Cholera in a Vaccinated American

Immunological Response to Vaccination and Disease

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A case of clinical cholera in an American physician and his serologic response to cholera vaccine and the illness are described. In July 1968 he participated in a study evaluating monovalent Inaba vaccine. Initially his vibriocidal antibody titers were lower than the geometric mean titers of the other nine study participants, but at 6 months his titer was comparable with titers of other Americans at 6 months after immunization. In December 1968 he traveled to East Pakistan from Atlanta, Georgia, and in January he had clinical cholera. Although the reciprocal vibriocidal antibody titer in the acute and convalescent serum specimens was unchanged (320), the reciprocal toxin neutralizing antibody titer rose from less than 1 on the day the illness began to 8 on the ninth day and 13 on the fifteenth day after onset. Whereas IgM vibriocidal antibody was detectable in sera collected before and after the illness, IgG vibriocidal antibody was detectable only in serum collected 15 days after onset. This case emphasizes that healthy persons inoculated with vaccine of proved efficacy can still develop clinical cholera when exposed to it.

IN SPITE OF increased travel in cholera-endemic areas and the spread of the disease into new areas, cases of *Vibrio cholerae* infection in Westerners are rarely reported (1-4). A case of cholera occurred in an American physician exposed in East Pakistan 6 months after primary immunization and 3 months after a booster inoculation for cholera. This case had several unique aspects in that before becoming ill, the physician participated in a study of serologic responses to a cholera vaccine that was subsequently field tested and shown to be efficacious in East Pakistan. Thus, serologic tests were run before and after immunization, as well as during the course of illness. This case clearly illustrates that although a healthy person may be repeatedly inoculated with a vaccine of proved efficacy, he can still develop clinical cholera when exposed to the infection.

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Case Report

The patient was a 28-year-old male American physician stationed at the National Communicable Disease Center (NCDC), Atlanta, Ga. He had no history of prior travel in cholera-endemic areas and had never received cholera vaccine. His general health was excellent, although he had had an acute abdominal illness in May 1968 and again in September 1968; however, these episodes were self-limited. They were characterized by epigastric pain, nausea, vomiting, and anorexia. The only significant finding each time was a leukocytosis. Gastrointestinal series, intravenous cholangiogram, and intravenous pyelogram (IVP) were normal, as were a variety of serum enzyme tests and the serum protein electrophoresis.

In July 1968 the patient was one of a group of volunteers who participated at NCDC in a collaborative study sponsored by NCDC and the Pakistan-SEATO Cholera Research Laboratory (PSCRL) and designed to test a monovalent Inaba vaccine that was subsequently used in fields trials in rural East Pakistan. The study group re-

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ceived two 0.5-ml doses at an interval of 9 days in July 1968 and a booster inoculation 3 months later.

The patient and a colleague arrived in Dacca, East Pakistan, on 14 December 1968 to conduct a clinical trial of oral therapy for cholera. They were stationed at the field hospital in Matlab Bazar and participated in day-to-day patient care. The patient had close contact with 5 to 10 acute cholera patients daily, including physical examinations, administering of intravenous and oral fluids, measuring intake and outputs, especially diarrheal output from stool buckets, and obtaining rectal swabs for culture. They lived in a small building adjacent to the hospital, but they did not eat hospital food.

After 3 weeks the patient and his colleague had a mild episode of nausea and vomiting from which they both recovered within 12 hr. Two days later, on 7 January 1969, at approximately 8 AM, the patient had the acute onset of profuse, brown, watery diarrhea; diffuse abdominal cramps; and anorexia. Between 9 and 9:30 AM he began taking fluid orally, obtained a rectal swab, and took, by mouth, 20 ml of paregoric, 250 mg of tetracycline, and 500 mg of ampicillin. About 11 AM he noted light-headedness and nausea, and at 12 noon he vomited 50 ml. At this time his blood pressure was 80/60 mm Hg; pulse was 116. Intravenous normal saline therapy was begun, and 500 ml were administered in 15 min. About 12:20 PM he noted persistent, severe muscle cramps in both lower legs. Twenty milliequivalents of potassium chloride were added to the infusion, and carbon dioxide rebreathing was started. Fifteen minutes later the muscle cramps stopped, and carbon dioxide rebreathing was discontinued.

He was transferred by speedboat and ambulance to the PSCRL hospital in Dacca. During the 5-hr trip the systolic blood pressure varied between 100 and 80 mm Hg and the pulse between 116 and 100. At 3 PM the patient was passing rice-water stool. By the time he arrived at the hospital in Dacca, he had received approximately 3 liters of intravenous fluid.

On admission to the PSCRL hospital, the patient had sunken eyeballs, decreased skin turgor, and dry tongue. Blood pressure was 100/76 mm Hg; pulse, 106; respirations, 24; and temperature, 99 F rectally. He weighed 73.3 kg, approximately 4 kg less than recorded 2 days earlier. His hematocrit was 55, plasma specific gravity, 1.030; and plasma protein, 8.4 g/100 ml. Serum glucose was 70 mg/100 ml; creatinine, 1.5 mg/100 ml; sodium 141 mEq/liter; and potassium, 5 mEq/liter. Stool sodium was 135 mEq/liter; potassium, 13.8 mEq/liter; and carbon dioxide, 29 mEq/liter. The stool darkfield examination was positive for *Vibrio cholerae*, and two stool cultures confirmed the diagnosis of *V. cholerae*, classical biotype, Inaba serotype.

The patient was treated with 5-4-1 solution* intravenously, and oral tetracycline, 500 mg every 6 hr. Between 5 PM and 12 midnight on the day of admission the patient's stool volume was 5,070 ml. Between 12 midnight and 8 AM on 8 January the stool volume was 2,950 ml, and between 8 AM and 2 PM, 850 ml. At 2 PM on 8 January the patient was discharged on tetracycline after having passed 8,870 ml of stool and having received 10.4 liters of intravenous solution during his 21-hr hospitalization. Four days later the patient returned to duty at Matlab.

* Composition: the 5-4-1 solution contains 5 g sodium chloride, 4 g sodium bicarbonate, and 1 g potassium chloride per liter; this solution is administered routinely to patients at the PSCRL.

Serologic Results

The patient was 1 of 10 healthy adult male American volunteers who participated in a study designed to evaluate serologic responses to a lyophilized whole cell monovalent Inaba vaccine prepared under special contract by a commercial manufacturer. This vaccine was reconstituted to contain 8 billion cells/ml. It was designated vaccine H in the controlled field trial in rural East Pakistan during the 1968 to 1969 cholera season (5).

The volunteers had not traveled in cholera-endemic areas and had not received cholera vaccine previously. After prevaccination venous blood specimens had been obtained, the volunteers were inoculated with 0.5 ml of vaccine intramuscularly. Subsequently, on days 9 and 90 after vaccination 0.5 ml booster doses of vaccine were given subcutaneously. In addition to prevaccination venous blood specimens, specimens were collected on days 1 to 4, 7, 9, 90, and 95 after vaccination. Inaba vibriocidal antibody titers of these specimens were determined with the microtechnique described by Benenson, Saad, and Mosley (6).

The patient's vibriocidal antibody response is compared with the rest of the group in Table 1. His titer was consistently lower than the geometric mean titer of the study participants during the first 9 days after initial inoculation; however, at days 90 and 95 he had as high a titer as study participants 5 and 7.

A more detailed analysis of his serologic responses, including acute and convalescent titers, is shown in Table 2. In addition to testing for vibriocidal antibody, the sera were fractionated by density gradient ultracentrifugation to test for vibriocidal antibody activity in the IgM and IgG fractions by methods described elsewhere (7). Further, toxin neutralizing antibody titers in these sera were determined by a method previously described (8).

As Table 2 indicates, there was no change in the patient's vibriocidal titer during the course of his illness. Fractionation of the sera showed IgM vibriocidal antibody in all sera tested; IgG vibriocidal antibody was detectable only in the serum collected 15 days after onset of his illness. The toxin neutralizing titer showed a small, but detectable, rise during early convalescence, which fell during late convalescence.

For comparative purposes the sera obtained from study participants 6 and 7 (Table 1) 90 days after vaccination were also fractionated by density gradient ultracentrifugation. These sera were chosen because they had high and low vibriocidal antibody titers. In

Table 1. Inaba Titers (Reciprocal) in American Men Vaccinated with Monovalent Inaba Vaccine, 1968

Subject Number	Days After Vaccination								
	0*	1	2	3	4	7	9†	90†	95
1	40	40	20	40	40	1,280	2,560	—	—
2	0	0	0	0	0	2,560	20,480	20,480	—
3	20	0	20	0	20	2,560	5,120	1,280	1,280
4	40	20	40	40	80	10,240	20,480	2,560	2,560
5	0	0	0	0	0	320	1,280	320	640
6	40	—	80	80	160	10,240	20,480	1,280	1,280
7	0	0	0	0	0	320	640	320	320
8	20	80	40	80	40	2,560	2,560	—	—
9	0	0	20	20	40	5,120	20,480	1,280	—
Geometric mean titer	19	17	20	23	29	2,195	5,530	1,413	970
Present patient	0	0	0	20	20	80	160	320	320

* Day 0, 0.5 ml of vaccine given intramuscularly.
† Day 9 and 90, 0.5 ml of vaccine given subcutaneously.

each of these sera vibriocidal activity was demonstrable only in the IgM globulins. No activity was detectable in IgG. This pattern was similar to that seen in the patient 90 days after vaccination. In contrast, sera from one of the authors (EG) was also fractionated. He had received multiple booster doses of cholera vaccine, lived in cholera-endemic areas, and worked frequently with the organisms in the laboratory. His sera demonstrated activity in both IgM and IgG, with most of the antibody activity in the IgG fractions.

Discussion

This American physician developed cholera after intimate exposure to cholera patients 3 weeks after arriving in rural East Pakistan. The infecting strain was *V. cholerae*, classical biotype, Inaba serotype. His illness occurred 6 months after primary immunization and 3 months after a booster inoculation with a whole cell monovalent Inaba vaccine. In the 1968 to 1969 cholera vaccine field trial in rural East Pakistan a single 0.5-ml injection of this vaccine (designated vaccine H) was shown to have protective efficacy of 90% in the first 3 months after inoculation, with protection extending beyond 6 months (5).

Although the initial vibriocidal antibody response of the patient to cholera vaccination was poor, titers 6 months after vaccination were consistent with other participants in this study and were in the range usually found for healthy Americans 6 months after immunization*. In addition, although density gradient fractionation of his serum 90 days after inoculation showed vibriocidal antibodies detectable only in the IgM globulins, this same pattern was found in the sera from two other recipients of the same vaccine.

After his illness there was no rise in the whole serum vibriocidal antibody titer, although vibriocidal antibodies appeared in the IgG globulins. He also had a small, but detectable, rise in the toxin neutralizing antibody titer during convalescence. The patient's serologic responses to his illness were not inconsistent with the antibody patterns observed in other cholera patients hospitalized at the PSCRL (9). The typical adult cholera patient on admission generally has a detectable vibriocidal antibody titer with activity primarily in the IgM, although some have IgG antibody on admission also. During convalescence in most cases there is a brisk rise in vibriocidal titers in both the IgM and IgG globulins.

* W. M. McCormack: Unpublished data.

Table 2. Patient's Serologic Response to Monovalent Inaba Vaccine* and to Clinical Infection with *Vibrio cholerae*

Days After Vaccination	Vibriocidal Antibodies			Toxin Neutralizing Antibody Titer
	Reciprocal Titer in Whole Serum	Density Gradient Fractions		
		IgM	IgG	
				Craig units
0	0	Not tested	Not tested	Not tested
9	160	Not tested	Not tested	<1
90	320	Present	Absent	<1
168†	320	Present	Absent	<1
178	320	Not tested	Not tested	8
184	320	Present	Present	13
303	Not tested	Present	Absent	5

* On Day 0 patient received 0.5 ml of monovalent Inaba vaccine intramuscularly; on days 9 and 90 he received 0.5 ml of vaccine subcutaneously.
† Acute phase serum (day of onset of cholera).

Occasionally, when patients have relatively high titers on admission, a rise in titer is detectable only in the IgG and not in the whole serum. The poor toxin neutralizing antibody response is not atypical, since up to 15% of acute cholera patients may not develop a detectable toxin neutralizing antibody titer rise in convalescence (9).

The early and vigorous administration of antibiotics very likely affected the patient's antibody response to disease. Karchmer and associates (10) have shown that antibiotic therapy inhibits the vibriocidal antibody response, and Pierce, Banwell, and Sack (11) have demonstrated a similar effect of antibiotics on the antitoxin titers.

This case emphasizes that, in addition to vaccine potency, other factors are operative in protecting against cholera—for example, the immunologic responses of the host to vaccine, physiologic factors in the host that influence susceptibility, and the exposure to the organism. This physician's serologic responses show that he had no inherent immunologic deficiency. The possibility that he had some predisposing gastrointestinal condition related to his earlier episodes of abdominal pain cannot be excluded; he has remained healthy, however, for more than 2 years since these episodes, and thus this seems unlikely. It is likely that this illness occurred because the patient's immunity was marginal at the time of heavy exposure. It should be noted, however, that since the establishment of the PSCRL in 1959, more than 25 American physicians have had similarly intimate exposure to cholera patients ranging from a few weeks to 3 years, and none has developed cholera. Obviously, there are factors related to host susceptibility to cholera that remain undefined.

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