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The Incident at Tuol Chrey: Pathologic and Toxicologic Examinations of a Casualty After Chemical Attack

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ABSTRACT: The results of the pathologic and toxicologic examinations of specimens from a casualty who died several weeks after a chemical attack in Kampuchea are discussed. While the effects of tricothecene mycotoxins have been described in domestic and experimental animals, there is a paucity of information about the pathologic effects of these toxins in humans. The possible effects of endemic diseases such as falciparum malaria, viral hepatitis, and nutritional deficiencies, as well as of the sudden, unexpected death syndrome among refugees from Southeast Asia, have been reviewed. If the results of the histologic examinations in this case are considered alone, it is not possible to establish a cause-effect relationship. However, the circumstances of injury, the relationship of pathologic findings to the studies of experimental animals, and the results of the toxicologic examinations of environmental and biologic specimens indicate that the combinations of tricothecene mycotoxins detected are not consistent with natural occurrence and provide evidence that the pathologic effects are related to a toxic agent.

KEYWORDS: pathology and biology, toxicology, tricothecene mycotoxins, yellow rain, chemical warfare

The use of several kinds of incapacitating, vesicant, and lethal chemical warfare agents in Southeast Asia, particularly in Kampuchea and Laos, has been reported since 1975. International efforts began seriously in 1980 not only to confirm those reports, but also to identify the chemical agents. Analyses of environmental and biologic specimens, as well as of medical history and physical examinations, obtained at or near sites of attack indicate that both traditional agents and mycotoxin-containing mixtures have been used. Aerial attacks, usually by spray, dispersed yellow to yellow-brown liquid or semi-solid particles that fell and sometimes sounded like rain when striking thatched rooftops. This combined chemical agent, popularly known as "yellow rain" or "medicine from the sky" caused rapid onset of protracted symptoms resulting in incapacitation and sometimes death to those who were very young, old, infirm, or unprotected when contacted directly by the spray [*1*]. Tricothecene toxins, detected in physi-

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cal evidence from sites of attack and in biologic specimens from survivors, indicate at least that mycotoxins are sometimes one constituent of "yellow rain" [2].

During 1982, lethal and incapacitating chemical agents and toxins were used by Vietnamese forces against Khmer Rouge guerillas in Kampuchea. Methods of attack included aerial spray and artillery munitions. Examination of physical evidence and biological specimens confirmed the presence of tricothecene mycotoxins [3–5]. As the result of an attack at Tuol Chrey on 13 Feb. 1982, there were numerous casualties and one death. The pathologic and toxicologic examinations of tissues from the victim provided the basis for this report.

Circumstances of Injury

During the day of 13 Feb. 1982, the encampment of Khmer Rouge guerillas at Tuol Chrey, 30 Km south of Nong Pru and 300 m from Thai-Kampuchea border near Khao Din, Kampuchea, had been subjected to artillery bombardment by Vietnamese forces (Fig. 1). At dusk, after the patrols of soldiers had returned for the evening meal, three artillery shells exploded upwind of the camp. The soldiers smelled a sweet, perfume-like odor and experienced the rapid onset of incapacitation. Although the attack rate is unknown, there were at least 100 casualties. Some of the soldiers were evacuated to Nong Pru, while others sought medical assistance at Phum Tmey [3,5,6].

Epidemiological Investigation

A Canadian Forces medical team conducted an extensive investigation of alleged chemical warfare incidents in Kampuchea and Laos in March 1982 [6]. Members of the team inter-

FIG. 1—*Map of Kampuchea showing the site of the incident at Tuol Chrey near the border between Thailand and Kampuchea.*

viewed 15 of the Khmer Rouge casualties at Nong Pru on 18 March 1982. The ages of soliders ranged from 20 to 29 years and they had previous exposure to chemical agents. The incapacitating agent dispersed at Tuol Chrey caused fear and discomfort, and the unprotected soldiers attempted to flee. Soldiers at 100 to 300 m from the impact of the artillery shells had onset of symptoms 2 and 5 min after exposure, respectively. The most significant symptoms included pain or tearing of the eyes, blurred vision, burning eyes, dryness of the mouth, bitter taste, nasal obstruction, voice change or loss, dyspnea, vomiting, tachycardia, muscle tremors or weakness, as well as one or more of the following: incoordination, collapse, confusion, drunkenness, and paralysis. Among the 15 soliders interviewed, the duration of illness for 8 soldiers lasted from 8 to 14 days. Four of the fifteen soldiers remained in the hospital thirty-three days after the incident.

Case Report

One of the casualties at Tuol Chrey had been treated at Nong Pru hospital and had shown signs of recovery. He was known to have previous exposure to attack by chemical agents on 19 Sept. 1981. On 11 March 1982, he was admitted to the field hospital at Tuol Chrey for evaluation of fever, cough, hemoptysis, anuria, and jaundice. Recurrent falciparum malaria was suspected, and treatment included quinine, penicillin, and intravenous fluids. The patient became comatose and died 16 March 1982. Four hours before death, blood-tinged urine was obtained by catheter. He vomited blood shortly before death. A limited autopsy was performed to obtain samples of tissue for pathologic and toxicologic examinations [5,6]. Portions of the tissues, submitted for pathologic examination to the National Defense Medical Center, Ottawa, Canada, included lung, kidney, heart, and small intestine [6]. One of us (CJS), also received five containers of specimens, labeled M-25-A, B, C, D, and E. Information concerning the identity and geographic location of the subject, the past medical history, the circumstances of death, and the gross pathologic findings at autopsy was not provided with the specimens. The remainder of the tissues were retained for toxicologic examinations.

Pathologic Examinations

The five containers of specimens in small glass jars with white screw caps were received in good condition on 29 May 1982. After photographs of the containers and their contents were obtained, the specimens were examined, as follows:

M-25-82-A: Heart

Gross Examination—The triangular, brownish-tan segment of heart, preserved in formalin solution, weighs 12.3 g and measures 4 by 3.2 by 1.5 cm. Focal brownish, linear areas of hemorrhage, measuring up to 1 cm in length and 0.5 by 0.3 cm in area, are noted within the myocardium. The epicardial surface is not remarkable and no major coronary arteries are noted. The segment includes a portion of a ventricular chamber, and the endocardial surface, including papillary muscles, is not remarkable. Five sections are obtained for histologic examination.

Microscopic Examination—Five sections of heart are examined, including areas of the left and right ventricles, and the atrioventricular sulcus. Hematoxylin and eosin, Masson trichrome, and Van Gieson elastic stains were performed. The epicardial fat is not remarkable and contains several medium-sized coronary vessels that show focal intimal arteriosclerosis and focal intramural hemorrhage extending from the medial layer to the boundary of the internal elastic lamina. Some foci of intramural coronary artery hemorrhage appear to extravasate beyond the distended spaces within the vessel wall. There is no inflammatory response associated with the hemorrhage.

The myocardium shows extensive areas of wavy myofibers undulating in a regular pattern of wavy bundles. These areas are most prominent in the inner third of the myocardium, and

spare the outer 10 to 20 cell layers of endocardium. In areas of wavy myocardium, there is an absence of myofiber fragmentation which is obvious in nonwavy areas. However, the most striking finding is the presence of hemorrhagic foci in the interstitium that appear to separate the bundles and fibers of myocardium (Fig. 2). This interstitial hemorrhage appears in every section examined, and is located in the middle myocardial or subendocardial areas. Its relationship to the wavy areas is not consistent; sometimes the interstitial hemorrhage is within a wavy area, and other times it appears at the transition areas between fragmented and wavy myocardium.

The section of atrioventricular junction shows hemorrhage extending into the epicardial fat. In approximately half of the areas of hemorrhage, there is a centralized aggregation of acute and chronic inflammatory cells that separate the myofibers and bundles. These leukocytes are mixed evenly with the interstitial erythrocytes (1 : 1 ratio) and appear to show a slight predominance of segmented leukocytes over lymphocytes. Rare plasma cells and eosinophils are also present. There is no evidence of myofiber necrosis in adjacent areas, but several cells show dissolution of cytoplasm with granularity of myofilaments, consistent with myofibrillar degeneration.

One section from the atrioventricular sulcus shows a proliferation of reactive endothelial cells and single, irregular, round to ovoid cells with vesicular chromatin and central linear chromatin material similar to an Anitschkow myocyte. The myocardium shows mild nuclear pleomorphism, with large, round to rectangular shapes and prominent nucleoli. Refractile, slightly basophilic material is deposited adjacent one pole of the nucleus in a minority of myofibers. The cytoplasm is uniform throughout, except for thin, attenuated fibers in the areas of wavy change. Sharp staining quality of the striations and intercalated disks is consistent throughout all sections. There is no abnormality of myocardial vessels and they do not appear related to the areas of interstitial hemorrhage and inflammation.

Diagnoses—Acute interstitial hemorrhage of epicardium and myocardium; intramural hemorrhage of medium-size coronary arteries; acute, focal myocarditis; hyperacute ischemic changes of myocardium.

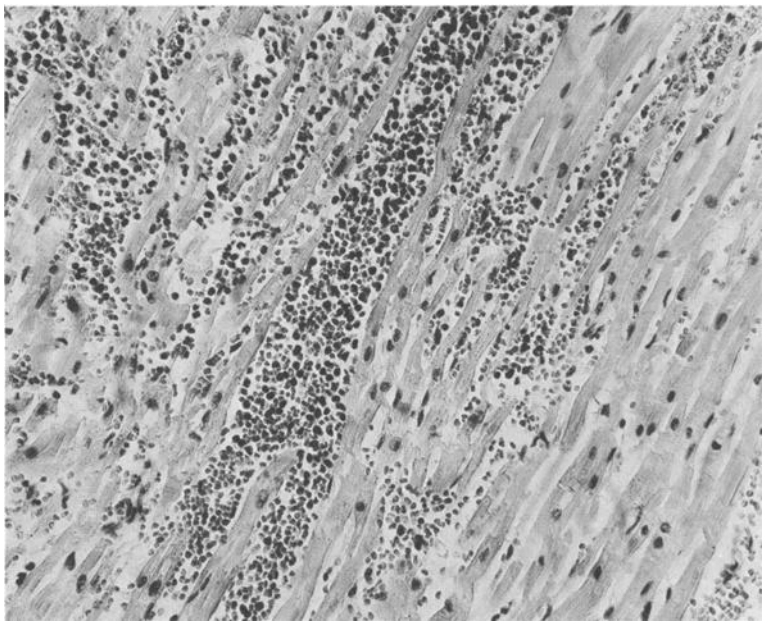

FIG. 2—*Photomicrograph of heart with interstitial hemorrhage and inflammation in myocardium (hematoxylin-eosin stain, × 236).*

M-25-82-B: Stomach

Gross Examination—The circular, cross section of stomach is grayish tan and preserved in formalin solution. It weighs 7.6 g and measures 4.7 cm in diameter and 1.5 cm in thickness. There are no unusual features. Three sections are obtained for histologic examination.

Microscopic Examination—Three sections are examined with hematoxylin and eosin, as well as elastic and trichrome stains, including the body and a transitional zone of antrum. The columnar epithelium shows remarkable preservation, with autolysis of only focal superficial columnar cells. The surface is covered with scant, eosinophilic, bile-stained amphorus material. The lamina propria shows a normal population of mononuclear cells with intact architecture of deep and superficial glands in both body and antrum. The parietal cell mass is intact. There is focal congestion of blood vessels adjacent to the muscularis mucosa, with minimal extravasation. Focal lymphoid aggregates are noted in the same location. The submucosa, muscularis propria, and serosa are not remarkable.

Diagnoses—Focal congestion of blood vessels and superficial autolysis of mucosa, stomach.

M-25-82-C: Liver

Gross Examination—There are two segments of liver, preserved in formalin solution, weighing 2.8 and 2.3 g, respectively, and measuring 4.7 by 1.3 by 1.0 cm and 2.5 by 1.5 by 1.2 cm, respectively. The segments are partially covered by a smooth, intact capsule. The parenchyma has a brown color with a greenish hue and shows punctuate, grayish-white micronodular areas measuring less than 3 mm in diameter. Six sections are obtained for histologic examination.

Microscopic Examination—The sections of liver are examined by hematoxylin and eosin, trichrome, reticulin, elastic, periodic acid-Schiff (PAS), Diastase-periodic acid-Schiff (D-PAS), iron, bile, and copper stains, as well as by aldehyde fuchsin and hepatitis B surface antigen (HB_sAg) immunoperoxidase stains, and by electron microscopy.

There is a haphazard pattern of incompletely rounded, uneven small nodules (2 to 3 mm) with intervening irregular areas of lobular collapse and early fibrosis (Fig. 3). The nodular process involves all lobular units, and no normal lobular components are identified. There are focal capsular depressions, reflecting collapse of underlying parenchyma. Central veins are barely recognized within irregular areas of central-portal or central-central fibrosis and collapse. Original portal areas are centered within extensive areas of peri-portal fibrosis and collapse that engulf confluent lobules of hepatic parenchyma and bridge portal and centrizonal areas of necrosis and fibrosis. The injury pattern appears most dominant at the portal areas, but centrizonal areas also show similar, lesser changes.

The hepatic parenchyma shows total disarray of lobular architecture with no discernible orientation of liver plates and uneven sinusoidal spaces. Edges of remnant parenchyma show an irregular interdigitation with the confluent areas of necrosis and fibrosis. Some of the hepatic nodules show a smooth, rounded contour adjacent to the compressed fibrous capsule. Double plates are observed in regenerating parenchymal nodules. Hepatocytes show marked nuclear and moderate cytoplasmic pleomorphism with prominent binucleation, vesicular nuclei, and macronucleoli. Kupffer cells are increased and laden with fibrinoid and refractile pigmented material. Bile thrombi appear in peripheral hepatocytes distending the canalicular area and mimicking an acinar formation. Occasional peripheral hepatocytes also show hepatocellular cholestasis in addition to the dominant canalicular pattern. Random, rare, pyknotic hepatocytes are extruded into the sinusoidal space. Scattered, sparse to moderate chronic mononuclear inflammatory cells appear in all areas of parenchymal collapse or previous portal triads. Foci of early collagen production appear in all areas of collapse, with confluent lobular necrosis, or extensive bridging necrosis between central and portal zones (Fig. 4). Early collagen production is intermingled among the compressed reticulin framework of previously viable hepatocytes. There is a moderate proliferation of bile ducts, as well as pseudoductular reaction of hepatocytes in or adjacent to original portal areas. Numerous, original portal areas

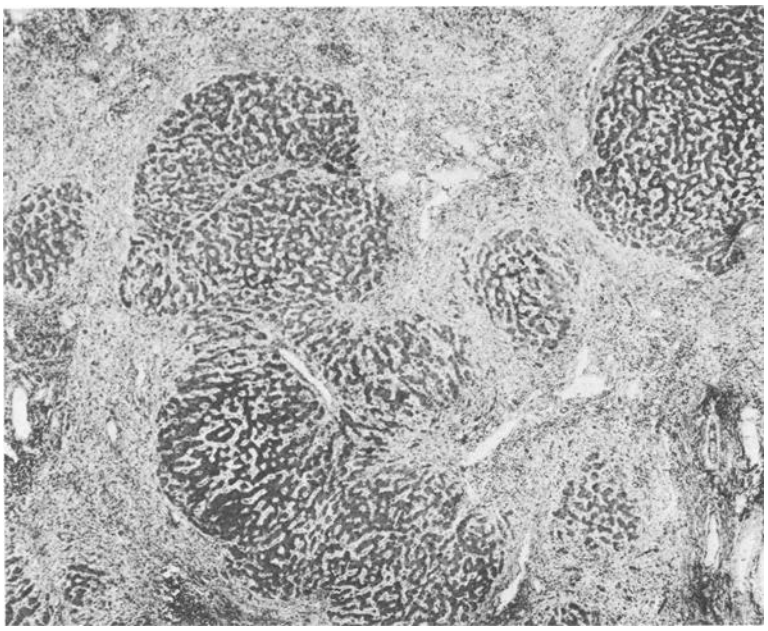

FIG. 3—*Photomicrograph of liver with haphazard micronodular pattern, irregular areas of lobular collapse, and early fibrosis (Masson trichrome stain, ×37).*

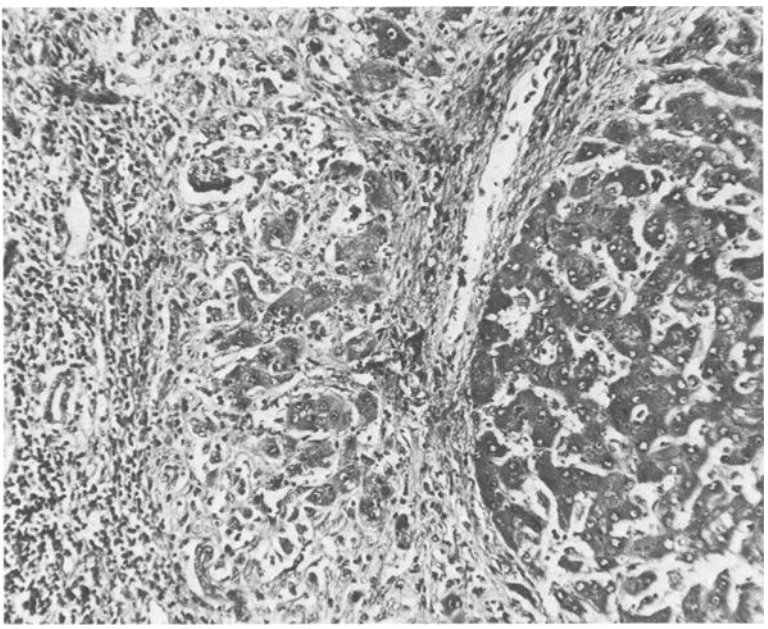

FIG. 4—*Photomicrograph of liver showing lobular necrosis and bridging necrosis between central and portal zones (Masson trichrome stain, ×151).*

show dense lymphoid aggregates that appear to surround small portal vessels or lymphatics. Some lymphoid aggregates appear centered on small bile ducts which show intact epithelium. Rare eosinophils are identified in old triad areas. There is no evidence of phlebitis, alcoholic hyalin, or ground-glass cells. In portal macrophages and sinusoidal Kupffer cells there is birefringent black-brown, granular pigment.

Trichrome stains show collagen fibers arising in collapsed areas and forming fibrotic capsules around occasional regenerating nodules. There is a subtle pattern of pericellular fibrosis originating in areas of existing fibrosis and previous collapse. Multiple central veins show a stellate pattern of fibrosis in areas of complete collapse, as evident by immediate juxtaposition to previous triads. The reticulin stain best demonstrates areas of confluent lobular necrosis and bridging necrosis with condensation and collapse of the hepatocyte framework. No vascular abnormalities are demonstrated with the elastic stain. The PAS and D-PAS stains highlight areas of hepatocyte necrosis with irregular margins of the lobular remnants and the Kupffer cell hyperplasia with dense staining of lysosomal contents. Canalicular cholestasis is confirmed by D-PAS stain and bile stain of the same area. Iron stain shows trace staining in portal macrophages, which is not related to the previous description of black-brown pigment. Copper stain is noncontributory. The aldehyde fuchsin and HB_sAg immunoperoxidase stains are negative. Antigenic particles or products of the hepatitis B virus are not observed by electron microscopy.

Diagnoses—Early micronodular cirrhosis, with focal regenerative nodules, arising from diffuse hepatic necrosis of confluent lobular and bridging types; canalicular and hepatocellular cholestasis; brown-black pigment, consistent with malarial pigment, in portal and sinusoidal macrophages.

M-25-82-D: Kidney

Gross Examination—The oval segment of kidney, including a small segment of ureter, weighs 29 g and measures 5.5 by 4.0 by 1.8 cm. The capsule of the kidney is smooth, glistening, and intact. The parenchyma, as well as the formalin solution in which the specimen is preserved, has a greenish color. Five sections are obtained for histologic examination.

Microscopic Examination—Five sections are examined, including the entire cortex and medulla, using hematoxylin and eosin, trichrome, reticulin, bile, and iron stains, as well as electron microscopy. The cortex appears thickened and the transitional zone at the outer medullary portion of the pyramid is poorly defined. Conspicuous pigmented, mixed casts appear in tubules of the cortex, as well as in distended tubules of the medulla and papilla. Cortical and deep glomeruli are intact with inconspicuous afferent and efferent arterioles. Bowman's space is mildly distended, with some compression of the glomerular tuft. There is focal cuboidal cell proliferation of the surface of the Bowman's capsule in rare glomeruli. Cellularity of the glomerulus is not remarkable, with normal thickness of basement membranes and absence of capillary thrombi.

There is a mild periglomerular interstitial edema that extends to intertubular spaces of distal and proximal convoluted tubules. The proximal convoluted tubules show mild dilatation and tortuosity of the lumens in cross section, with accentuation of the external contour by interstitial edema that separates slightly the various tubules (Fig. 5). The cells of the proximal tubules show a delicate, pale eosinophilic, granular cytoplasm with dissolution of the luminal brush border in a majority of the cells of each tubular cross section. Some proximal tubular cells show a rough, granular clumping in the cytoplasm with formation of pigmented, smooth aggregates. Nuclei are absent in 25 to 75% of proximal tubular cells, depending on the sampled area. The basal nuclei are round and vesicular with a prominent rim of finely granular chromatin and variable chromatin bodies. Although pleomorphic nuclei are observed, there is no evidence of regenerating tubular cells. Some proximal tubules show epithelium with dense eosinophilic cytoplasm and compact nuclei making distinction from damaged distal tubules a

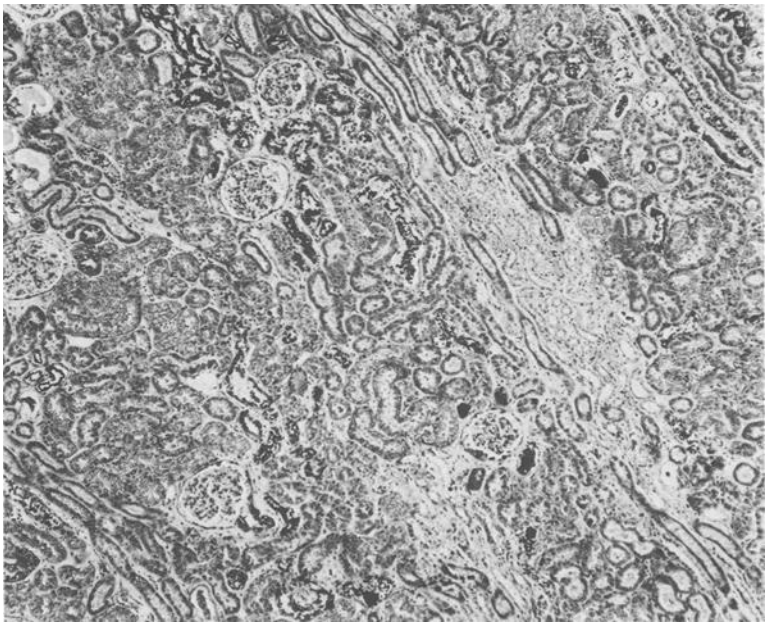

FIG. 5—*Photomicrograph of kidney with dilated, tortuous proximal tubules and interstitial edema (Masson trichrome stain, ×59).*

difficult task. Contents of the proximal convoluted tubules are limited to granular, eosinophilic debris and rare, extruded cytoplasmic fragments or pyknotic nuclei. The paraglomerular distal convoluted tubules are distended with a variable mixture of red-brown, rounded, irregular globules (3 to 6 μm) that form casts.

These pigmented casts are further combined with cellular ghosts of proximal tubular cells, recognized by their granular cytoplasm and pyknotic nuclei (Fig. 6). Within the pigmented casts are occasional laminated, basophilic concretions that are nonrefringent and range from 30 to 60 μm in diameter. The mixed, pigmented casts compress and distort the distal tubular cells, causing a random, frequent dropout of nuclei and pyknosis of remaining nuclei. In some areas, the distortion of distal tubular cells mimics an endothelial cell lining. However, the interstitial cortical blood vessels appear intact and contain scant erythrocytes. Collecting tubules in the cortex show epithelial cells with vacuolated, clear cytoplasm and intact central nuclei. The contents of lumens show an identical mixture of pigmented casts, as previously described, but the material is less dense and less frequent than in the distal convoluted tubules. The junction of the cortex and medulla shows a prominent interstitial edema greater than in the cortex. Arcuate vessels are unremarkable and there is no congestion of the smaller vessels. Contents of collecting, straight proximal, and straight distal tubules in this area show minimal or no pigmented casts. The outer medulla shows a continuation of interstitial edema that extends to the papilla. There is moderate distension of the collecting tubules, which are filled with pigmented, granular, and globoid casts and mixed cellular debris (Fig. 7). Some epithelial cells within the casts are nearly intact; others show nuclear pyknosis and cytoplasmic fragmentation.

Because of the tubular distension and compression by the mixed casts, the tubular epithelium of the deep collecting tubules shows marked distortion and is difficult to identify. Therefore, the distinction between an ascending Henle's loop and collecting tubule may be impossible. Normal tubules of ascending Henle's loop are readily identified and do not contain pigmented casts. The vasa recta show no congestion by erythrocytes. However, there is a consistent, scattered infil-

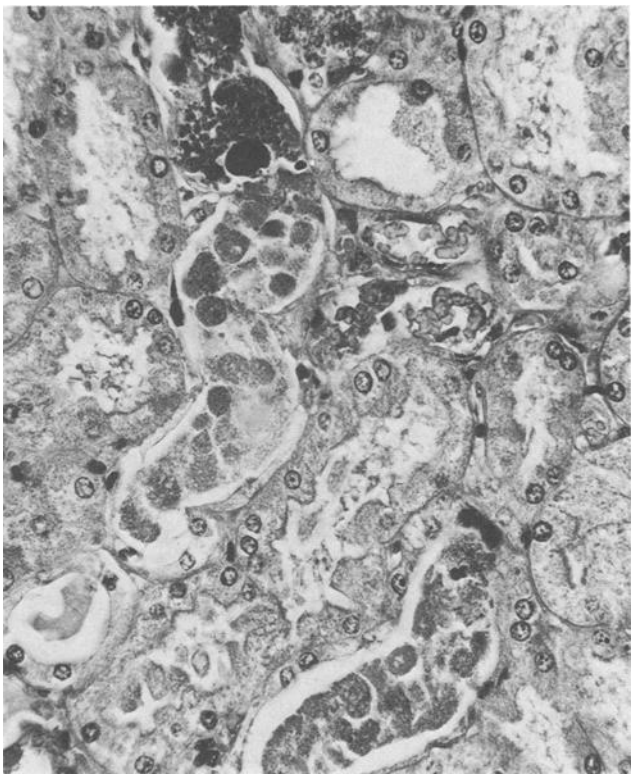

FIG. 6—*Photomicrograph of kidney. The distal tubules contain ghosts of exfoliated epithelial cells from the proximal convoluted tubules, as well as pigmented casts and nonrefrigent, laminated, basophilic concretions (hematoxylin-eosin stain, ×378).*

tration of leukocytes in the vasa recta unrelated to any other interstitial process (Fig. 8). The greatest concentration of pigmented casts appears in the collecting tubules of the papilla. The packed pigment casts within the tubules alternate with normal components of the thin segment of Henle's loop, all within an edematous interstitium. A single section of ureter shows submucosal congestion and hemorrhage in the adventitia.

Trichrome and reticulin stains help to delineate the interstitial edema and distortion of tubular architecture (Fig. 5). Bile stains confirm the presence of bile in the golden-brown globular aggregates, but not in the granular, red-brown material of the tubular casts. Iron stain of the tubular casts is negative. Neither malarial parasites nor parasitized erythrocytes are observed by electron microscopy.

Diagnoses—Early, acute tubular necrosis, ischemic type, consistent with hepatorenal syndrome, with mixed bile, hemoglobin, and epithelial casts.

M-25-82-E: Lung

Gross Examination—There are two wedged-shaped segments of lung, preserved in formalin in solution, weighing 9.3 and 9.0 g, respectively, and measuring 4.0 by 3.5 by 0.8 cm and 3.5 by 2.5 by 1.8 cm, respectively. One surface of each segment is covered by smooth, glistening, bluish-gray visceral pleura. The parenchyma is spongy and brownish-tan. Six sections are obtained for histologic examination.

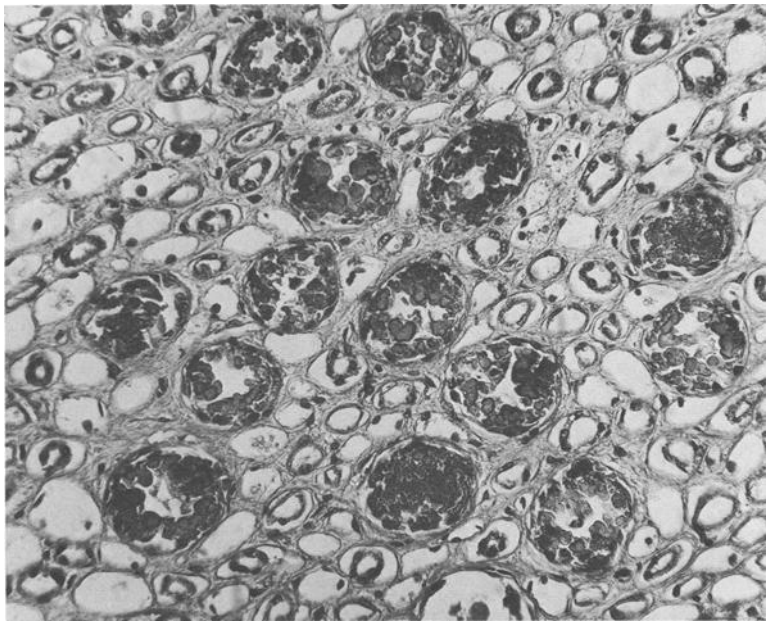

FIG. 7—*Photomicrograph of kidney. The collecting tubules contain pigmented, granular, and globoid casts (hematoxylin-eosin stain, ×256).*

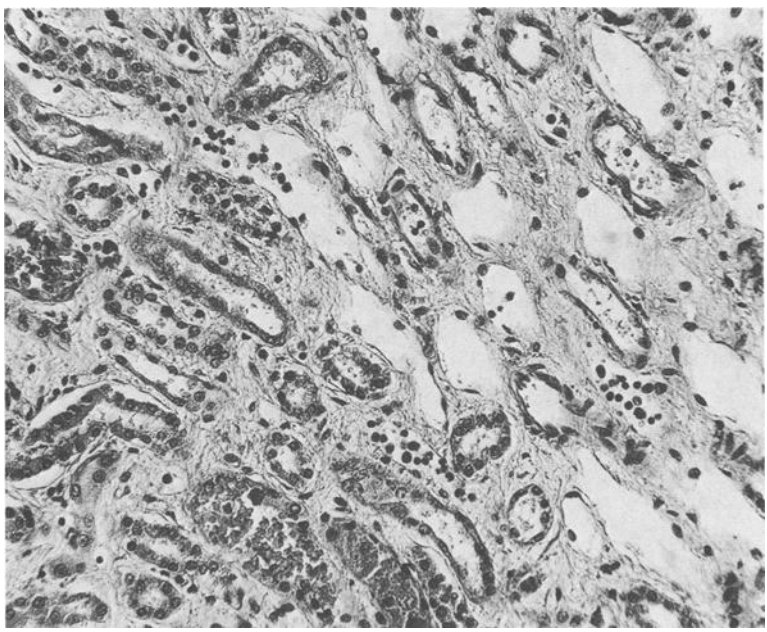

FIG. 8—*Photomicrograph of kidney. Within the mid-medullary zone, the vasa recta show infiltration by leukocytes (hematoxylin-eosin stain, ×256).*

Microscopic Examination—The six sections of lung are examined by hematoxylin and eosin, trichrome, and elastic stains.

The pleural surface shows an intact single layer of mesothelial cells covering a thin layer of fibrous tissue. The parenchyma shows distended alveoli with pale, eosinophilic material filling approximately one fourth of the total space. Contents of occasional alveoli show a mixture of pale eosinophilic and hematin material. Alveolar walls are diffusely congested, but otherwise show no inflammatory cells or interstitial thickening. The overall alveolar pattern is irregular, with larger spaces between intact alveoli showing "free ends" of disrupted alveolar walls. This irregular alveolar pattern is consistent throughout all sampled areas. The bronchi show occasional mononuclear cells in the submucosa with intact mucosal basement membranes. The mucosa is hyperplastic, with stratification of tall columnar cells. Autolysis of columnar mucosa is rare. On the columnar mucosa, there are alternating layers of pink mucoid material, and granular hematin pigment. No inflammatory cells are present in the bronchi and bronchioles. Pulmonary arterioles are inconspicuous. Pulmonary arteries and veins are unremarkable and are filled with blood showing postmortem layering. Trichrome and elastic stains confirm the absence of fibrosis and vascular changes.

Diagnosis—Acute pulmonary edema.

Toxicologic Studies

Formalin-fixed samples of heart, stomach, liver, kidney, lung, and intestine from the victim of the Tuol Chrey incident were submitted for toxicologic studies coordinated by the Armed Forces Medical Intelligence Center. Toxicologic analyses for the tricothecene toxins, diacetoxyscirpenol (DAS) and T-2, as well as for HT-2, a metabolic product of T-2, were performed by Dr. Chester T. Mirocha, University of Minnesota, using positive chemical ionization in methane and gas chromatography-mass spectrophotometry with a DAS internal standard. Analyses of tissues for aflatoxin B_1, by high performance liquid chromatography were conducted by Dr. Tim Phillips, Texas A & M University. The summary of the results of these studies is given in Table 1 [3–5].

Subsequently, parallel studies of portions of the same tissues by Dr. Joseph D. Rosen, Rutgers University, detected 0.25, 0.28, and 2.01 ppm concentrations of T-2 toxin in liver, kidney, and intestine, respectively. These analyses were performed by the procedure of Rosen and Rosen [7], except that gas chromatography was accomplished with a 25-m by 0.32-mm OV-1701 bonded phase silica capillary column.[4]

TABLE 1—*Analyses of tissues for diacetoxyscirpenol (DAS), T-2 toxin, HT-2 toxin, and aflatoxin* B_1.

Specimen	DAS	T-2	HT-2	Aflatoxin, ng/g
A. heart	...[a]	...	1.2 ppm	not examined
B. stomach	...	25.1 ppb	4.02 ppm	19.8
C. liver	...	...	...	20.2
D. kidney	2.55 ppm	6.8 ppb	...	15.3
E. lung	...	8.5 ppb	...	not examined
F. intestine	...	88.0 ppb	9.6 ppb	11.2

[a]... = negative.

[4]Dr. Joseph D. Rosen, Rutgers University, New Brunswick, NJ, personal communication, 2 April 1984.

Discussion

A variety of naturally occurring toxins in fish, mushrooms, bacteria, and plants have been associated with sporadic poisoning in humans. The medical effects of the mycotoxins, produced by species of fungi, are less well-known, but their effects on domestic animals influence the availability of food supplies in the world and indirectly affect human health. The naturally occurring mycotoxins include ergot produced by *Claviceps purpura*, aflatoxins produced by *Aspergillus flavus* and related species, and tricothecene mycotoxins produced by species of *Fusarium* and of other fungi such as *Acremonium, Myrothecium, Stachybotrys*, and *Baccharis* [8]. Since 1891, sporadic outbreaks of human mycotoxicois have occurred in the Soviet Union, Europe, and Japan following ingestion of food made from overwintered grain contaminated by species of *Fusarium* [2,4]. Alimentary toxic aleukia, a syndrome manifested by vomiting, diarrhea, leukopenia, and gastrointestinal hemorrhage, caused a 10% mortality in the Orenburg district near Siberia in 1944 [2]. The contamination of food for domestic animals has caused a variety of mycotoxicoses known as moldy corn toxicosis, red mold toxicosis, stachybotryotoxicosis, fusariotoxicosis, dendrodochiotoxicosis, and bean-hull toxicosis [2, 8, 9, 10]. Although the aflatoxins, particularly aflatoxin B_1, cause hepatotoxic effects, including carcinogenesis, in animals, little is known about their pathologic effects in humans. However, they have been implicated in the high incidence of liver cancer in Africa and Asia [11, 12].

The tetracyclic sesquiterpene chemical structure of the tricothecenes includes a six-membered oxygen-containing ring, an olefinic double bond at carbon atoms 12 and 13, and *R* groups consisting of hydroxyls, esterified hydroxyls, epoxides, or esters [13]. The most common toxins produced by *Fusarium* include T-2 toxin, diacetoxyscirpenol (DAS), deoxynivalenol (DON), and nivalenol (NIV) [8]. Metabolites of the tricothecene toxins include HT-2, TMR-1, TMR-2, T-2 tetraol, and neosolaniol [8, 14, 15]. The principal toxic product of *F. tricinctum* and *F. sporotrichioides* is T-2 toxin [8]. *F. roseum* produces not only DAS as the principal toxin, but also DON, or vomitoxin [4, 8]. Macrocylic tricothecene toxins, as well as satratoxins, H and G, verrucarin J, and roriden E, are produced by *S. atra*, a saprophytic fungus found in straw and hay [16].

The clinical signs and symptoms of tricothecene mycotoxicosis in man are similar to those of radiation injury [2] and are exemplified by alimentary toxic aleukia which is manifested by fever, nausea, vomiting, diarrhea, leukopenia, hemorrhagic diathesis, and sepsis. A summary of the stages of illness in tricothecene mycotoxicosis is given in Table 2, but the pathologic findings in man have not been documented.

The radiomimetic effects of tricothecene mycotoxins have been applied to chemotherapy. The antitumor drug, anguidine, contained DAS elaborated by *F. equiseti* and related species of the genus *Fusarium* [17, 18]. The antitumor activities of analogs of anguidine (DAS), measured by inhibition of P-388 and L-1210 murine leukemia systems, as well as of L-38 murine colon adenocarcinoma, were evaluated [19, 20]. Preliminary studies of effects in dogs after single doses of 5 mg per m^2 revealed tremors, vomiting, diarrhea, congestion of sclerae, leukopenia, anemia, and thrombocytopenia [19]. Phase I and II clinical evaluations of anguidine in patients with cancer disclosed significant toxicity with intravenous doses above 3.0 mg per m^2 daily for five days, particularly in patients with hepatic metastases. The signs and symptoms included nausea, vomiting, diarrhea, burning erythema, confusion, ataxia, chills, fever, hypotension, and hair loss [17–19, 21]. Anguidine was not effective for suppression of cancer. Because of the marked toxicity of the drug, the life-threatening hypotensive effects, and the poor tolerance by patients, these chemotherapeutic efforts were discontinued.

In humans, the effects of the tricothecenes are very similar to those found in the victims of many of the "yellow rain" attacks. Overlapping symptoms and signs include rapid onset of violent nausea and vomiting, seizures and central nervous dysfunction, chills, fever, hypotension, epithelionecrosis, myelosuppression, and acute gastroenteritis with hematemesis, melena, and death in about 25% of those persons exposed to doses consistent with aerial spray

TABLE 2—*Clinical symptoms and signs of tricothecene toxicosis.*[a]

Stage	Duration	Clinical Findings
I	3 to 9 days	Burning sensation of skin and mucous membranes Headache, dizziness, and weakness Vomiting, diarrhea, and abdominal pain Fever and sweating Tachycardia and cyanosis
II	2 to 4 weeks	Leukopenia, granulocytopenia, and lymphocytosis Thrombocytopenia Anemia Headache, fatigue, vertigo Petechiae
III	Indeterminate; may result in death or progress to convalescence	Petechiae and focal necrotic lesions of skin and mucosa; ulcerative pharyngitis Hemorrhages of mucous membranes Gastrointestinal hemorrhage Lymphadenopathy Progression of hematologic abnormalities complicated by sepsis
IV	3 weeks to 2 months	Resolution of necrotic lesions and hemorrhages Gradual improvement in hematologic findings Continuing risk of complication by infection

[a]Adapted from Special Report 98, United States Department of State [2].

[2]. Minor differences among the effects are probably related to the differences in the route and rate of exposure, as well as the concentration of the agent.

Although the signs of tricothecene mycotoxicosis in domestic and experimental animals are similar to those in humans, variations are related to the specific toxins and to the species of animals. As the result of the sporadic outbreaks of mycotoxicosis among domestic animals, with economic losses and endangerment of food supplies, studies were undertaken to identify the toxins and their pathologic effects in experimental animals. In 1969, T-2 toxin was isolated from moldy corn in Wisconsin after an incident of mycotoxicosis in animals [22]. Analytic methods were not available at that time, however, to detect small concentrations of toxins in biologic specimens. Subsequent quantitative analytic studies have required the use of radioimmunoassay, high performance liquid chromatography, gas chromatography-mass spectrophotometry, tandem mass spectometry, and other sensitive methods to detect minute concentrations of toxins in biologic specimens [2, 13].

The toxic effects and metabolism of purified toxins have been evaluated in several species of animals. Single doses of T-2 toxin administered to poultry by intubation resulted in multifocal necrotic lesions of the mucosa in the gizzard and crop, as well as lethargy, anorexia, diarrhea, tachypnea, coma, and death. There were no significant hemopoietic effects or changes in blood chemistry [10, 23, 24]. In broiler chicks that died after intubation with tritiated T-2 toxin, enlargement and radioactivity of the gallbladder indicated excretion of T-2 toxin or its metabolites in bile [25]. Recently, Hoerr [26, 27] reported hepatic lesions in chickens given single oral doses of T-2 toxin or DAS. Within 1 to 24 h after dosing, disseminated hemorrhagic foci of coagulative necrosis, as well as bile duct hyperplasia adjacent to these foci of necrosis, were observed. With multiple does of T-2 toxin or DAS, the histologic changes included necrosis of bile duct epithelium, cholestasis, and cytoplasmic vacuolation of hepatocytes. Hoerr also observed necrotic lesions in the renal tubular epithelium of chickens after single or multiple doses of T-2 toxin or DAS. The brains of chickens given T-2 toxin had greater concentrations of dopamine than control animals at 12 h after dosing [28]. The excreta of chickens given tritium-

labeled T-2 toxin, examined at 48 h, revealed T-2 toxin, as well as the toxic metabolites HT-2, neosolaniol, T-2 tetraol, and TB-1 through TB-8 [*14*].

The administration of purified T-2 toxin to swine caused vomiting, diarrhea, lethargy, and posterior paresis. Hemorrhagic and chemical effects were not observed, but pyknotic nuclei and karyorrhexis in the epithelial cells of intestinal mucosa, were observed [*23,29,30*]. Hyperemia of the gallbladder mucosa suggested the concentration and excretion of T-2 toxin or its metabolites in bile [*29*]. Distribution studies of tritium-labeled T-2 toxin in swine showed significant concentrations in muscle, liver, bile, and kidney, as well as greater concentrations in urine and feces [*31*].

Moldy corn toxicoses of cows is manifested by bloody diarrhea and petechial or ecchymotic hemorrhages of serosal and mucous membranes, lymph nodes, heart, turbinates, and small intestine [*30,32*]. These pathologic findings are produced by intramuscular administration of purified T-2 toxin, but not by intubation of cows with purified T-2 toxin, suggesting that other mycotoxins cause the hemorrhagic effects in moldy corn disease [*32*]. Based upon the metabolism of tritium-labeled T-2 toxin administered orally to lactating cows, there is evidence of delayed excretion in feces as compared to urinary excretions. It is believed that T-2 toxin and its metabolites circulate in the enterohepatic system of cows before biliary excretion and elimination into the intestinal tract [*33*].

Stachybotryotoxicosis in horses, caused by contamination of straw and hay with saprophytic fungus *S. atra*, results in damage to blood cells, endothelium, and blood vessel walls [*16*]. The hemorrhagic effects of this tricothecene mycotoxicosis suggest a vascular target for these toxins, but this assumption has not been confirmed by experimental studies. When given in feed, T-2 and DAS do not cause the hemorrhagic lesions observed after parenteral administration of the purified toxins [*9,23,24,30,32,33*].

The toxicity of monoacetoxyscirpenol, produced by the species *F. roseum* Gibbosum, is similar to that of DAS [*34*]. The oral administration of DAS to chickens causes classical bilateral, proliferative necrotic lesions at the angle of the mouth and yellowish, caseous, or plaque-like lesions of the tongue and beak [*35*]. The intravenous administration of DAS to swine causes lethargy, vomiting, watery or bloody diarrhea, staggering gait, paresis, and death. The pathologic findings include hemorrhage in the myocardium, hemorrhagic necrosis of intestinal mucosa, and acute necrosis in the germinal centers of lymphoid tissues [*9,23*]. When purified DAS is given orally to pigs, however, hemorrhagic lesions are not found and there are no effects on hematologic findings in blood or bone marrow. Within seven weeks after oral administration, multifocal, proliferative lesions are noted in the oral mucosa and the small intestine shows glandular and mucosal cell hyperplasia [*33*]. The oral ingestion of DAS and T-2 in moldy feed by pigs and cows, therefore, does not seem to cause the hemorrhagic bowel lesions which may result from contamination of the rations by other toxic agents [*23,33*].

Based upon reports of the use of chemical warfare agents in Southeast Asia, and the similarity of the clinical signs and symptoms to the effects of mycotoxicosis in animals, efforts were devoted to the collection of physical evidence at sites of attack in Southeast Asia. The examination of physical evidence, water, and vegetation has revealed the presence of DAS, T-2, DON, and NIV [*2–5*]. If mycotoxins, as well as aflatoxins, occur naturally from contamination of food by fungi, is it possible that these studies reflect natural contamination? There is overwhelming scientific evidence that this is not true. Analysis of a yellow powder scraped from vegetation in Laos in 1981 disclosed formulation of T-2, DAS, and DON with the emulsifier, polyethylene glycol [*7*]. The combinations of DAS, T-2, DON, and NIV in these samples are not consistent with natural occurrence [*4*]. Another issue concerns the detection of minute concentrations of T-2 and DAS in biologic specimens several weeks after human exposure [*36*]. Long-term storage of aflatoxin B is known. The tricothecenes are also bound in tissues not only by ribosomal proteins, but also by proteins such as albumin, and they react with sulfhydryl compounds such as glutathione [*3,4*].

The results of the pathologic examinations described in this report are similar to those examinations of heart, lung, kidney, and small intestine conducted by pathologists at the Canadian National Defense Medical Center [6]. Since the pathologic effects of tricothecene mycotoxins in humans have not been documented previously, it is not possible to establish a cause-effect relationship for this case if the results of the histologic examinations are considered alone. The Canadian studies did not include examination of the liver and the pathologic effects of the tricothecenes on the liver have not been described adequately in the studies of experimental animals.

Limited medical and autopsy data were obtained or observed by one of us (CCG) for six victims of a different attack, but with circumstances similar to the present case. After the spray was delivered, those persons most directly affected had seizures after initial onset of violent vomiting. Exposed areas of the skin became erythematous and developed homogeneous, small blisters in several hours. Within 12 to 24 h, the victims vomited copious amounts of blood. Autopsies in the field of victims who died 24 to 48 h after the attack disclosed severe gastroenteritis, with bleeding in the lower esophagus, stomach, and duodenum. In two victims, the capsule of the spleen was ruptured without evidence of traumatic injuries. There were no histologic examinations or toxicologic studies of these casualties.For two days post-attack, the site was covered by large, irregular patches of yellow powder measuring from about 2 to 10 cm^2. An odor reminiscent of rancid milk and nicotine was obvious until the third day when the yellow residue disappeared. Samples of vegetation obtained 24 h post-attack were positive for NIV (109 ppm), DON (59.1 ppm), and T-2 (3.15 ppm) [2]. Unusually high levels of cyanide, as well as chloride and fluoride ions, were also detected.

Refugees from Southeast Asia have required treatment for both intestinal parasites and malaria. Among 100 patients examined at the Mayo Clinic [37], 53% were treated for intestinal parasites and malaria and 43% of the stool specimens from these patients contained two or more types of parasites. Kampuchea is an hyperendemic area for malaria and intestinal parasites. Eighty percent of malarial infections are caused by *Plasmodium falciparum*, and Khmer Rouge soldiers have chronic malaria with repeated reinfection [6]. The clinical signs of malaria include confusion, disorientation, dyspnea, and hypotension, as well as epigastric pain, vomiting, diarrhea, and hematemesis. The course of the disease in falciparum malaria may result in blackwater fever manifested by jaundice, albuminuria, hemoglobinuria, and oliguria and by hemoglobin casts in renal tubules, tubular necrosis, and deposition of birefringent malaria pigment in Kupffer cells, portal areas, glomeruli, and corticomedullary capillaries [38]. In the present case, birefringent black and brownish-black pigment was seen in phagocytes, including Kupffer cells, of the liver, but neither pigment, parasites, nor parasitized erythrocytes were observed in other histologic sections. Neither cirrhosis, hepatic cell necrosis, nor bile stasis are features of malaria. While chronic falciparum malaria cannot be excluded from consideration based upon the histologic examinations, the absence of parasites and parasitized erythrocytes, the circumstances of exposure to the toxic agent, the relationship of the pathologic findings to the studies of experimental animals exposed to tricothecenes, and the results of the toxicologic examinations, provide evidence that the pathologic effects are related to a toxic agent.

During the past 5 years, 51 sudden, unexpected deaths have been reported among 50 men and 1 female Laotian, Kampuchean, and Vietnamese refugees living in the United States. The Center for Disease Control [39] has conducted an epidemiological investigation, but has not determined the cause of these deaths. Of the 51 deaths, 29 (57%) occurred in Hmong refugees. All of the deaths of these previously healthy persons occurred at night. The pathologic findings in 49 of the 51 cases for which autopsy reports were available include absent or minimal coronary atherosclerosis (92%), myocarditis (2%), pulmonary edema (50%), and, in the majority of cases, nonspecific chronic portal triaditis, splenic eosinophilia, and chronic mucosal inflammation with eosinophilia in mucosa of the gastrointestinal tract. Active parasitic disease was not observed in any case, but possible abnormalities of the conduction system were seen in

the hearts of five men. None of these deaths were related to previous exposure to chemical and biological warfare agents in Southeast Asia or to exposure to toxins or to use of alcohol or drugs in the United States.

Recently, Wagner [*40,41*] has attempted to correlate the exposure to "yellow rain" in Southeast Asia with the sudden, unexpected deaths of refugees living in the United States. While the majority of these 51 deaths (57%) did involve Hmong refugees [*39*] only 3 of the Hmong (6%) were reportedly exposed to chemical warfare agents. Myocarditis is not a significant feature in this sudden death syndrome, and it has not been described in mycotoxicosis of domestic and experimental animals. The examination of conduction systems in hearts of five men who died suddenly and unexpectedly has revealed the possibility of developmental conduction system abnormalities rather than reparative inflammatory response and fibrosis [*42*]. It is agreed, however, that focal hemorrhagic necrosis and inflammation of the myocardium may result from acute exposure to tricothecene toxins, that altered sensitivity of the conduction system could occur, and that certain mycotoxins, particularly *S. atra* may have a cytotoxic effect on vascular endothelium. At this time, however, there is no conclusive evidence to associate previous exposure to "yellow rain" with the sudden, unexpected death syndrome among Southeast Asian refugees living in the United States.

There is a worldwide distribution of viral hepatitis caused by hepatitis A and hepatitis B. Both types of hepatitis are endemic in Southeast Asia and may cause malaise, nausea, gastrointestinal inflammation, hemorrhages, hepatic necrosis, and cirrhosis. Viral hepatitis, complicated by either submassive hepatocellular necrosis or massive necrosis, may progress to macronodular, micronodular, or mixed forms of cirrhosis which are not pathognomonic [*43*]. The histologic features of the liver are similar in both hepatitis A and hepatitis B: ballooning degeneration; acidophilic degeneration with acidophilic bodies; intralobular, portal, and bridging necrosis; hypertrophy of Kupffer cells containing lipofuscin or hemosiderin pigment; and portal inflammation. "Ground glass" hepatocytes have been described in patients with persistant viral hepatitis who are carriers of hepatitis B antigen. Cholestasis, bile duct proliferation, and nodular regeneration may also be observed in both types. Okuna and associates [*44*] have compared the histologic features in patients with hepatitis A and hepatitis B using biopsy specimens of liver obtained within 30 days after onset of illness. They did not detect significant differences in the histologic features which included ballooning degeneration, bridging necrosis, portal fibrosis, and cholestasis. Kupffer cell mobilization was more conspicuous in hepatitis B, while portal inflammation, rich in plasma cells, was more evident in hepatitis A. These findings are similar to those of Teixera and associates [*45*] who studied 17 patients with hepatitis A who had liver biopsies from 2 to 27 weeks after onset of illness.

The possibility of viral hepatitis was considered in the present case, for portal inflammation, confluent lobular necrosis, bridging fibrosis, and cholestasis are prominent features. The hepatocytes, however, did not show "ground glass" appearance, or acidophilic degeneration, and the pattern of early micronodular cirrhosis is more extensive than expected for the same duration after onset of illness with viral hepatitis. Serologic studies were not available, but neither aldehyde fuchsin, HB_sAg immunoperoxidase, nor electron microscopic methods revealed antigenic particles or products of the hepatitis B virus.

Finally, the possibility of pathologic effects from nutritional deficiencies requires consideration. Although fatty change of the liver has been observed in children with protein-calorie malnutrition, this pathologic finding is not a feature of the present case. Neither parenchymal cell necrosis, portal fibrosis, nor cirrhosis are findings in protein-calorie malnutrition [*46*]. Deficiency of niacin causes pellagra which may occur in combination with protein-calorie malnutrition. The characteristic features of pellegra include weakness, chronic dermatitis, diarrhea, and central nervous system disorders resembling dementia [*46*]. None of these features are consistent with the acute onset of illness and the pathologic findings in the present case.

To determine the significance of the histologic findings in the present case, comparison may be made with other well-documented conditions of the heart, liver, and kidneys. Based upon

studies of endomyocardial biopsies, Fenoglio [47] has determined the pathologic aspects of acute, rapidly progressive, and chronic myocarditis. Interstitial fibrosis and favorable clinical course were features of chronic myocarditis. The rapidly progressive type of myocarditis also revealed a healing response and fibrosis, but was uniformly and quickly fatal. The histologic findings in the present case are consistent with Fenoglio's description of acute myocarditis manifested by interstitial inflammation, variable myocardial fiber injury, and absence of fibrosis. Although Davies [48] warned that approximately 5% of normal hearts may show insignificant aggregates of chronic inflammatory cells that should not be mistaken for acute nonspecific myocarditis, each section of heart in this case showed foci of inflammatory cells or interstitial hemorrhage. Drug-related myocarditis of the delayed hypersensitivity type may also show interstitial and perivascular infiltration by mononuclear cells, eosinophils, and occasional polymorphonuclear leukocytes, as well as focal myocytolysis and absence of fibrosis [49]. However, neither myocytolysis nor infiltration by eosinophils were significant histologic findings in our case.

Drug-related myocarditis has been compared to acute radiation injury of the heart. In patients who died three to six weeks after atomic bomb radiation, Liebow [50] observed epicardial and myocardial hemorrhage, perivascular edema, and focal myocardial necrosis with infiltration by mononuclear cells. These findings are similar to those in the present case which are suggestive of radiomimetic effect. The abundant wavy fibers and wavy fiber bundles of myocardium, often noted adjacent to hemorrhagic or inflammatory foci in this case, consistently spare the subepicardial and subendocardial regions of the heart. Bouchardy and Majno [51] believe that these wavy fiber changes are the earliest morphologic manifestation of myocardial ischemia. The hearts of patients who die from acute myocardial infarction caused by occlusion and thrombosis of coronary arteries induced by ameboid forms of *P. falciparum* may show epicardial petechial hemorrhages, diffuse miliary hemorrhages without leukocytes, and plugging of vessels by parasites and parasitized erythrocytes [52]. No malarial parasites were seen in sections of heart from the present case.

The histologic features of the liver in this case are not consistent with viral hepatitis, malaria, or nutritional deficiencies. The striking distortion and collapse of the hepatic architecture, however, are reminiscent of halothane hepatotoxicity. Halothane has not only a direct hepatotoxic effect when associated with hypoxia that promotes the reductive formation of toxic metabolites, but also an hypersensitivity or autoimmune effect resulting in hepatic necrosis, particularly after multiple exposures [53]. The histologic changes in halothane toxicity include submassive centrizonal necrosis, variable inflammatory cell components, occasional Councilman bodies, and evidence of parenchymal regeneration [54]. These pathologic features of halothane necrosis are not pathognomonic and by light microscopy are indistinguishable from similar changes in viral hepatitis, or drug-related injury. The third stage of hepatic injury by halothane, as described by Peters [55] parallels the histologic features of the present case. In the second to third week, after injury by halothane, the histologic findings include a compressed collagen network, ductal and pseudoductular hyperplasia, variable extent of cholestasis, and widespread regeneration of pseudolobules. In the present case, the evidence of early fibrosis with demarcation of regenerating cirrhotic nodules 31 days after the chemical attack, as well as the absence of viral markers by electron microscopy, indicates that the hepatotoxicity is not viral-induced. Furthermore, the production of collagen by the second to third week in viral hepatitis would be extremely unusual. The pattern of hepatic injury, similar to that of halothane, may suggest both a direct hepatotoxic effect and a hypersensitivity or autoimmune reaction.

The histologic changes in the kidney in this case are consistent with the hepatorenal syndrome manifested by acute tubular necrosis of the ischemic type. The hepatorenal syndrome is an irreversible, rapid, and nearly always fatal condition. The variable histologic features observed by light microscopy may not reflect the functional severity of the clinical disease. Renal failure may also occur in spite of apparently normal tubular function based upon evaluation of

normal excretion of urinary sodium [56]. When tubular necrosis is evident, the proximal tubules show greater involvement then the distal tubules with interstitial edema, loss of brush borders, and cellular necrosis [57]. Hyalinized, eosinophilic, granular, and pigmented casts are concentrated in the distal convoluted tubules and collecting tubules. The distal tubules are often difficult to distinguish from the distorted proximal tubules [58]. Calcific deposits and leucine crystals have been noted in the tubular lumens [56,58]. The appearance of leukocytes in the interstitium of the vasa recta is a remarkably consistent finding with light microscopy [59]. All of these histologic features were observed and documented in the present case.

As compared to nephrotoxic injury in which both proximal and distal tubules are damaged without disruption of basement membranes, acute tubular necrosis of the ischemic type shows focal, severe tubulorrhexis of the proximal tubules, with relative sparing of distal tubules [60]. The prominence of heme and bile pigments in the lower nephron of the present case may suggest a cause-effect relationship with tubular damage. However, there is no positive correlation of heme pigments to tubular lesions [60] and bile nephrosis may occur without accompanying acute renal failure. In acute tubular necrosis or the hepatorenal syndrome, the dysfunctional proximal tubular segments apparently allow bilirubin to pass unabsorbed to the distal tubular segments, accounting for the variable evidence of casts [60].

The hepatorenal syndrome has been associated with both alcoholic cirrhosis and fulminant hepatic failure from other causes. Ring-Larsen and Palazzo [61] studied the hepatorenal syndrome in an approximately equal number of patients with alcoholic cirrhosis and fulminant hepatic failure. They concluded that the incidence, frequency, pathophysiology, and prognosis of acute renal failure was nearly identical in both clinical situations. Another study also showed that the range of histologic findings in both groups of hepatorenal syndrome were identical [62]. The pathogenesis of the hepatorenal syndrome has been related to abnormal systemic and renal circulation. Because of arteriovenous shunting or significant volume changes in the intravascular and extravascular compartments, the resultant decreased peripheral resistance causes increased resistance in the renal vessels. The glomerular filtration rate is reduced, relative cortical ischemia prevails, and the consequence is acute tubular necrosis [63]. Many substances or processes have been proposed as initiators or facilitators of this cataclysmic event; none have been established or substantiated.

Conclusion

The victim of the attack at Tuol Chrey on 13 Feb. 1982 was among the casualties who had onset of acute symptoms within minutes after exposure to a mixture of chemical agents. He showed signs of recovery during a latent period lasting until 11 March 1982, when he was readmitted to the hospital for evaluation of fever, hemoptysis, anuria, and jaundice. Before his death on 16 March 1982, 31 days after the chemical attack, he was comatose and had evidence of hematuria and hematemesis. The clinical findings, believed originally to represent recurrent falciparum malaria, are consistent with those of tricothecene toxicosis as confirmed by toxicologic examinations. The histologic features of interstitial myocardial hemorrhage and acute myocarditis, early micronodular cirrhosis arising from diffuse hepatic necrosis, and hepatorenal syndrome manifested by acute tubular necrosis of the ischemic type were observed after clinical relapse, death, and autopsy. Light microscopy alone was not sufficient to determine the cause-effect relationship and to establish the diagnostic distinctions. The circumstances of injury, the clinical history, the results of toxicologic studies, and the temporal relationships, as well as the results of special stains and electron microscopy for viral markers, were used to exclude malaria, viral hepatitis, and nutritional diseases. The pattern of injury to the heart, liver, and kidneys, evident within a period of 31 days after exposure, suggests the direct effects of toxic agents, as well as the possibility of hypersensitivity reaction related to the previous chemical exposure on 19 Sept. 1981.

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