievements in this area. There is no need to debate whether the enteric diseases collectively are the leading cause of infant mortality in the developing world; all would agree that as a group they are one of the leading public health problems.

These diseases are also major contributors to the nutritional diseases that plague the

world; by aggravating and contributing to the pathogenesis of such diseases as marasmus and kwashiorkor, they thwart both physical and mental growth and development. They make it difficult for mothers to accept family planning because in most developing countries family security depends upon children and their potential earning power. The continuous and enduring specter of infant and childhood death removes the motivation for the planned family and makes it imperative that mothers provide large families to insure the survival of a few. Because of the great human and economic losses associated with enteric diseases, it is appropriate on this occasion that we ask what has been done to remedy the situation and what the prospects are for the future.

First, let us define the problem. I wish to talk about acute diarrhea, that is, the life-threatening intestinal infections of bacterial and viral origin. The parasitic infections, extremely important in their own

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right, most often involve subacute and chronic conditions in which life-threatening diarrhea does not occur, with some notable exceptions.

Progress in Cholera Research

In recent years there has been a renaissance of interest in the diarrheal diseases that can be attributed in large part to the emergence of cholera. Except for a few persisting endemic foci, cholera had essentially disappeared from most of the world following the sixth great pandemic that ended shortly after World War I. But in the late fifties, through the decade of the sixties, and especially in this last half-decade, cholera has emerged as a major public health problem, not only in Asia, but also in Africa, the Middle East, and even in parts of Europe.

The very presence of this disease has stimulated a great deal of new research directed not only at cholera per se, but also at diarrheal diseases generally. New and talented people, investigators with penetrating minds and researchers with diverse training and experience, entered the field in droves. This renaissance had its beginning in Bangkok in 1959, but the momentum extended through work conducted in Dacca, Calcutta, and Taiwan, and within the United States in Baltimore, Boston, and several other places. The contribution to our state of knowledge that has come from these cumulative efforts is most impressive. In fact, more has been accomplished in the field of enteric diseases since 1959 than in all the prior years of medical investigation. It would take many pages to recount all these accomplishments, but just a few will suffice to briefly summarize those bits of new knowledge relating to the theme that concerns us here.

From studies on the pathogenesis of cholera has come an understanding not only of the mechanism of cholera diarrhea, but of infectious diarrhea in general. Although

there are unanswered questions, we now have answers to the important questions: why and how diarrhea occurs in cholera, what precise pathophysiologic changes ensue, and how these need to be corrected.

The best data I can cite to illustrate how this new knowledge has paid off are case-fatality statistics. Prior to the cholera renaissance, it was accepted that 50 to 60 per cent of the persons who developed cholera gravis, the severe form of the disease, would die; and even if they could reach a treatment center that rate could, at best, be cut only by half or a third. But now, in most treatment centers of the world, the case-fatality ratio has fallen dramatically to less than 1 per cent. And it is now accepted that a cholera patient who arrives alive at a treatment center should leave that center alive within a few days. Nevertheless, in a developing country, how can a dehydrated patient get to a hospital in time?

A Treatment for Acute Enteric Disease

Cholera studies have also led to an even more important discovery, one that has implications for patients who can never get to a hospital and for those who have life-threatening diarrhea of whatever cause. Although the concept of oral rehydration is not new, the discovery of the critical role of glucose in the mechanism of fluid and electrolyte absorption in the intestine is new, and it is a breakthrough of major significance. Students of enteric diseases consider this discovery a major achievement, because investigators in several countries have impressively demonstrated that the absorption of glucose and electrolytes takes place, despite massive losses of fluid in stool and vomitus, not only in cholera but in other dehydrating diarrheal diseases as well. Studies have shown that for purposes of treatment the acute diarrheal diseases may be considered a more or less homogeneous group. Treatment has been so greatly simplified that it is no longer

necessary to consider as inevitable the formidable loss of life caused by diarrheal diseases of any etiology.

The logistics and economics of the diarrheal problem have been greatly simplified. It should no longer be necessary for dehydrated patients to be treated by physicians or even hospitalized, although a small percentage of very severe, neglected cases will still need physician care. The focus of attention, previously centered on the critical role of the physician and the hospital, is now shifting to the role of the paramedical worker in the health center and the local medicine men in the village setting. This shift is of vital importance for the disadvantaged countries and has implications not only for therapeutic medicine but for public health as well. By keeping careful records, the paramedical worker is now able to play a more vital role in surveillance. Furthermore, the paramedical worker's close working relationship with the family can be exploited by health educators to motivate changes in unsanitary habits, thereby generating a demand for better sanitation and a better way of life.

Enteric Disease Research

Stimulated by the cholera problem, investigators began looking into the other major intestinal infections. As a result, we now have a better understanding of the pathogenesis of most of the other common intestinal infections: shigellosis, salmonellosis (including typhoid), and *Escherichia coli* diarrhea. The past decade has also brought to light a new list of bacterial and viral agents. We now know that *E. coli* causes disease by two separate mechanisms: one is enterotoxin production that simulates that of *Vibrio cholerae*; the other is an invasive process that simulates the invasiveness of *Shigella* sp. Recent research demonstrates that *E. coli* ranks prominently among the major enteric pathogens in developing countries. *Vibrio parahaemolyticus*

is another newly recognized pathogen. This ubiquitous agent, the leading cause of foodborne diseases in Japan and an important cause in other countries (including the United States), was recognized when laboratory people began looking for vibrios, largely because of concern about cholera. The recognition of this pathogen in the United States is predominately an outgrowth of our own Center for Disease Control (CDC) cholera training activities of the late sixties. *Clostridium perfringens*, another leading cause of foodborne diseases, has been shown to simulate *V. cholerae* in its pathogenesis. Another major achievement, one that does not come from cholera research, was the demonstration that reovirus-like agents play a major role in diarrheal diseases of infancy and childhood. Some predict that these viruses will prove to be the principal cause of diarrhea in children. Other newly recognized viral agents, the parvoviruses, have been incriminated in epidemic diarrhea affecting adults. From all of this work have come new tools that will make possible a better understanding of the pathogenesis, epidemiology, and control of diarrheal diseases.

Vaccination and Drug Treatment Problems

There is another important trend in the wind that should be noted in discussing achievements in this field. Students of enteric diseases are increasingly coming to recognize that the single-disease approach to controlling diarrheal diseases is impractical. Since the beginning of the century, control efforts have focused in large part on the development of immunizing agents to protect man against specific intestinal infections. This was logical, because of success in using vaccines to achieve control over other diseases that were not enteric.

Thus, the thrust of much of the enteric research effort in this country and abroad has been to develop better vaccines. For years the World Health Organization's

major efforts in the enteric disease field emphasized the development of better enteric vaccines. The emphasis of the cholera program sponsored by the Agency for International Development, the National Institutes of Health, and the CDC in Bangladesh was on finding a better vaccine; and in fact the mandate to expand such work beyond cholera is really a very new one. Nevertheless, people are now beginning to take a good hard look at what has been accomplished. And they are finding that the results of this single-disease vaccine approach have really been disappointing in terms of the tools for control that have been forthcoming. For example, even though there is a reasonably good typhoid vaccine, this disease has not been controlled anywhere by vaccination.

The intensive use of vaccine in highly endemic areas has been to little avail. Witness the situation in Chile. Year after year, large urban outbreaks of typhoid have occurred in spite of mass vaccination programs. The same is true of cholera. Cholera vaccine has very limited usefulness as a control measure and has been used more for its political, psychological, and tranquilizing effects. More cholera vaccine has been used in the world since 1960 than ever before in history. But in recent years the Center for Disease Control has played a major role in provoking a reassessment of cholera vaccine, and this has encouraged health authorities to consider alternative control measures.

The efficacy of shigella vaccine has been well established, but multiple doses are required and immunity is both short-lived and strain-serotype specific. Only a few public health professionals seriously believe that shigella vaccines can control shigellosis.

Meanwhile, the fruits of many years of laboratory research aimed at developing selected genetic variants of intestinal pathogens to use as immunizing agents are not even remotely visible. The well-established

phenomenon of strain and serotype specificity of immunity to intestinal infections implies that a huge number of vaccines would be required to protect man from the array of pathogens that cause intestinal infections. Even if highly effective vaccines were available, the economics and logistics involved in their administration would be too formidable for realistic consideration. Clearly, enteric vaccines are not the answer to enteric disease control, nor are they likely to be in the foreseeable future, if ever.

Antibiotics have been useful, indeed life-saving, in selected clinical cases of enteric infection; but, from the public health and economic points of view, drugs have also been disappointing as a means of enteric disease control. Drugs by the ton were used in Iran, Africa, Italy, and other countries in attempts to stop cholera, but to no avail. In many developing countries, over-the-counter sale of antibiotics used for primary treatment of diarrheal diseases has contributed to the occurrence and spread of serious enteric disease epidemics. These drugs have had an unfavorable impact, primarily by fostering the emergence of multiple-drug-resistant bacteria. This was seen in the case of *Shigella dysenteriae*-1, which was responsible for a dysentery pandemic in Central America from 1968 through 1971 that claimed tens of thousands of lives; and the same was true of a drug-resistant *Salmonella typhi* strain responsible for a 1972-1973 outbreak of typhoid in Mexico—the largest such outbreak ever recorded and one attended by high mortality. Other illustrations of serious drug-resistant outbreaks could be cited: *Salmonella typhimurium* in Uruguay, Argentina, and Brazil; or *Salmonella wien* in North Africa and France. In sum, outbreaks due to multiple-drug-resistant strains of enteric bacteria are occurring more frequently than ever before.

One encouraging side of the picture is that not just people in public health, but also administrators and economists are

becoming increasingly disenchanted with the vaccine-drug approach to enteric disease control, and they are awakening to the reality that something must be done to reach the roots of the problem. Cholera, shiga dysentery, typhoid, and most of the other enteric diseases have an important common denominator—in that their transmission relates to poor sanitation in the form of faulty water supply and sewage disposal. There are growing signs that governments are planning to spend more for improved water supplies, striving thereby to correct this basic problem. A significant stimulus has been the occurrence or the threat of enteric disease epidemics. In this regard, cholera especially has served as a catalyst.

In most of the developing countries of the world, plans have already been made and funds have already been pledged, allocated, or budgeted for improvements during the next decade needed to assure that urban dwellers everywhere will have safe water to drink. There are not just plans; there is visible, tangible forward momentum. WHO and its several regional offices, the World Bank, and other agencies are actually working with developing countries to achieve this objective. This is just a beginning, but it is a gratifying beginning. It will require a major sustained commitment, not only to bring about these changes, but to educate the public to make the best use of these improvements.

SUMMARY

Much progress has been made, particularly in the last decade and a half, in our understanding of the causes, pathogenesis, and treatment of acute intestinal infections. Cholera has catalyzed a great deal of the recent enteric disease research, and there have been notable applied results. The case-fatality ratio in cholera has been dramatically reduced, and the treatment of cholera has pointed a way to a better and simpler method, oral-fluid therapy, to rehydrate patients who experience diarrhea of whatever etiology.

There have also been notable setbacks, particularly in attempts to control enteric diseases using a single-disease approach, with

both vaccines and drugs. At the same time, there is a growing awareness of the importance of an alternative control concept, one directed at the root of the diarrheal disease problem—faulty water supplies and poor sanitation. There are encouraging signs that authorities are increasingly drawing upon national resources to correct these basic problems, but there is a long road ahead before the citizens of all nations realize the ultimate goals of public health workers in the enteric disease field—a safe and abundant supply of water and a population literate enough to maintain sanitary standards now found in industrialized countries.