Outbreak of Suspected *Clostridium butyricum* Botulism in India

To the Editor: Foodborne botulism, particularly associated with *Clostridium butyricum,* is rare; no cases had been reported in India before this outbreak. A reported case of foodborne botulism represents a public health emergency because of the potential severity of the disease and the possibility of mass exposure to the contaminated product.

In September 1996, the anaerobic section of the All India Institute of Medical Sciences received serum and food samples from the National Institute of Communicable Diseases, Delhi, India, for investigating a possible outbreak of foodborne botulism.

In the early hours of September 18, 1996, 34 of 310 students of a residential school in rural Gujrat complained of abdominal pain, nausea, chest pain, and difficulty in breathing. One of the students, aged 14, died before he could be treated; two others, aged 13, died on their way to the hospital. The remaining 31 students were admitted to a rural hospital; eight were discharged 1 day later after being given symptomatic treatment, while the other 23 were transported by ambulance to an urban emergency department in Ahemdabad, Gujrat. Findings on examination included ptosis, pupillary mydriasis, extraocular palsies, and impairment of conciousness. All students were given symptomatic treatment in the form of stomach lavage and intravenous administration of antibiotics and steroids. Over the subsequent 24 hours, 21 improved clinically and were discharged; however, two (aged 14 and 17 years) had respiratory distress and required mechanical ventilation. Differential diagnosis included botulinum food poisoning, and both patients were administered trivalent (A,B,E) botulinum antitoxin. They responded well to the treatment and were discharged from the hospital 1 month later.

Patients reported that 24 hours before onset of symptoms, they had eaten ladoo (a local sweet), curd, buttermilk, sevu (crisp made of gram flour), and pickle. Food samples were assayed for botulinum toxin and were cultured anaerobically (1). Anaerobic culture of leftover sevu yielded an organism in pure culture whose cultural and biochemical properties were consistent with those of *C. butyricum;* i.e., it was lipase-negative, fermentative, and did not liquefy gelatin (2). Enrichment cultures of the sevu specimens in enriched chopped meat–glucose–starch medium contained toxin after 5 days of anaerobic incubation at 30°C. This was shown by mouse toxicity test in which the enrichment broth of the specimen was injected intraperitoneally into mice; botulinum toxin was detected by observing its lethal effect on mice. This effect was neutralized by specific polyvalent botulinum antitoxin types A, B, E (Biomed, Warsaw, Poland). Cultures of other food items tested negative for toxigenic organisms. Serum specimens (obtained more than 1 week after the onset of illness) from eight patients with mildly symptomatic illness were negative for toxin.

To test the presence of toxin gene in the isolated strain of *C. butyricum*, polymerase chain reaction (PCR) was performed. Degenerate primers BoNT 1 and BoNT 2 were used, which amplify a specific 1.1-kb fragment of neurotoxin gene *C. botulinum* types (A, B, E, F, and G) as well as toxigenic strains of *C. baratti* and *C. butyricum* (3). Five *Escherichia coli* strains containing clones encoding fragments of the *C. botulinum* neurotoxin genes were used as positive controls in the PCR assay (kindly provided by Alison East, Institute of Food Research, United Kingdom). PCR profile used was as follows: 94°C for 2 min, followed by 25 cycles of 92°C for 1 min, 42°C for 1 min, and 62°C for 5 min, then held at 4°C (Alison East, pers. comm.). An amplified product of 1.1 kb was detected from the culture isolate of sevu.

The outbreak described in this report draws attention to the emergence of new foodborne pathogens and to their association with unusual foods. Human botulism is commonly caused by *C. botulinum* neurotoxin type A, B, and E (4). In the present study, we showed that a neurotoxigenic *C. butyricum* was present in the food implicated in a clinically suspected outbreak of botulism in Gujrat, India.

Laboratory studies could not confirm the diagnosis of botulism because clinical materials (such as contents of the gastrointestinal tract, feces) were not submitted for examination for the presence of the botulinum toxin or organisms. It is not surprising that toxin could not be detected in the eight serum samples received by our laboratory. Because of the delay in clinical diagnosis, early serum samples could not be obtained. Toxin is detected in only 13% of serum samples collected more than 2 days after ingestion of botulinum toxin (5). However, the clinical presentation of the patients, response to trivalent botulinum antitoxin, and isolation of toxigenic *C. butyricum* from one of the consumed food articles strongly suggest that the outbreak was caused by food contaminated with toxigenic *C. butyricum*.

Neurotoxigenic *C. butyricum* was first reported in 1986 in two cases of infant botulism in Rome (6). Recently, neurotoxigenic *C. butyricum* was isolated from the food implicated in an outbreak of clinically diagnosed type E botulism in China (7). In this outbreak, it appears that sevu, because of improper storage, was contaminated with the spores of *C. butyricum*, which subsequently germinated and produced toxin. To the best of our knowledge, this is the first report of neurotoxigenic *C. butyricum* causing foodborne botulism in India.

The changing epidemiology of foodborne disease as highlighted in this report calls for improved surveillance, including the development of new technology for identifying outbreaks.

We thank Alison East, Institute of Food Research, Reading Laboratory, United Kingdom, for supplying *E. coli* clones with BONT gene for PCR; Pradeep Seth, professor and head, Department of Microbiology, All India Institute of Medical Sciences for facilities provided; Biomed Warsaw, Poland, for polyvalent botulinum antitoxin; and the medical and paramedical staff of Civil Hospital, Ahemdabad.

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Molecular Analysis of *Salmonella paratyphi* A From an Outbreak in New Delhi, India

To the Editor: In the context of emerging infectious diseases, enteric fever caused by *Salmonella paratyphi* A deserves increased attention and vigilance, although its severity is often milder than that of *S. typhi* disease. Outbreaks associated with this organism are exceedingly rare but have recently been reported in India (1) and Thailand. In India, the first reported outbreak of disease associated with *S. paratyphi* A (1) provided an opportunity to study the molecular epidemiology of infection caused by this organism.

A total of 18 human blood isolates of *S. paratyphi* A, 13 from the outbreak in New Delhi, India (from September to October 1996) (1) and 5 sporadic isolates from cases unrelated to the outbreak, were used in this study. A total of 36 culture-positive cases were detected during the 6-week outbreak. All strains were phage type 1 and were sensitive to all antibiotics tested. Isolates were analyzed by ribotyping and pulsed-field gel electrophoresis (PFGE) (2,3). PFGE/ribotype profiles were assigned arbitrary designations and analyzed by defining a similarity (Dice) coefficient, F (3), where F = 1.0 indicates complete pattern identity and F = 0, complete dissimilarity.

The five sporadic isolates of *S. paratyphi* A gave PFGE patterns following *Xba*I (5'-TCTAGA-3') digestion that were unique and distinctly different, with differences of 8 to 12 bands (F = 0.63-0.70). In contrast, the 13 outbreak isolates shared only four closely related PFGE patterns differing only in 1 to 6 bands (F = 0.8-1.0). Among the outbreak strains, two distinct clones were observed, X1 and X2, which differed by 5 to 6 bands. Furthermore, outbreak isolates X3 and X4 were closely related to X1, differing by four and three DNA fragments, respectively. Similar results were obtained after digestion with a second restriction endonuclease, *Spe*I (5'-ACTAGT-3'; pattern designation S). Although fewer bands were seen compared to PFGE, ribotyping of these isolates using *Spe*I-digested genomic DNA largely confirmed the PFGE results in that the sporadic isolates gave unique profiles and only three closely related ribotype profiles were detected among the outbreak isolates. Two Malaysian isolates of *S. paratyphi* A included for comparison gave patterns very different from the Indian isolates by both PFGE (F = 0.44-0.65) and ribotyping. Also, it was determined that isolates A-117 (X1/S1) and A-123 (X2/S2) belonged to the index cases and that, as the outbreak progressed, other patterns (X3/S3 and X4/S4), which differed from the original patterns by one to four bands, appeared during weeks 2 to 3 of the outbreak. Notably, patterns X1 and X2 reappeared at the end of the outbreak.

Although molecular analysis of *S. typhi* and *S. paratyphi* B by ribotyping (2,4) and PFGE (3) has been reported, to the best of our knowledge the present study is the first performed with *S. paratyphi* A. The data obtained agree with those observed for *S. typhi* (3) in that outbreak isolates are more clonal and limited in diversity, whereas sporadic isolates are more diverse genetically and belong to unrelated clones. According to the criteria of Tenover et al. (5), it seems likely that the present outbreak was associated with two distinct clones/strains of *S. paratyphi* A (X1/S1 and X2/S2) that are related (5) but have distinct PFGE profiles. This observation is perhaps not surprising given the fact that both clones are phage type 1 and that contaminated potable water was incriminated in the outbreak (1). The PFGE results were largely confirmed by ribotyping, although this technique appears to be slightly less sensitive and discriminating in that fewer bands were seen and the differences between outbreak isolates were much less obvious.

We thus conclude that the outbreak in New Delhi, India, was caused by two related but distinct clones of *S. paratyphi* A. There also appears to be substantial genetic diversity among *S. paratyphi* A strains as the Malaysian isolates were very different from those from India. The data also suggested minor genetic changes among the *S. paratyphi* A isolates during the 2-month outbreak. This observation agrees with the high mutation rates noted among pathogenic *Salmonella* spp. (6) and the plasticity of the genome of salmonellae associated with enteric fever (7). How these changes affected the biologic behavior of these isolates will be the subject of further study. Our study reaffirms the usefulness of PFGE and ribotyping in the molecular typing and discrimination of individual *Salmonella* isolates for epidemiologic investigations.

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Unrecognized Ebola Hemorrhagic Fever at Mosango Hospital during the 1995 Epidemic in Kikwit, Democratic Republic of the Congo

To the Editor: We report here the clinical description of a hemorrhagic syndrome observed in Mosango General Hospital that, retrospectively, was one of the first cases of the Ebola hemorrhagic fever outbreak in the Bandundu province of former Zaire in the spring of 1995 (1).

Case

On April 20, 1995, a 70-year-old nun, working as a nurse in Kikwit General Hospital, was admitted to Mosango General Hospital with a 5-day history of fever, despite antimalarial treatment. The day before hospitalization she had profuse diarrhea, vomiting, high fever, and severe agitation with delirium. On arrival, quiet and apyretic, she complained of headache, loss of appetite, and severe asthenia, but she walked to her room without help. On examination, the only abnormalities recorded were severe dehydration and oral thrush-like lesions, raising a suspicion of candidiasis. Pulse rate was 80/min and blood pressure 120/80. Medical history included an amebiasis liver abscess 15 years ago and chronic coronaritis since 1990.

Electrocardiogram (ECG) abnormalities were consistent with chronic diffuse ischemia. Laboratory investigations showed the following values: few trophozoites on a thick film; erythrocyte sedimentation rate (ESR) 15 mm/h; bleeding time (BT) 7½ min; coagulation time (CT) 9 min; and white blood cells (WBC) 8.4x10^9/L (73% neutrophils, 23% lymphocytes, 2% eosinophils, 1% basophils, 1% mastocytes). Urinalysis showed proteinuria (++), hyaline cylinders (+++), 50 white cells per field, and hematuria (+). The patient was perfused with 4L/day of glucose and 1.5 g of quinine. She was kept in a private room in the nearby nuns' convent.

Later during the day, high fever (40°C) and severe diarrhea with melena developed; the pulse rate was normal (80/min). Typhoid fever was suspected despite the lack of hepatosplenomegaly; Widal test was not available for confirmation. Treatment was started with intravenous (i.v.) amoxicillin (1g/6h during the first 24 h and then 1g/4h) and i.v. chloramphenicol (2g/24h). Subsequently, coagulation abnormalities developed in addition to the melena; vitamin K and epsilon amino caproic acid were added to i.v. therapy. Watery vomits remained frequent and abundant, and the patient's condition was unresponsive to treatment.

On hospitalization day 2, the clinical picture remained the same, with severe asthenia, anorexia, abundant blackish diarrhea, and watery vomits. An intractable hiccup developed. The fever remained in plateau around 40°C with spikes. Obnubilation occurred during episodes of high fever. Pulse and blood pressure remained stable. ECG showed no modifications. Cutaneous examination detected for the first time a maculopapular rash and petechiae on flanks and limbs, and the patient complained of gastric pain for which the neurologic examination was normal. Urine was abundant and clear.

On hospitalization day 3, high fever continued, with some defervescence during which the patient regained lucidity, although she responded only with monosyllables because of the extreme asthenia and somnolence; diarrhea persisted but without hemorrhage. The patient had less vomiting. Laboratory data showed ESR 35 mm/h; BT 10 min; CT 12 min; WBC 12.6x10^9/L (70% neutrophils, 24% lymphocytes, 2% eosinophils, 1% basophils, 3% mastocytes). During the night, the patient maintained a high temperature, still with temperature-pulse disparity. The diagnosis of typhoid fever was questioned, and other diagnostic possibilities were reconsidered (shigellosis, mononucleosis); leukocytosis was considered against the possibility of Ebola hemorrhagic fever. Chloramphenicol was switched to rifampicin (1,200 mg/24h).

On April 23, the patient's status was unchanged with fever, asthenia, and diarrhea. Later in the day, her condition deteriorated: petechiae could be seen on the entire body, and for the first time, bruises and bleeding at injection sites were observed and precluded intramuscular injections. The patient had bleeding cracks on the lips and diffuse bleeding in the oral cavity (i.e., gums, tongue). The volume of urine was low, and antibiotic therapy was changed to cephalosporin.

On hospitalization day 5, hemorrhages increased, and fever remained high until the end of the day, when it started to normalize. Urine volume was still low (verified by vesical catheter) despite the i.v. rehydration of 4 L/day. Fresh blood transfusion (300 ml) did not slow the hemorrhaging; disseminated intravascular coagulation was suspected, and heparin treatment was started. The patient became comatose. The laboratory results showed ESR 55mm/h and WBC 30.2x10^9/L with an unchanged formula. No coagulation was observed on BT and CT. Blood pressure fell (80/50); the clinical status remained unchanged until the patient's death on April 25 at 10:00 a.m.

No special nursing precautions were taken either during the hospitalization or after the death, and the body was transferred to Kikwit to be buried. On April 30, another nun who took care of the index patient during the night of April 23 became ill with fever, headache, and myalgia. Over the next few days, the second patient had a clinical picture identical to that of the index patient, including high fever, severe asthenia, vomiting, hiccups, and diarrhea. On May 5, epistaxis and coagulation abnormalities developed, followed by other clinical signs of the hemorrhagic syndrome. The second patient was transferred to Kikwit General Hospital, where she died 6 days later. A laboratory confirmation of Ebola hemorrhagic fever was made on a blood specimen collected on May 5 and sent to Special Pathogens Branch (Centers for Disease Control and Prevention, Atlanta, GA).

These cases of unrecognized Ebola hemorrhagic fever were part of the hospital outbreak that precipitated and mobilized international community efforts (2). Retrospectively, the clinical symptoms observed were typical of Ebola hemorrhagic fever (3,4) and were described again in subsequent patients during this outbreak (5). In tropical Africa, the presence of hemorrhagic symptoms in the course of a febrile illness should raise the possibility of one of the viral hemorrhagic fever diseases. In viral hemorrhagic fevers, maculopapular rash is constantly observed only in filovirus disease. Typically, the clinical laboratory findings include an early lymphopenia and marked thrombocytopenia. Containment and barrier nursing procedures should be initiated until the diagnosis of viral hemorrhagic fever can be ruled out. The index patient described here was the third patient transferred from Kikwit General Hospital in less than 1 month to die of a hemorrhagic illness after a few days of an unexplained febrile syndrome. Two patients were health-care workers in Kikwit General Hospital. This cluster of hemorrhagic illness and possible human-to-human transmission, particularly among hospital staff, was (and should always be) sufficient to suspect a viral hemorrhagic fever. The laboratory confirmation of this presumptive diagnosis was the clenching factor in the multinational effort in Kikwit.

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Classification of Reactive Arthritides

To the Editor: We read with interest J.A. Lindsay's article on sequelae of foodborne disease (1). However, we believe that there are errors in the classification of the reactive arthritides. Lindsay states that ankylosing spondylitis (AS) is a "rheumatoid inflammation of synovial joints and entheses within and distal to the spine." Although not the primary focus of the article, the classification and etiopathogeneses of rheumatoid arthritis (RA) and the seronegative spondyloarthropathies, including AS, should be clarified. The term spondylitis, from the Greek *spondylos*, for vertebra, means inflammation of the vertebrae. The term rheumatoid is generally taken to apply to rheumatoid arthritis, while rheumatic is a more general term applying to all connective tissue diseases.

AS is a chronic, systemic, inflammatory disorder primarily affecting the axial skeleton, with sacroiliac joint involvement as its hallmark. Back pain is the first clinical manifestation in approximately 75% of the patients (2). The backache is usually insidious in onset, dull, and difficult to localize. After several months, it generally becomes bilateral and persistent. The ache is often worse in the morning or after periods of inactivity and improves with movement. The course is highly variable. Involvement of peripheral joints other than hips and shoulders is uncommon.

AS is strongly associated with human leukocyte antigen (HLA) B27, a major histocompatibility complex (MHC) class I allele, and may show familial aggregation. More than 90% of patients with AS have the HLA-B27 allele (3). HLA-B27 is believed to be directly involved in disease pathogenesis. Transgenic rats expressing human HLA-B27 develop a broad spectrum of disease closely resembling human disease. These rats have peripheral and axial arthritis, gastrointestinal inflammation, and diarrhea. Psoriatic-like skin changes and inflammation of the heart and male genitalia are also seen. Histologically, the joint, gut, skin, and heart lesions resemble those seen in HLA-B27-related disease in humans (4).

The inflammatory process in AS involves the synovial and cartilaginous joints, as well as the osseous attachments of tendons and ligaments (entheses). Much of the skeletal pathology of AS can be explained by the changes that take place at the entheses. After an initial inflammatory, erosive process involving the entheses, there is healing in which new bone is formed. The final outcome of this process is an irregular bony prominence with sclerosis of the adjacent cancellous bone (5). This can be contrasted with the pathology of RA, in which there is a greater tendency to affect cartilaginous joints such as the intervertebral discs and symphysis pubis. The process in RA is one of bony erosion rather than new bone formation.

The term ankylosing spondylitis, derived from the Greek for "bent spinal vertebrae," by definition requires exclusion of the other spondyloarthropathies, such as Reiter syndrome and reactive arthritides due to enteric (or urogenital) organisms. Spondylitis may occur in reactive arthritis, psoriatic arthritis, or the arthropathy associated with inflammatory bowel disease, but is less common in these diseases (approximately 50% in reactive arthritis, 20% in enteric arthritis or psoriatic arthritis). All of these diseases can be viewed as seronegative spondyloarthropathies in that, by definition, rheumatoid factor is not present.

RA is a systemic autoimmune disorder of unknown etiology. It is a chronic symmetric arthropathy of peripheral joints, associated with erosive synovitis. Enthesopathy is generally not found. The majority of patients have elevated titers of serum rheumatoid factor, as opposed to the seronegative spondyloarthropathies. Spinal involvement in RA is seen but most often involves the cervical spine. The pathogenesis of the spinal disease is that of synovitis of the odontoid-atlas joints. The major HLA association is with HLA-DR4, an MHC class II allele.

Reactive arthritis is so named because it is felt that the arthritis and other inflammatory manifestations are an immune reaction to a distant infection. There is an association with HLA-B27 but less so than that found in AS (60% to 80%, compared with more than 90% in AS). While bacterial antigens can be found within the joint, the offending infectious process most often subsides before the onset of arthritis, and no living organisms are found in the joint (2). In many cases, no infectious trigger can be identified. Persistence of microbial antigens has been demonstrated and is likely to play a prominent role in the pathogenesis of acute and chronic inflammation. Antigens to several gastrointestinal pathogens have been isolated from the synovial fluid in patients with reactive arthritis. *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter,* and *Borrelia* are the most common pathogens capable of initiating reactive arthritis (2). The arthritis is generally an asymmetric oligoarthritis predominantly affecting the lower extremities and typically develops 6 to 14 days after a bout of diarrhea. However, onset can occur up to 3 months later. Diarrhea can also be absent, and there is no relationship between the severity of the arthritis and the severity of the diarrhea.

Reiter syndrome is in fact a reactive arthritis. In 1916, Hans Reiter described a triad of arthritis, urethritis, and conjunctivitis in a soldier with dysentery. However, the disease was actually first described by Sir Benjamin Brodie in the early 1800s (6). The complete triad is actually seen in only a minority of patients. Arthritis develops 1 to 3 weeks after the diarrhea or urethritis. It is generally asymmetric, involving large joints, especially in the lower extremities. The term Reiter syndrome actually refers only to the triad of arthritis, urethritis, and conjunctivitis. Reiter syndrome is both clinically and historically more accurately termed reactive arthritis. Nevertheless, the term reactive arthritis does not reflect the systemic nature of the disease.

In summary, while both reactive arthritis and ankylosing spondylitis are seronegative spondyloarthropathies, they are separate entities. Both are distinct from rheumatoid arthritis.

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Reply to Drs. Blumberg and Sloan

To the Editor: I concur with your comments. After reviewing the literature related to foodborne disease, it appears that the original classification of reactive arthritides has been in error for some time. I certainly appreciate the correction.

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Cost of Blood Screening

To the Editor: In reference to G.A. Schmunis' article on the risk for transfusion-transmitted infections in Central and South America (1), I would like to comment on the cost of blood screening. In a screening program, the objective is to have safe blood units, not to assess the prevalence of different infections among potential or actual donors. Thus, while acknowledging all infections present in a given donor or potential donor is not required, detecting at least one of the infections that would make a donor noneligible is. If samples from every potential donor are subjected (by default) to all the tests, information on every infection present is provided, and the cost of screening this donor is the sum of the cost of every test applied; in this case, both the information and the cost are greater than necessary.

Information on the prevalence of bloodborne infections among the general population or, preferably, among potential donors (particularly where professional donors are frequent) along with information on the costs of the tests to be used can form the basis of a stepwise screening scheme. Tests for infections with the highest prevalence would be applied first. For example, in many areas of Peru, using the Venereal Disease Research Laboratory (VDRL) test (for screening *Treponema pallidum* infection) first would reduce the number of samples to be subjected to other more expensive and often less available tests (e.g., HIV enzyme-linked immunosorbent assay [ELISA] or hepatitis C virus [HCV] ELISA); in others areas, a test for hepatitis B virus antigen (HB_sAg) should be used before HIV ELISA. The reduction in cost provided by stepwise screening will depend on the prevalences of the more frequent infections and the frequency of concurrent infections.

The questionnaires applied to candidate donors should be validated, and the benefit of using them should be assessed. In most settings, candidate donors are either ignorant of their status as carriers of bloodborne infection or ready to deny it; therefore, the questionnaire is of little use. In some cases candidate donors are turned down because of "hepatitis history" when in fact they have not had bloodborne hepatitis.

Finally, screening tests seem to be quite more expensive than reported in Table 4 of the Schmunis article. In Lima, at a ministry of health facility, some prices are as follows: HIV ELISA US$12.50, VDRL US$6.40, HB_sAg US$13.90.

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