PUBLIC HEALTH Chronicles

HISTORICAL PERSPECTIVES ON PUBLIC HEALTH ISSUES

Diethylene Glycol Deaths in Haiti

SUZANNE WHITE JUNOD, PHD

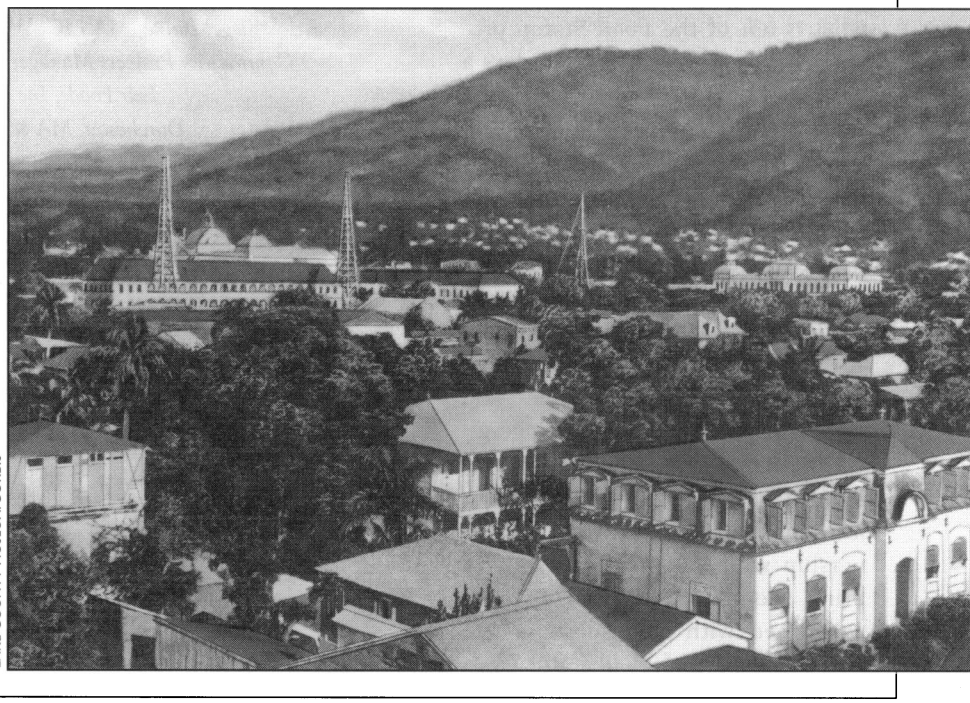
Many illnesses and injuries go untreated in a country like Haiti, considered the poorest in the Western Hemisphere. The World Health Organization (WHO) estimates that only 50% of the Haitian population has access to primary health care services.[1] In part, this is a distribution problem; 70% of health care providers work in the cities, while 70% of the population lives in the rural areas of the country.[1] According to 1997 WHO figures, Haiti has only 1.2 doctors per thousand inhabitants and only one hospital bed per 1300 inhabitants.[1] Pediatric deaths are tragically common. In the summer of 1996, however, a cluster of pediatric deaths due to acute renal failure attracted worldwide attention.[2]

The first of the children with acute renal failure admitted to the General Hospital in Port-au-Prince died in November 1995. By May 1996, after more than 30 children admitted to the same hospital with similar symptoms had died, the situation was no longer a medical curiosity—it had become a medical crisis. Most of the children were younger than 5 years old, and their median age was only 29 months.[2] Their story was later told in the US on the television program *60 Minutes*, but the details of the successful investigation spearheaded by two US agencies, the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), are being published here for the first time. In 1997 and 1998, while the investigation was still recent history, the CDC and FDA participants recounted their experiences for the FDA History Office. The following account is based largely on the transcripts of these interviews.

An Epidemic of Renal Failure

On May 9, 1996, the CDC in Atlanta received its first information about the burgeoning epidemic. Neal Halsey, MD, a Johns Hopkins School of Public Health and Hygiene professor who had conducted research for decades in Haiti, was in the country to discuss his latest project, a study of HIV transmission between mothers and infants. Halsey, who had begun his career as an officer in the CDC's Epidemic Intelligence Service (EIS), immediately sensed that a rapid, full-scale CDC investigation would be much more effective in pinpointing the cause of the epidemic than the ad hoc work then underway at the General Hospital.

Halsey called two former Johns Hopkins fellows at the CDC's National Center for Infectious Diseases (NCID) who had worked under his guidance in Haiti. Halsey also arranged for biopsy and autopsy kidney specimens to be shipped back to



LAKE COUNTY MUSEUM/CORBIS

Diethylene Glycol (DEG) in History

Both ethylene glycol and diethylene glycol (DEG) originated in France in the mid-19th century. In 1925, the first US plant began producing glycols. Ethylene glycol proved useful in a variety of industrial settings as an antifreeze, but DEG proved more useful as a solvent and was employed in minute quantities in the manufacture of tobacco products, ink, glue, cellophane, and some pharmaceutical products. In 1937, the US experienced the first epidemic of DEG poisoning.[4] A chemist at a pharmaceutical company, looking for an effective solvent in which to suspend the new "wonder drug," sulfanilamide, was impressed with DEG's solvent properties. More than a hundred people, including many children, died after taking Elixir Sulfanilamide before an effective recall could be completed. This drug disaster prompted the US Congress to pass a law in 1938 mandating premarket safety testing of all new drugs.[5] Unfortunately, this did not prove to be the last incident of DEG poisoning on record.

In 1969, seven children in Capetown, South Africa, died from renal failure after taking sedative preparations in which DEG had been substituted for propylene glycol, a common (and safe) drug diluent.[6] From 1986 through 1992, there were three new epidemics linked with DEG, prompting the WHO to issue several alerts on the subject. In 1986, 21 people in India died after being treated with glycerin for a variety of medical conditions. The glycerin prescribed was found to be of industrial rather than medicinal grade and was contaminated with 18.5% DEG. In 1990, 47 children in Nigeria died from renal failure attributed to DEG. (DEG had been sold as propylene glycol to local chemists, who had used it in formulating acetaminophen syrups.) Similarly, 236 children died in Bangladesh in 1990–1992 when DEG was substituted for glycerol in fever medications.[7] Thus, prior to the Haitian epidemic, more than 400 deaths attributed to DEG poisoning had been reported worldwide.

Johns Hopkins, where a pathologist concluded that the specimens showed evidence of damage from some kind of toxin.

Renal failure is an uncommon diagnosis in children or adults, and an epidemic of renal failure is particularly unusual. Most often, infectious agents are the cause. Hemorrhagic fever with renal syndrome, for example, was observed in more than 3000 United Nations troops involved in the Korean conflict, caused by one of several hantaviruses transmitted through inhaled rat excreta. In children, however, acute renal failure is more commonly associated with hemolytic uremic syndrome. Undercooked hamburgers from fast food establishments have been blamed for many recent US outbreaks of the syndrome, with *E-coli* 0157 identified as the pathological culprit.[3] A report on the Haitian specimens by the Hopkins pathologist, however, effectively ruled out hemolytic uremic syndrome.

The second most logical diagnosis was, according to one epidemiologist, one that most pediatricians encountered only as a popular test question on pediatric exams. Poisoning with ethylene glycol, a component of antifreeze, can cause renal failure. Most physicians, however, would not have been familiar with diethylene glycol (DEG), a closely related compound but one that presents an entirely different pathology profile in cases of kidney failure. (See "Diethylene Glycol [DEG] in History." DEG poisoning was eventually shown to be the cause of the Haitian epidemic.

CDC Invited to Intervene

At the CDC, NCID officials eagerly awaited an invitation from Haiti's Minister of Health to assist with the crisis. Meanwhile, EIS officers and others began to meet regularly, speculating on the causes of the epidemic and devising possible approaches to solving the mystery. After one such meeting, the discussion spilled out into the hall, where a chance meeting with a staff epidemiologist who had worked on a DEG poisoning in Nigeria in 1990 focused the group's attention on the possibility that renal failure had been caused by toxic exposure to DEG. Having heard nothing from the Haitian Ministry of Health, in mid-May NCID officials took the extraordinary step of faxing a letter to the Minister, Rudolph Mallebranche, MD, alerting him to the possibility of DEG poisoning. NCID officials received no reply, and, indeed, they heard nothing more about the Haitian epidemic until mid-June.

Dr. Mallebranche in the meantime had contacted the Pan American Health Organization, which had an office in Haiti, asking PAHO to assemble a team to help stop the epidemic. PAHO staff members and officials, unaware of the pathology reports from Johns Hopkins, were proceeding on the assumption that the epidemic's cause might be hemolytic uremic syndrome linked with *E-coli* 0157. PAHO contacted the CDC, but the Foodborne and Diarrheal Disease Branch rather than the Respiratory Diseases Branch (RDB). Luckily, friendships between the two branches soon breached the communications gap. Officials of the Foodborne and Diarrheal Disease Branch studied the pathology reports and concluded that

the epidemic was not likely to be foodborne in origin, so the RDB took over the investigation. RDB officials suspected that the epidemic was not infectious, but continued their inquiry because their office was responsible for investigating "unexplained deaths," both nationally and internationally.

At PAHO's invitation, the CDC elected to send Katherine L. O'Brien, MD MPH, then an EIS officer, to Haiti to conduct the epidemiologic investigations. EIS officers serve for two years and, among other assignments, are responsible for conducting outbreak investigations. By tradition, the EIS officers are designated by classes according to the year they entered the Service. O'Brien had completed her pediatric residency at Johns Hopkins and then spent a year in Haiti researching HIV transmission. There she had improved her French and learned some Creole before joining the EIS Class of 1995.

Even humanitarian efforts in a country such as Haiti are often vastly complicated by both national and local politics. In retrospective interviews, O'Brien and her colleagues expressed appreciation for and amazement at the Haitian government's willingness to put aside issues of power and control to stop the epidemic. Nonetheless, national politics as well as public health politics in Haiti remained a matter of concern as the investigations unfolded.[8]

The Politics of Public Health in Haiti

Public health politics in Haiti have been dominated for decades by the Boulos family. The patriarch of this influential and wealthy family, Carlos Boulos, MD, founded a nonprofit organization known by its initials CDS (in English: the Center for Development and Health) in the 1970s. Adroitly securing funding from diverse sources such as the WHO and the US Agency for International Development, CDS became an important public health and primary care organization serving the poorest of the poor in Haiti. Johns Hopkins professor Neal Halsey's work in Haiti was largely conducted under the auspices of CDS.

Carlos Boulos had three sons. Reginald ran CDS after his father's death, and it was he who supported and collaborated with Halsey on studies of new vaccines and HIV, among other projects. Reginald's brother Rudy ran a pharmaceutical manufacturing company named Pharval. The youngest Boulos brother, Franz, ran a cosmetics firm.

As NCID officials began speculating on the possibility of DEG contamination as a source of the epidemic, they shared their suspicion with Halsey. He, in turn, shared the CDC's suspicions with Reginald Boulos, who mentioned them to his brother Rudy. The CDC's suggestion that someone begin collecting medication bottles from those currently ill and recently deceased led to an offer by Rudy Boulos to have his labs at Pharval test the samples. Kate O'Brien told Halsey in no uncertain terms that this should not be allowed, pointing out that the source of the contamination was still not known and that Pharval may have been involved.

Observers, including O'Brien, have been impressed with the ability of the Boulos family, especially Reginald and CDS, to survive within the volatile political climate in Haiti over the past three decades. "They never wholly aligned themselves with anyone, and they avoided making enemies," according to O'Brien.

Nonetheless, in the year before the outbreak of the epidemic, there had been increasing signs of strain between Reginald Boulos and Jean-Bertrand Aristide's government. According to the *New York Times*, once Aristide returned to power in Haiti in 1994 after having been ousted in 1991, his supporters denounced Reginald Boulos as an associate of the *Tontons Macoute*, paramilitary thugs who had flourished under the 30-year Duvalier family dictatorship and its military successors. Boulos disputes this charge, as do some outside observers. Boulos acknowledges that during the three-year period between Aristide's 1991 overthrow and 1994, when American troops restored Aristide to power, he tried not to antagonize the military regime in order to protect CDS and its programs.

As Rudolph Mallebranche, Haiti's new Minister of Health, attempted to regain control over the delivery of health care services in Haiti, Reginald Boulos and CDS fell out of his favor. In 1995, at Mallebranche's bequest, PAHO had launched an investigation of pharmaceutical manufacturing companies in Haiti, including Rudy Boulos' firm, Pharval. In September 1995, Rudy Boulos and Pharval were heavily criticized in a PAHO report on the operations of the country's three pharmaceutical manufacturers. Although Rudy Boulos was inclined to dismiss the investigation as politically inspired, PAHO consultant and industrial pharmacist Ludo Martens described the Pharval operation as "a plant which has fallen asleep." Ironically, FDA and CDC investigators later learned that the PAHO inspection took place the very month that the first lot of DEG-contaminated acetaminophen syrup was produced in Haiti.

CDC Personnel Arrive

When Kate O'Brien arrived in Haiti on Friday, June 14, 1996, to launch the epidemiologic investigation, she immediately went to the General Hospital, where she met with pediatricians and epidemiologists to discuss the approaches they would employ to

pinpoint the cause(s) of the epidemic. The weekend of her arrival, a physician with whom she had worked in Haiti in 1991 dropped off the medications he had collected from two children then in the hospital with renal failure. She noticed that both children had taken Pharval acetaminophen preparations, one labeled Afebril and the other Valodon. She also noted that the two drugs had sequential lot numbers, but she was not sure whether this had any significance.

O'Brien was soon joined by a colleague from the CDC's National Center for Environmental Health, Joel Selanikio, MD. Selanikio, also a member of the "Class of '95," would conduct the investigations of pharmaceutical companies, including Pharval. By the time Selanikio arrived in Haiti, O'Brien and her colleagues suspected that the epidemic was due to DEG contamination and that Pharval's products were involved. In an increasingly tense situation, Selanikio's arrival freed O'Brien for the ongoing medical effort.

The CDC investigators recall with grim humor that in Haiti, in contrast to everything they had learned at the CDC, the epidemic did not stop the moment they arrived. O'Brien and Selanikio worked with a tremendous sense of urgency. Children were dying before their eyes, usually within approximately three days of admission, and approximately three children were being admitted to the General Hospital every day.

Efforts to treat these children proved nearly impossible. By the time that O'Brien arrived in Haiti, equipment for performing simple peritoneal dialysis was available. This technique would have been safe, effective, and adequate had the Haitian children merely suffered from renal failure. Renal failure, however, was not the only symptom requiring treatment; most of the children suffered from symptoms such as severe vomiting, hepatitis, pancreatitis, neurological problems including respiratory failure, facial paralysis, encephalopathy, and even coma. The General Hospital in Haiti was not equipped to offer intensive care for these multiple, life-threatening conditions.

Into this void stepped a group of nephrologists from the University of Michigan led by Tim Bunchman, MD, and Rulan Parekh, MD MPH. Upon learning of her son's prognosis, one Haitian mother had contacted UNICEF and other international relief agencies asking for help in saving her child. The International Services of HOPE responded by flying her two-year-old son to Ann Arbor for treatment. After two weeks of intensive care for neurological problems as well as renal failure, the child was alert, active, and recovering. Working largely over the Internet, Bunchman and his colleagues located medical centers that agreed to provide intensive care services for the Haitian children, and the International Services of HOPE arranged to Medivac as many children as possible to the US for treatment. Of 98 children who remained in Haiti with anuria (inability to urinate) and renal failure, 11 were removed from the hospital, presumably to die at home. Of the remaining 87, only two survived. Eleven children were flown to the United States for intensive care. One died in flight, and two died shortly after arrival. Two more died later, but the remaining six survived and made full recoveries following intensive treatment.

The Epidemiologic Investigation

Although CDC epidemiologists had generated a long list of possible causes of the epidemic before arriving in Haiti (including infectious agents, ingestible substances, and toxins), the initial phases of the investigation yielded some important clues. Pathology reports had initially suggested a toxic exposure, and the duration of the epidemic suggested an ongoing exposure rather than a single point source. The patients were young, which suggested to the researchers either a unique exposure of some kind (for example, bottles, pacifiers, or baby food), a disease manifestation unique to children, or a dose-response relationship that would render young children most susceptible. Moreover, the presence of a fever in almost all of the presenting cases suggested an infection or other predisposing illness for which a medication or herbal remedy might have been used.

O'Brien began by creating what epidemiologists refer to as a case definition. In the Haitian epidemic, a case was defined by a diagnosis of anuria (failing to urinate) for more than 24 hours for unknown reasons in a patient younger than 18 years old occurring after November 3, 1995. Locating cases meeting this definition was significantly more challenging. The General Hospital had no admission or discharge diagnosis log books, and no systematic method of collecting or maintaining medical records. Researchers had to depend largely on physicians' own recall of cases. The Ministry of Health did have records stemming from an ongoing investigation of meningococcal infections at the General Hospital that had picked up some cases of renal failure. Private practitioners in Haiti as well as health care workers in the community also identified cases fitting the case definition. Soon after O'Brien arrived, 84 confirmed and 24 possible cases had been identified. In looking over their identified cases, researchers discovered that despite the fact that almost all of the children had siblings younger than age 18, there was only one set of siblings with renal failure. This clue virtually ruled out an infectious agent as a cause of the epidemic, and the researchers began to con-

centrate in earnest on commonly ingested substances taken by the affected children.

Identifying the Chemical Culprit

Once O'Brien and her colleagues in Haiti had identified the cases comprising the epidemic, they set up a classic case-control study to identify common elements or risk factors in the histories of case patients. Control subjects were comparable to case subjects in age and sex and were enrolled as they were admitted as inpatients to the General Hospital. These hospital control subjects had a history of fever but no history of anuria. The case-control study had its limitations: parents often didn't recall all of the medications taken by their children, hospital charts were often absent or not detailed, and bottles had been thrown out or were unidentifiable because they had been cleaned and reused. Nonetheless, the study was large enough to give the researchers some measure of confidence, and unfortunately, more children with renal failure were entering the hospital every day.

Researchers painstakingly collected histories and bottles of all medications used by case and control subjects and sent them to CDC for analysis. O'Brien and her colleagues noted that among 453 bottles of medication that had been either mentioned or collected in their study, only two medications, both acetaminophen preparations manufactured by Pharval, were associated with illness in the case-control study. One was labeled Afebril and the other Valodon. All medications taken by case subjects had come from three consecutive lot numbers. The researchers sent out a driver to buy as much Afebril and Valodon as he could locate to see if there were other lot numbers on the market or if C1, C2, and C3 were the only ones available. When the driver returned with preparations from many other lot numbers, the researchers began to focus on C1,C2, and C3 as potentially contaminated.

The case-control study revealed that 55 case subjects had been exposed to either Valodon or Afebril, while only eight case subjects appeared to have no exposure. Among the controls, the situation was even more striking. Only five control subjects had been exposed to Afebril or Valodon, while 47 had no such exposure. Given such a high odds ratio, the researchers began to feel confident that they had discovered the culprit.

They immediately began looking at the common ingredients in Afebril and Valodon: acetaminophen, sodium cyclamate, potassium sorbate, glycerin, propylene glycol, citric aid, sodium citrate, red coloring, strawberry and raspberry flavoring, and water. Was there too high a dose of one of the ingredients? Was a toxin present? More likely was the possibility that a toxic substance had been substituted for one or more of the usual ingredients. At that point, however, all they could do was to speculate and wait for laboratory results. By June 21, exactly a week after O'Brien's arrival in Haiti, the presence of approximately 15% DEG had been confirmed in samples of both Valodon and Afebril by the CDC lab in Atlanta. Concerned about the security of their communications, O'Brien's supervisor in Atlanta merely confirmed over the phone that "it was what we thought it was."

Once the CDC had confirmed the presence of DEG, O'Brien immediately called the head of the PAHO mission, Marie-Andrée Diouf, MD. In what the participants describe as "a long night," a succession of people were notified concerning the DEG findings. Dr. Diouf came to the hotel where the epidemiological team was assembled. The head of the Caribbean health organization CAREC was notified, as was the American embassy. Because the team had concerns about how the news would break in Haiti, the Ambassador himself was rousted from sleep. In a late-night meeting hastily convened at the PAHO office, the Haitian Minister of Health, an advisor, and a fully armed bodyguard learned of the DEG contamination. Dr. Mallebranche tried to contact Rudy Boulos at Pharval but learned that both Reginald and Rudy were in Miami. Only the youngest brother, Franz, appeared at the meeting. When he was told that Afebril and Valodon had both tested positive for DEG, his initial response was a denial that Pharval even made these drugs. He then claimed that the products involved must be counterfeit.

The rest of the night was spent in drafting a statement for the Minister of Health and in devising a strategy for initiating a drug recall. Although there were discussions about a broad recall of all acetaminophen products or all Pharval products, in the end the recall was limited to the two Pharval acetaminophen products implicated by the laboratory findings.

At 7:00 a.m. on Saturday, June 22, Dr. Mallebranche briefed the President of Haiti. At 8:30 a.m., the Minister announced to a startled Haitian population that an "unintentional poisoning" had been discovered and that no one should take Pharval's Afebril or Valodon—that they were, in essence, being outlawed. Police officers were instructed to go around the country and confiscate all available Afebril and Valodon. A broad media campaign in the newspapers, on radio, and on television featured frequent and repetitive spots; however, many poor Haitians had limited access to these media outlets. (Many of the spots, in addi-

tion, were broadcast in the US and other countries with large Haitian immigrant populations.) Flyers were sent home with Haitian schoolchildren, and notices were issued to Haiti's medical societies while police moved with bullhorns through the streets. The Ministry of Health sent employees to visit all 10 departments (provinces) in Haiti to conduct spot checks of pharmacies. To help speed up the government's efforts, the FDA sent its drug specialist in San Juan, Puerto Rico, Jorge Guadalupe, to assist in the Haitian drug recall. The Haitian Minister of Health's Saturday a.m. announcement was picked up by Reuters International, and on Monday, June 24, a PAHO press release about the epidemic was posted on the Internet.

The first week following issuance of the public warnings, seven Haitian children were admitted to the hospital with DEG poisoning, all of whom had taken either Afebril or Valodon prior to the public warning. After that first week, however, only three children were diagnosed with the syndrome, and no cases were reported after July 1996.

After telling reporters that he was "100% sure" that his plant was not at fault, Rudy Boulos allowed Selanikio to examine the firm's quality control records and procedures. To his surprise, Selanikio learned from production records that Afebril and Valodon were identical, named separately for marketing and promotion purposes. Selanikio found that suspect Lot C1 had been produced on September 12, 1995, Lot C2 on November 6, 1995, and C3 on December 19, 1995. These dates were all consistent with the onset of the epidemic. For suspect lots C1 and C2 the firm had kept quality control samples known as "retain" samples of the finished products, and Selanikio promptly shipped them to CDC for analysis along with samples from other products made around the same time. The retain samples proved to be contaminated with anywhere from 12% to 30% DEG. Samples were also collected from the other two Haitian pharmaceutical manufacturers.

The FDA's Role

On Monday morning, June 24, the CDC contacted officials in the Office of Emergency Operations at the FDA about the Haitian crisis. Over the course of the week, the FDA worked with the Haitian press to fax "Alert Bulletins" to 24-hour French and Creole radio stations, service agencies, nurses' associations, and other Haitian organizations. On Wednesday afternoon, the FDA issued an Import Bulletin (#60B02). Photographs of the Valodon and Afebril labels were distributed to US postal and Customs officials, who were instructed to be alert for these products entering the US. The FDA screened all liquid medications imported into the US from Haiti, while computer searches assured the agency that no acetaminophen shipments from Haiti had been imported in the past year. By the end of the week, FDA officials felt certain that the contaminated Haitian acetaminophen would not create a problem in the US.

When FDA Commissioner David Kessler learned on Monday afternoon, June 24, that the CDC was faced with a drug manufacturing problem, he offered his agency's assistance and expertise. CDC epidemiologists were concerned about many of the practical aspects of a drug investigation, such as sampling techniques and maintaining a chain of custody, all routine matters for the FDA. The CDC was also facing a touchy political situation in Haiti because by Monday, following the public announcement of the crisis, the Haitian Ministry of Justice had ordered both PAHO and the CDC not to have further contact with the company owners, citing legal concerns. The FDA offered the expertise of its specialized forensic laboratory in Cincinnati. Reginald Boulos was still claiming that the problem drugs were counterfeit, and the FDA assured O'Brien that its forensic lab was experienced in investigating counterfeit drugs.

FDA officials knew they had no jurisdictional authority in Haiti and feared that their experts would not be welcomed. Although the agency can close ports and borders to foreign products entering the US, the FDA's overseas inspections are conducted to insure the safety and efficacy of products offered for import into the US by foreign manufacturers. Like the CDC, the FDA had to be invited by PAHO and the Ministry of Health to assist with the epidemic. In addition, some FDA staffers feared that Haitians still resented the agency's recommendations to exclude Haitians, among others, as blood donors during the early years of the AIDS epidemic. These difficulties did not prove insurmountable, however, for in a rare stroke of good fortune, Dr. Mallebranche was in Dr. O'Brien's office when the offer of assistance came from the FDA. He immediately accepted it. The details were worked out, and PAHO and the WHO sent a message to the CDC requesting the FDA's assistance in handling the products associated with the investigation. FDA drug expert Dave Pulham, PhD, was dispatched to Haiti, where his practical on-the-ground knowledge of drug investigations immediately broke the ice with the Haitian authorities and helped eliminate growing tensions.

As a National Drug Expert, Pulham had worked some high profile cases in his 20 years with FDA, but this Haitian case hit close to home. Pulham himself had lost a son to contaminated drugs. As soon as he

arrived in Haiti, Pulham, who was fluent in French, arranged a meeting with Pharval and its attorneys, the Haitian government, and the CDC epidemiologists in a quiet and neutral location. He emphasized that he was there on a humanitarian mission, "not to find guilt or blame, just to stop the epidemic."

The Traceback Investigation

Once the groundwork had been laid and the legal hurdles surmounted, the traceback investigation was launched in earnest. Initially, Selanikio and Pulham suspected that contaminated propylene glycol might be the chemical culprit as in the 1990 Nigerian epidemic of renal failure and the 1990 Bangladesh outbreak. The two men went to the Pharval facility, trying to identify the ingredients used in the manufacture of lots C1, C2, and C3 of Afebril and Valodon. They were able to obtain samples of the leftover propylene glycol used in these lots, but the company's records and retain samples were incomplete for many of the other ingredients in the acetaminophen syrup. In the wake of its own 1938 DEG crisis, the US had adopted stringent good manufacturing practice (GMP) standards. At a US firm, it would have been relatively easy to locate raw materials on shelves and match them with the appropriate paperwork. At Pharval, however, the documentation was limited.

Selanikio and Pulham then turned to the facility itself to try to pinpoint a source or route of contamination. In their inspection report they documented many lapses in quality control—from filthy production floors and dirty production surfaces to a poorly maintained ingredient storeroom where powders were not kept in sealed canisters and the contents of top canisters could easily drift into bottom canisters. Bottles were dusty and their ingredients were exposed to the open air. In the ingredient storeroom, some storage drums of raw materials were labeled with the country of origin—for example, China or Brazil—but they were missing lot numbers. The scale used to measure active ingredients looked more like a supermarket scale than a pharmaceutical scale. When the investigators asked how it was calibrated, they could not understand the Creole response until they saw what the workers were referring to—a "little plastic tub." This object, weighing exactly 14 pounds, was the company's only apparent means of calibration.

The CDC's National Center for Environmental Health and the FDA's Forensic Lab in Cincinnati immediately began analyses of samples collected at Pharval by Selanikio and Pulham. The CDC lab found that the quality control retain samples were contaminated with DEG. Propylene glycol samples, however, were not contaminated. The FDA laboratory compared the retain samples with the patient samples, attempting to determine the likelihood that the problem drug was counterfeit. Analyses of the product composition, glass, paper, labels, and glue all indicated that the two products were produced at the same time and virtually eliminated any possibility that the patient samples were counterfeit.

When Selanikio and Pulham returned to Pharval on Saturday, June 29, they learned that Everglade, an independent US laboratory hired by Boulos, had reached similar conclusions. The Miami laboratory had found 20% DEG in Pharval's Afebril and Valodon samples. Consulting with Pharval officials, Pulham and Selanikio determined that the propylene glycol could not be the sole or even the main source of the problem. Even if DEG had been substituted for 100% of the propylene glycol, this

JOEL SELANIKIO

ingredient constituted only 12% of the company's "recipe" for acetaminophen syrup and could not account for the 20% level of DEG contamination found in the samples. According to the company's production records, only glycerin was present in quantities sufficient to account for a contamination level of 20% or more. But the independent laboratory, Everglade, had detected only trace amounts of DEG in the glycerin sample it had tested. Only when the Atlanta CDC lab, Everglade, and the FDA's forensic lab compared their testing methodologies was an error detected. Everglade then retested its samples and found that the glycerin was indeed contaminated with DEG. Convinced at last that its product had caused the epidemic, Pharval responded by initiating its own recall of the contaminated products about a week after the government's recall had begun.

The investigators quickly discovered that virtually all of the contaminated glycerin had already been used by Pharval. (Several other Pharval products were found to contain lesser levels of DEG, and ultimately Pharval recalled 17 of its glycerin-containing products.) The single remaining glycerin drum showed no address or phone number. The investigators tried to identify the supplier through the Certificate of Analysis that should have accompanied the glycerin shipment, indicating that the product had been tested for purity and strength.

Standards organizations such as the US and British Pharmacopeias require that drug manufacturers test all excipients for purity, grade, potency, and heavy metal contamination. If a manufacturer has a long-running and well-established relationship with a supplier, it may test excipients only sporadically and rely more heavily on Certificates of Analysis, but the burden of proof is on the manufacturer to ensure the safety and potency of all raw ingredients. Pharval's quality control chief later received the Certificate of Analysis for the glycerin, nearly a year after the shipment had arrived. It was clear that Pharval had never tested the glycerin or even checked for a Certificate of Analysis.

The CDC identified and contacted the Haitian distributor from which Pharval had purchased its raw ingredients—Chemical Trading and Consulting (CTC), headquartered in Reinfeld, Germany. CTC representatives confirmed having sold Pharval the propylene glycol used in Afebril and Valodon. Checking their records again, they found they had also supplied Pharval with the glycerin through a Haitian distributor that had received 72 drums on June 27, 1995. The crisis began to assume international dimensions, however, when CTC representatives told investigators that although they could readily identify the manufacturer of the propylene glycol sold to Pharval, they could not identify the manufacturer of the glycerin. CTC had received the glycerin from a Dutch trader, VOS, a subsidiary of a large German chemical conglomerate, Helm AG. In one conversation with Pharval officials, CTC officials mentioned, almost parenthetically, that they had heard that there were problems with Chinese glycerin but insisted CTC did not buy from China at all.

By Monday afternoon, July 1, the FDA's Forensic Chemistry Center had completed its analysis of the glycerin samples it had received and concluded that it was not USP grade glycerin, but was contaminated with 24% DEG. The acetaminophen syrup made by Pharval, as a result, had a 12% to 20% contamination level.

At this point in the investigation, the FDA took over the international traceback of the contaminated glycerin. Based on the information provided by CTC, the FDA sent a drug specialist from its Philadelphia office, Ann deMarco, to VOS to determine the manufacturer of the glycerin and to find out whether any other drums of contaminated product may have been distributed. On Friday, July 4, deMarco arrived at VOS, where she determined that the company was not the original source of the glycerin shipped to Pharval. Documentation obtained at VOS showed that VOS had served as a broker and had received the contaminated glycerin from Metall-Chemie in Hamburg, Germany. VOS personnel informed deMarco that the company had also purchased a second lot of glycerin from Metall-Chemie, which was stored in a warehouse in Rotterdam. deMarco collected product samples from this shipment and forwarded them to FDA's Forensic Chemistry Lab for analysis. Documentation provided by VOS showed that both the glycerin sold to Pharval and the glycerin in storage in Rotterdam had been shipped from Xingang, China. Analysis of the second shipment found the same profile of contamination as in the glycerin that had been shipped to Haiti.

Since it was critical to determine the source of this material, deMarco set out for Germany to visit Metall-Chemie. She determined that Metall-Chemie, also a broker, had arranged the purchase of the contaminated glycerin from a Chinese trader, Sinochem International. Personnel from Metall-Chemie explained how they had photocopied their company letterhead onto the Certificate of Analysis provided by Sinochem in order to obliterate the identity of the supplier. They explained that bulk chemical traders do this routinely to protect their role as middlemen. In the case of the glycerin that had reached Pharval in Haiti, neither the Certificate of Analysis nor the product labeling indicated the manufacturer or country of origin.

Although the labeling and the Certificate of Analysis indicated that the glycerin shipped to Haiti met the strict standards of the US Pharmacopeia (USP), all personnel that deMarco interviewed at Metall-Chemie and VOS denied knowing that the glycerin was contaminated and failed to meet USP requirements. A Dutch journalist later reported that a sample of glycerin from the lot shipped to Haiti had been tested by an independent laboratory shortly after shipment and was found to be only 53.9% pure. (USP standards for glycerin call for 98% purity.) This discovery became the basis for several lawsuits, although it is not clear who requested the testing.

Attempts to trace the contaminated glycerin within China proved inconclusive. The glycerin was reportedly made not by a pharmaceutical company but by a fine chemical manufacturing plant, which was said to have manufactured the product according to specifications for a USP grade product. Only the invoice stamp indicated that the product met USP standards, and there was no record of an analysis having been conducted before shipment from the factory. The inspectors discovered that the firm had ceased production at the site, had moved its operations, and was making a different product. No production records were available, and the Chinese officials noted that they did not normally keep production records past two years. The investigation did not reveal when or where the contamination occurred, although the firm's officials did tell investigators that the product had been produced by fermentation, rather than by chemical synthesis as had been previously assumed.

In Haiti, however, a vigorous investigation was launched to account for the disposition of the entire shipment of 72 drums of glycerin. Sixty-two of the 72 drums had been sold to Pharval by the Haitian distributor. The search for the last 10 drums of presumably contaminated glycerin required extensive investigative work, which went on alongside the ongoing recall effort.

Investigators found that the Haitian distributor had stored the 10 drums of Chinese glycerin not sold to Pharval along with four drums of glycerin from Brazil in his own factory. The factory had scanty records, but investigators determined that 12 of the 14 drums had been sold to 11 local pharmacies in Haiti. FDA and CDC investigators visited nine of the pharmacies and learned that most of the glycerin had been sold for use as a moisturizer or hair tonic, both topical applications. One pharmacy did sell some as a laxative, but none of the pharmacists had received any complaints. Unfortunately, there were no records of sale and there was no remaining product to be sampled, closing that part of the investigation.

The last two drums of glycerin were sold to another Haitian pharmaceutical company. This company used the glycerin in the manufacture of 15 liquid products, not including any acetaminophen preparations; none of their product formulations required more than 10% glycerin. Residues from the first drum tested negative for DEG, but there were no remains to test from the second drum. Dr. O'Brien and the CDC team speculate that this second drum, if it were contaminated, might account for some of the eight identified cases of renal failure for which they could demonstrate no exposure to either Valodon or Afebril.

The FDA followed up its active investigations by sending San Juan drug investigator Jorge Guadalupe back to Haiti to conduct a two-week training course on good manufacturing practices and recall procedures for the Ministry of Health. Later, under the sponsorship of the WHO, a Haitian Ministry of Health pharmacist came to the United States for two months of intensive training in photography, sample collection, evidence development, report writing, lab techniques, and good manufacturing practices.

In an unusual epitaph to an excellent investigation, the investigative team learned that even if Pharval had used a recommended method of testing, it would not necessarily have detected the contamination. Virtually all pharmacopeias worldwide, including that of the United States, recommended that infrared spectrometry be used in testing glycerin. CDC and FDA lab experts, however, determined that this method does not detect DEG contamination in glycerin. The only other method recommended as a test for glycerin purity, gas/liquid chromatography, was expensive. Poor countries, the investigators realized, would never be able to afford this methodology. In an amazing "small world" story, a solution was reached. While stationed in Botswana in 1996, one of O'Brien's former classmates and a fellow EIS Officer (Class of 1994), Thomas Kenyon, MD MPH, heard a BBC broadcast about the Haitian epidemic. He e-mailed O'Brien about the work that his father had done at the FDA in developing a simple and inexpensive kit to test chemicals and raw materials for purity. Alan Kenyon, PhD, a physical chemist who had worked for 38 years at Monsanto, was 80 years old at the time of the Haitian crisis and still volunteering at the St. Louis FDA lab, working on thin layer chromatography. Dr. Kenyon had spent the summer of 1995 working with an international group of college students to refine a method of detecting DEG contamination in glycerin. Finalizing the research with the help of visiting scholars from Australia, Shanghai, and Singapore, Dr. Kenyon and his team developed an inexpensive and portable test kit for DEG in glycerin and made it available to the WHO, which is making some modifications prior to distributing it. Meanwhile, US officials hope that the Haitian tragedy will serve as a springboard for international efforts to tighten control over bulk drug ingredients and fine chemical shipments. In 1997, a first step was achieved when an international workshop on DEG contamination was held, raising awareness of the problem among health officials and prompting some countries to make changes in their export procedures for drug excipients and fine chemicals.

Dr. Junod is a Historian with the US Food and Drug Administration.

References

1. Dieng A. Report of the Independent Expert on Haiti to the Commission on Human Rights, Economic and Social Council. Geneva: World Health Organization; 1997.
2. O'Brien KL, Selanikio JD, Hecdivert C, Placide MF, Louis M, Barr DB, et al. Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. JAMA 1998; 279:1175-80.
3. Lorber B. Are all diseases infectious? Ann Intern Med 1996;125:847-8.
4. Young JH. Sulfanilamide and diethylene glycol. In: Parascandola J, Whorton J, editors. Chemistry and modern society: historical essays in honor of Aaron J. Ihde. Washington: American Chemical Society; 1983. p. 108.
5. Jackson CO. Food and drug legislation in the New Deal. Princeton (NJ): Princeton University Press; 1970.
6. Wax PM. It's happening again—another diethylene glycol mass poisoning. Clin Toxicol 1996;34:517-20.
7. Hanif M, Mobarak M, Ronan A, Rahman D, Donovan JJ Jr, Bennish ML. Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. BMJ 1995;311:88-91.
8. Rohter L. Quarrel imperils health care in Haiti. New York Times 1996 May 26;1:10. ■

Address correspondence to Dr. Junod, FDA History Office, HFC-24, Rm. 1351, 5600 Fishers Lane, Rockville MD 20857; tel. 301-827-3759; fax 301-443-7270; e-mail <sjunod@ora.fda.gov>.