Fatal Accidental Diglycolic Acid Intoxication

Arno A. Roscher, M.D.,[1] Eugene Jussek, M.D.,[2]
Thomas Noguchi, M.D.,[3] and Stanley Franklin, M.D.[4]

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INTRODUCTION

Environmental concern about pesticides, air pollution, water contamination with chemicals--phosphate in particular, is well known. This certainly and unquestionably is related to the tremendous increase in chemical technology and, thus, the production of substances which are utilized in many chemical and technical processes and products which ultimately reach the consumer. Stringent toxicity labeling of such substances, such as carbon tetrachloride, phosphorus-containing substances, and many more, have kept accidental fatalities to a minimum and are well recognized. The recent finding of angiosarcoma in persons exposed to vinyl chloride, manufactured widely for a variety of plastics and plastic derivatives, has produced an alarming awareness in environmental concern about chemicals and the need for experimental testing of substances to insure human safety.

Recently, a substance, produced for approximately twenty years, (Diglycolic Acid - HOOC-CH2-O-CH2-COOH-*DUPONT*) has led to a fatal accidental ingestion in a human. Its chemical relationship to ethylene glycol is shown in Table I. Search of the literature as of now has been unyielding of any comparable experience. The only data in the published literature concerning human exposure with diglycolic acid appeared in 1949 (1). This paper describes eye fogging in industrial workers who have contact with the substance; however, this phenomenon is said to be transient, occurs without prior warning, without irritation, and disappears following a period of blurring of vision and/or partial or total blindness within twenty-four to forty-eight hours. This is thought to be on the basis of corneal epithelial swelling and considered a transient phenomenon. A biochemical product data sheet *(DUPONT)* describes the physical and chemical characteristics and the potential uses of the substance in industry. Their data indicate that animal feeding tests suggest that the acid dissolves and is relatively toxic when taken internally. The use in applications which might involve ingestion by human beings or animals should be avoided. Preliminary tests indicate that aqueous solutions below 5% of the acid are no more injurious to the skin than solutions of other organic acids of comparable pH. Reference is also made to temporary blurring of vision, and contact with vapors by workers should be avoided.

SOME USES OF DIGLYCOLIC ACID

Diglycolic acid is a dibasic acid and has been utilized in the manufacture of adhesives, as cleaning compounds for automotive radiator cooling systems, in the chemical industry as organic synthetizers, in buffers for pH control in chemical operations, as a sequestering agent for calcium and iron, and generally as a neutralizing agent. It has been utilized in finishes for coatings for metal and wood. It has been utilized in inks in the form of resins. It is found in metal, petroleum, plastics, rubber, and textile industries for a variety of purposes. It has also found use as a descaling agent for radiators and sterilizer equipment. It is the purpose of this communication to report the first accidental fatal diglycolic acid intoxication in a human. The substance, which has gross superficial similarity with granulated sugar, was accidently and mistakenly ingested as sugar solution, resulting in fatal toxicity.

CASE REPORT:

The accident happened in a general practitioner's office, where a patient was scheduled in association with a general physical for a "glucose tolerance test." The accident occurred January 6, 1968. The patient was a 42-year-old male, Caucasian, the employee of a foreign consulate general of Los Angeles. The patient was given a 100-gram "glucose water solution" for the tolerance test. The patient indicated that the liquid did

[1] Clinical Assistant Professor of Pathology, U.S.C. School of Medicine, Director of Pathology, Granada Hills Hospital and Henry Mayo Newhall Hospital, Los Angeles, CA 91344.

[2] Medical Consultant, German Consulate General, Los Angeles, CA 91344

[3] Chief Medical Examiner-Coroner, Los Angeles, CA ; Clinical Professor of Pathology and Forensic Medicine, U.S.C. School of Medicine, Los Angeles, CA 91344.

[4] Associate Professor of Medicine, U.C.L.A. School of Medicine, Los Angeles, CA 91344.

Requests for reprints should be sent to Dr. Roscher.

not taste very well; however, he was instructed to get it down. He complied. Immediately after the intake, the patient history indicates that he felt a burning sensation in his stomach. He started to gag, and the nurse's assistant notified the doctor immediately; it became immediately apparent that the "glucose" utilized turned out to be a substance called "Peltoner," used for descaling the doctor's autoclave. The Peltoner crystals were in a plastic bag without chemical designation or evidence of warning indicating possible toxicity. The patient was subjected immediately to induced vomiting. Following this, the patient felt better, and he was sent home with instruction to call if any further side effects should develop. The patient was, for most of the remaining afternoon, comfortable; and he was given no further medication except an injection for sleeping. The following morning, the patient experienced pain in both flank areas as well as the right anterior upper abdominal area. Because this type of pain appeared to increase and did not subside, the patient's wife insisted on a consultation (E.J.).

SYSTEM REVIEW:

The patient was seen in the afternoon of the following day by the consulting internist. There were no complaints relative to eyes, ears, nose, and mouth, with the exception of the stated ill taste and burning following the Peltoner ingestion. No problems related to cardiovascular and respiratory system were noted. The patient stated he had burning in his stomach as well as pain in the kidney region and some tenderness over the liver area. The patient indicated that he had pain in the kidneys and, since ingestion of the substance, was unable to urinate.

PHYSICAL EXAMINATION:

At the time of consultation, the patient was a well-built and well-nourished Caucasian, 42-year-old male with pale skin and mild edema of both ankles. Ears, eyes, nose, and mouth were essentially unremarkable. The neck organs were unremarkable. Cardiorespiratory system was essentially unremarkable. There was tenderness in both flank regions; the liver was approximately one finger below the right costal margin and was tender on palpation as well. Remainder of the physical examination was unremarkable.

Because of anuria and the history of ingestion of the "glucose tolerance," which was learned to be "Peltoner," the patient was felt to have suffered some toxicity by a substance not yet known; and immediate transfer to the University Medical Center, in Los Angeles, was carried out. Following the patient's admission to the University Medical Center, the patient was immediately put on hemodialysis. Physical examination at the Center was essentially identical to that performed by the consultant, who was the continuous observer of the consulate during the patient's stay at the Medical Center. X-ray examination on January 7, 1968, included a supine examination of the abdomen as well as PA and lateral chest on the following day. No abnormalities were noted. Initial laboratory data on admission was as follows; hemoglobin 13.7, hematocrit 41%, WBC23,000, Segs. 86%, bands 4%, lymphocytes 1 %, and monocytes 9%. The peripheral smear revealed no abnormalities; however, the platelets appeared to be reduced. Urinalysis revealed 4+ protein, 2+ sugar, pH was 5.5. No blood or ketone were noted. Microscopic examination revealed in the sediment many white blood cells and red blood cells, and no casts apparently were noted. The urine culture was negative. Chemistries on January 8,1968, were as follows: serum creatine 9.2 mg%, BUN 90 mg%. Electrolytes were as follows: serum sodium 131 Meg/L, serum potassium 4.1 Meg/L, chloride 92.8 Meg/L, bicarbonate 15.2 Meg/L, SGOT 320, SGPT 290, calcium 5 mg%, amylase 400 units, bilirubin 1.5 mg%, urine sodium 115 mg, potassium 25 mg, and creatine 15 mg%. (This was performed on a total volume of 4.5 cc. of urine.)

HOSPITAL COURSE:

On January 10, 1968, chest x-ray disclosed infiltrates in the left base with prominence of ,the left hilar vascular structures. On January 13, 1968, discoid atelectasis of the right base, as well as persistence of the left lower lobe infiltrate, was noted. On January 15, 1968, the patient became hypotensive, which initially responded well to Aramine. On January 16, 1968, diffuse bilateral bronchopneumonia was noted. Electrocardiographically, no abnormalities were noted. The patient, during the entire hospital stay, ran a low temperature. During the last day of the hospital stay, the patient became somewhat mentally confused; although no localizing neurological signs developed, the patient did have a spinal tap, which revealed essentially normal ·pressures and no abnormalities of the cell count. The culture of the spinal fluid was negative, but the CNS glucose was elevated (132 mg%), and the protein was 9.1 mg%. In spite of vigorous hemodialysis, the patient continued to deteriorate.· He developed cranial as well as peripheral neuropathy, showed no improvement of liver functions, stayed completely anuric and, in spite of continued hemodialysis, on numerous occasions the patient became severely acidotic. The patient developed increasing respiratory insufficiency, for which he was placed on artificial respiration. During mid-course, the first neurological symptoms appeared and were characterized by inability

to close his eyelids, neuromuscular irritability, as well as loss of speech. On January 17, 1968, the patient went into severe hypotension and bradycardia. He subsequently arrested, and all resuscitative efforts including cardiac massage, intracardiac adrenalin, etc., were unsuccessful. The final clinical diagnoses were: (1) acute renal failure, probably secondary to ingestion of Peltoner (diglycolic acid). (2) central nervous system involvement, probably toxic neuropathy secondary to diglycolic acid, and (3) pneumonia, secondary to uremia, bacterial over- growth, and/or combination of those with associated chemical pneumonitis.

AUTOPSY EXTERNAL AND INTERNAL
GROSS FINDINGS:

The autopsy was performed at the medical examiner's office, in Los Angeles, January 18, 1968, at 3:00 p.m. The body was an unembalmed, well-nourished, white male. The skin was grayish, and there was rigor mortis and lividity. No abnormalities of the head were noted, with the exception of oral mucosal cyanosis and conjunctival petechia. The neck was unremarkable, with the exception of a tracheostomy opening with some yellow fluid around the os. The thorax was unremarkable. The abdomen was flat with no gross palpable organomegaly. A small abdominal incision was noted (from peritoneal dialysis). The extremities were unremarkable except for evidence of recent arteriovenous shunt for hemodialysis. The external genitalia was unremarkable.

INTERNAL FINDINGS:

THORAX: The lungs weighed 1,230 and 1,270 grams, respectively. The lungs were edematous and hemorrhagic and appeared consolidated. There was no hilar adenopathy. BODY CAVITIES: The left and right thoracic spaces contained approximately 500 cc. of clear fluid. ABDOMEN: The abdomen contained approximately 1500 cc. of clear, yellowish-amber-colored fluid. CARDIOVASCULAR SYSTEM: The visceral aspect of the pericardial surface was smooth and glistening; however, petechia were noted. There was no increase in the amount of fluid within the pericardial sac. HEART: It weighed 390 grams. The epicardial surface was smooth and glistening except for petechiae. There was slight ventricular hypertrophy. No dilatation of the chambers except for the right atrium was noted. The valves were thin and delicate. There was no evidence of stenosis or insufficiency. The aorta showed moderate atherosclerosis. The coronary arteries were moderately atherosclerotic with maximum compromise of the LAD to 30% by athero-occlusive process. The remainder of the vascular system was unremarkable. GASTROINTESTINAL TRACT: The esophagus was smooth; however, some superficial erosions were noted. No varices were noted. The stomach contained some turbid, dark gray-brown liquid without suspended food particles. The stomach wall was thin; the mucosal folds were not prominent. No ulcerations were noted. Grossly the duodenum, jejunum, ileum, and colon showed no abnormalities. The appendix was surgically absent. There was no mesenteric adenopathy. The omentum was unremarkable. SPLEEN: The spleen weighed 250 grams. The capsule was smooth. The parenchyma was soft but not liquified. LIVER: The liver weighed 2,340 grams. The capsule was tense, and the lower edge was rounded. The cut surface showed extensive pale, tan-red mottling throughout. The areas of red and tan patchiness varied from 0.5 up to 1.0 cm in greatest dimensions. There were no indurations or tumefactions. GALLBLADDER: The gallbladder was anatomic. The ductal system was unremarkable, and the bile was retained for toxicology studies. There were no calculi. PANCREAS: Unremarkable grossly. KIDNEYS: The perirenal fat was rather hemorrhagic, and the capsule of both kidneys stripped with ease. The combined weight of both kidneys after removal of the capsules was 460 grams. The cortices were edematous and had numerous petechia on the surface. The cut surfaces revealed diffuse cortical circumferential hemorrhage.

The cortical hemorrhage extended from the subcapsular zone down to approximately 0.5 em into the cortical parenchyma. The pyramidal rays were clearly delineated; however, they were also hemorrhagic. The papillae appeared intact and showed no necrotic changes. The intrinsic vascular channels were unremarkable; the ureters were patent, and the pelvic mucosa was unremarkable. BLADDER: Unremarkable. It contained some small amount of yellow fluid consistent with urine. PROSTATE: Unremarkable. SEMINAL VESICLES: Unremarkable. MUSCULOSKELETAL SYSTEM: Essentially unremarkable. No fractures or tumefactions were noted. SCALP AND SKULL: The scalp was unremarkable. There was no evidence of trauma. The dura was unremarkable, and there was no epidural, subdural, or subarachnoidal hemorrhage. The sinuses were anatomic, and no occlusive phenomena were noted. BRAIN: The brain weighed 1,660 grams. It appeared quite edematous; there was compression of the sulci, and the gyri were bulging (Fig. la-b). There was some petechial mottling and dilatation of the superficial subarachnoidal vessels. There was an area of indentation over the right temporal region which was consistent with an old contusion, showing some yellowish discoloration. The remainder of the central nervous system showed nothing grossly remarkable. The same applied to the Circle of Willis. The pituitary was unremarkable. The adrenals, thyroid, and testes were

unremarkable. The bone marrow showed no gross abnormalities.

SUMMARY MICROSCOPIC DESCRIPTION OF AUTOPSY:

The heart revealed areas of fibrosis, interstitial fatty infiltrate, and subepicardial as well as interstitial lymphocytic and plasmacytic infiltrates, non-specific, associated with moderate numbers of polymorphs, as well as with foci of necrosis (Fig. II). AORTA: Moderate atherosclerosis. LARYNX: Status-post tracheostomy with reactive inflammatory infiltrate and laryngitis. LUNGS: Sections of the lungs revealed diffuse, fibrinopurulent exudate, and intraalveolar eosinophilic amorphous proteinaceous matter; no crystaloid matter was noted (Fig. III). SPLEEN: There were leukocytic infiltrates (acute splenitis, reactive). ESOPHAGUS: Erosive esophagitis. GASTROINTESTINAL TRACT: Non-specific gastroenteritis. LIVER: Diffuse mononuclear and polymorphonuclear infiltrates were noted within the periportal triads. Severe central lobular polymorphonuclear infiltrates were noted with necrosis of liver cells. The process was diffuse (Fig. IV). GALLBLADDER: No pathologic diagnosis. PANCREAS: Marked acinar dilatation consistent with uremia (Baggenstoss Syndrome). Foci of fat necrosis were noted, showing leukocytic infiltrates, and fat necrosis with beginning calcification. KIDNEYS: Sections of the kidneys revealed extensive cortical necrosis. The cortical region was in areas severely hemorrhagic and showed various degrees of destruction. The tubules were dilated. They contained red blood cells as well as granular and globular structures. and casts. Also, the tubular structures contained globular spherules which proved to be calcium positive on calcium stain. The intrinsic vascular tree was unremarkable. Some glomerular hyalinization was noted which was considered old. The pyramids showed round cell infiltrate without necrosis (Figs. VI-XI). PROSTATE: Unremarkable. BLADDER: Unremarkable. ENDOCRINE SYSTEM: Adrenals - unremarkable; thyroid unremarkable; testes - unremarkable; pituitary - unremarkable. CENTRAL NERVOUS SYSTEM: Sections of the brain revealed non-specific changes, but perivascular edema was conspicuous (Fig. XII). There was no evidence of tumor, unequivocal inflammation, or necrosis. The intrinsic vascular tree was not remarkable.

FINAL DIAGNOSIS: CARDIOVASCULAR:

HEART - Non-specific chemical myocarditis with edema. LUNGS - Massive terminal bronchopneumonia (shock lung). G. I. TRACT - Non-specific enterocolitis. SPLEEN - Splenitis. LIVER - Massive centro-lobular necrosis. PANCREAS - Pancreatitis with acinar dilatation, multi focal. KIDNEYS - Diffuse, cortical circumferential renal necrosis, with tubular calcium deposits. The remainder of the systems were unremarkable, with the exception of an old cerebral contusion and diffuse cerebro-cerebellar edema. Azotemia, clinical.

DISCUSSION:

From the available clinical history and anatomical and histological findings, it is apparent that diglycolic acid (approximately 100 grams) is a fatal substance which leads predominently to hepatorenal failure due to massive cortical renal and hepatic necrosis. Hepatotoxicity is also rather severe and is essentially characterized by a centrolobular type of necrosis, as seen in carbon tetrachloride and like substances. The kidneys do not reveal the type of intratubular crystal deposits, as seen in ethylene glycol poisoning, where inflammatory and necrotic changes are rather minimal as contrasted to diglycolic acid intoxication (Fig. XIII). The pancreatitis noted in this patient is considered chemical. The hepatorenal derangement following intoxication is characterized by massive circumferential renal necrosis which is histologically characterized by massive hemorrhage, cortical glomerular and tubular necrosis, cast formation, inflammatory change's, as well as calcium deposits in tubules, however, not akin to those seen in ethylene glycol poisoning where inflammatory changes are less conspicuous than the massive oxalate deposits (2).

The centro-lobular necrosis of the liver is considered a direct chemical hepatitis. No peripheral necrosis was noted. The pancreatitis which was noted is considered to be chemical by inference; however, it must be noted that pancreatitis occurs in many conditions. In this instance, it is most probably a direct result of diglycolic acid. The striking acinar dilatation (Baggenstoss Syndrome) is considered the result of pre-renal azotemia. The clinically manifested neuromuscular disturbances and also the patient's other signs of neuromuscular involvement suggest chemical encephalitis. This could not be substantiated histologically; however, significant edema was noted throughout the brain. The neuromuscular disturbances were probably on the basis of micromolecular and electrolyte changes associated with azotemia. Preliminary survival experiments on rats indicate an LD5Q in the order of 500 mg per kg body weight (3).

SUMMARY:

A case of fatal accidental diglycolic acid intoxication is presented, which represents the first recorded case of such an incident in the World Literature. The substance, diglycolic acid, is utilized in a multitude of chemical op-

erations and has been manufactured for approximately twenty years; however, no human data in relation to intoxication have appeared up to now. The paper depicts the clinical gross 'anatomical and histopathological findings of this type of intoxication.

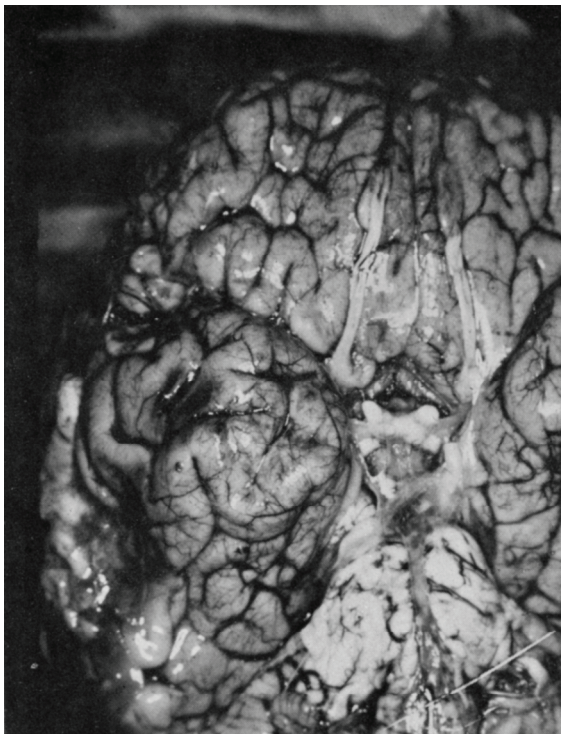

Fig. Ia
Brain of patient showing marked cerebral and cerebellar edema as well as tonsillar herniation. (Mag. reduced 1/2 from normal.)

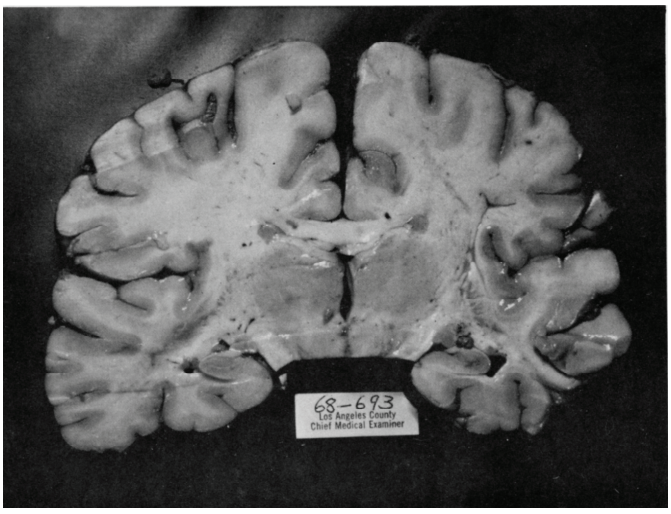

Fig. Ib
Coronal section showing marked edema, some petechiae, and flattening of the gyri. (1/2 normal size.)

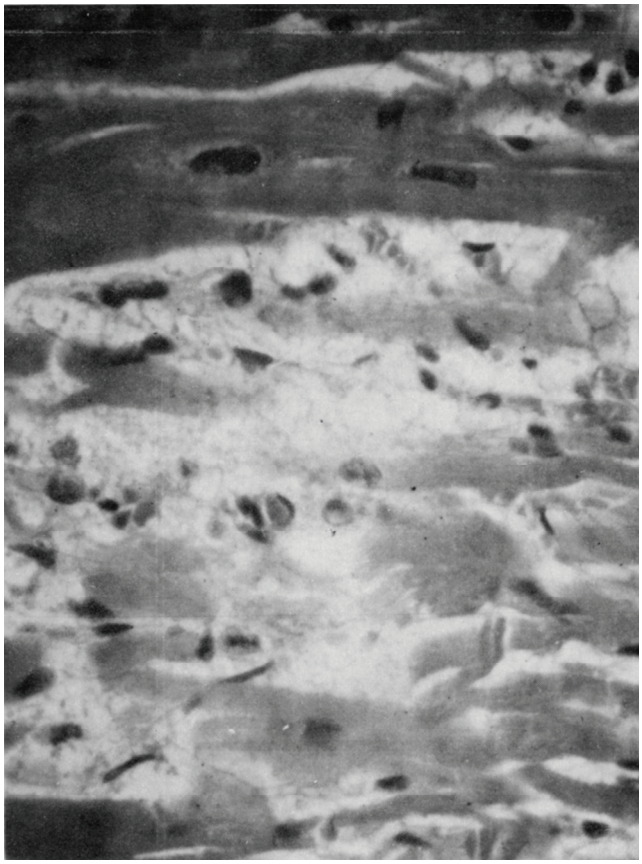

Fig. II
High-power magnification of heart section showing myocytolysis, inflammatory infiltrate, and edema, indicative of toxic myocarditis. (Mag. 450, H&E.) Contraction bands are quite prominent.

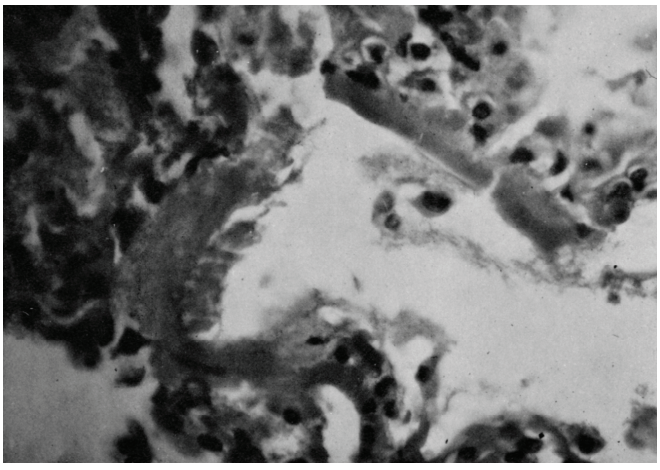

Fig. III
High-power magnification of lung showing inflammatory infiltrates as well as hyaline membranes indicative of shock lung syndrome. (Mag. 450, H&E.)

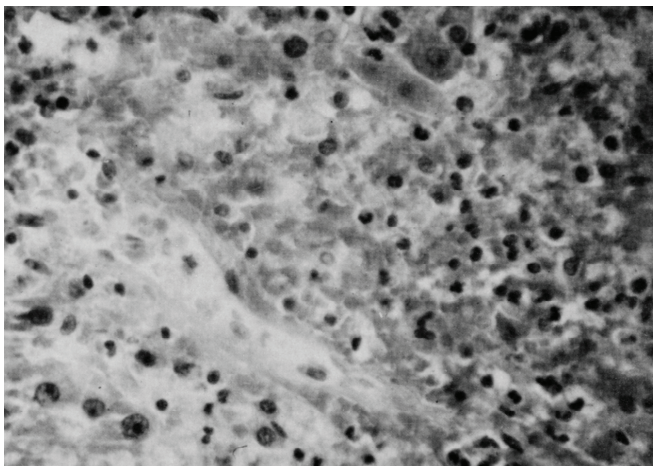

Fig. IV
High-power magnification of central lobular area of the liver showing central lobular hepatocytic degeneration: leukocytic infiltrates, and peripheral sparing of the hepatocytes. (Mag. 450, H&E.)

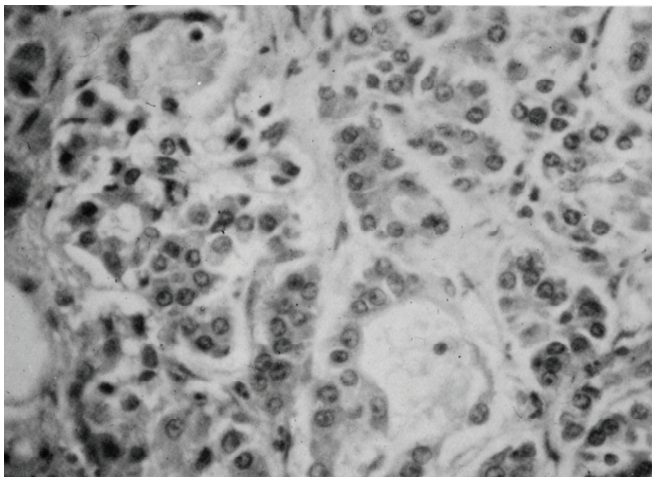

Fig. V
High-power magnification of pancreas showing conspicuous acinar dilatation (Baggenstoss Syndrome) typical for uremia. (Mag. 450, H&E.)

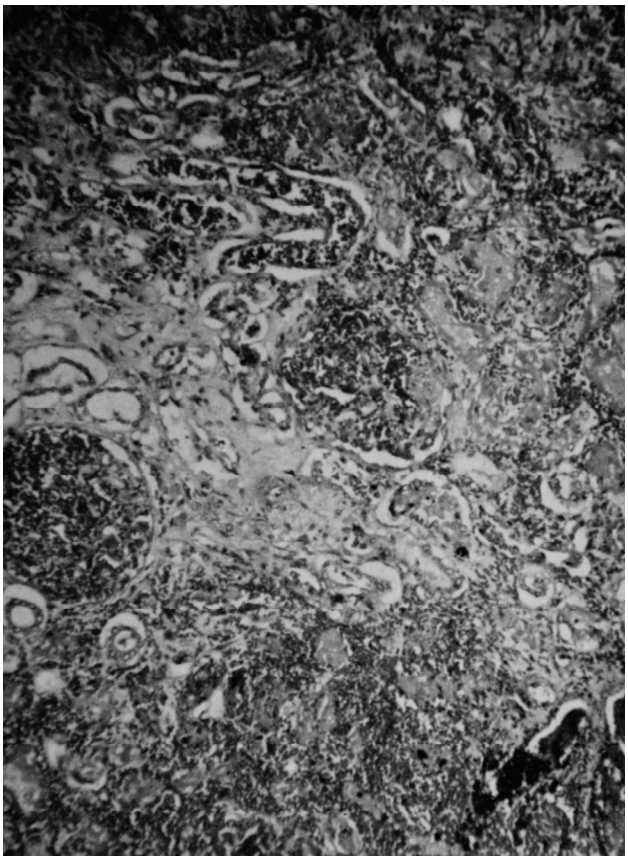

Fig. VI
Low-power magnification of kidney showing massive tubular and glomerular hemorrhage as well as diffuse degenerative necrotizing changes. (Mag. 100, H&E.)

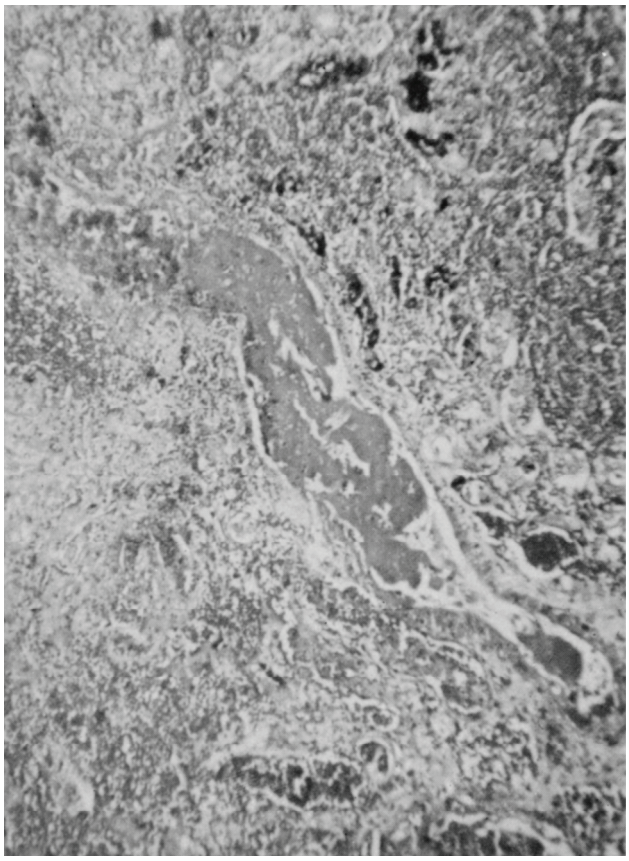

Fig. VII
Low-power magnification of medullary portion of kidney showing massive intratubular proteinaceous material deposition, red cell casts, and peri tubular calcification. (Mag. 100, H&E.)

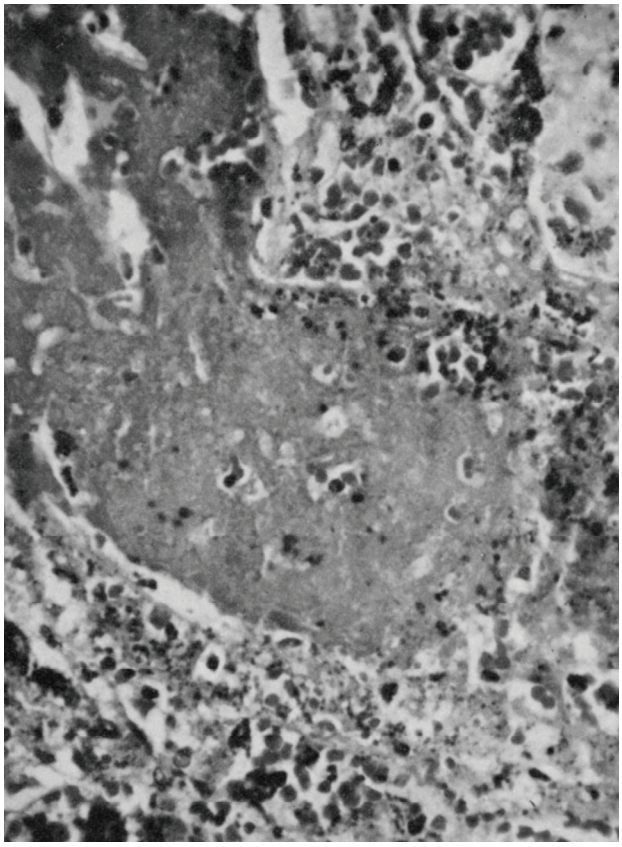

Fig. VIII High-power magnification of tubules showing marked distention, proteinaceous material, peritubular calcification, necrosis. (Mag. 450, H&E.)

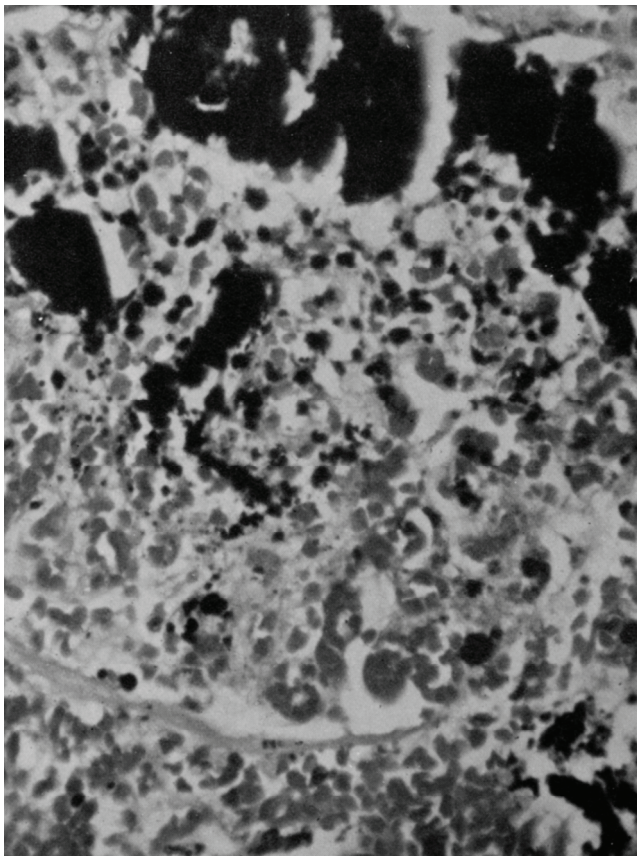

Fig.IXa
High-power magnification of single glomerulus showing necrosis of glomerular capillaries, peri-glomerular and intraglomerular calcification, and necrosis. (Mag. 450, H&E.)

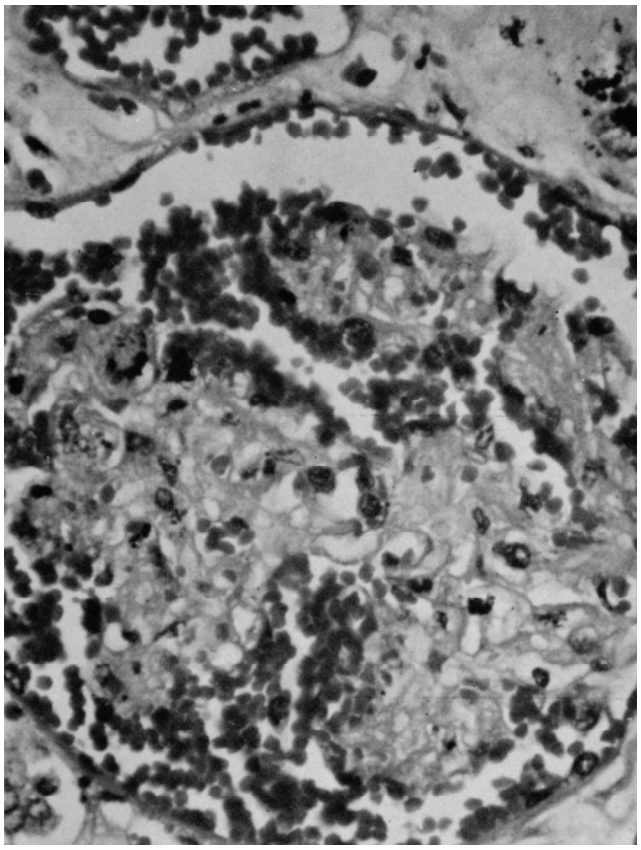

Fig.IXb Hemorrhage into Bowman's space. (Mag. 450, H&E.)

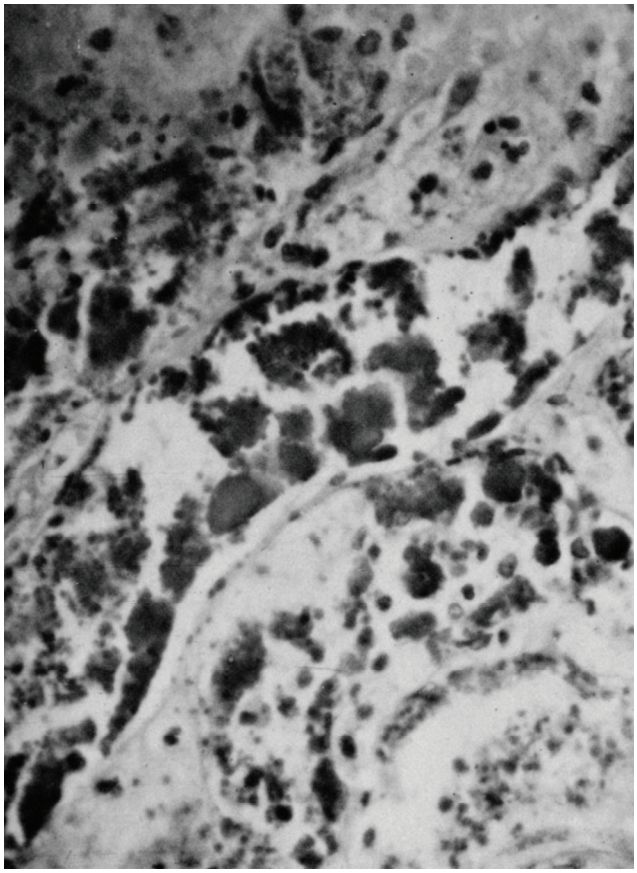

Fig. X
High·power magnification of tubules showing peritubular and intratubular calcium deposits and some necrotizing changes. (Mag. 450, H&E.)

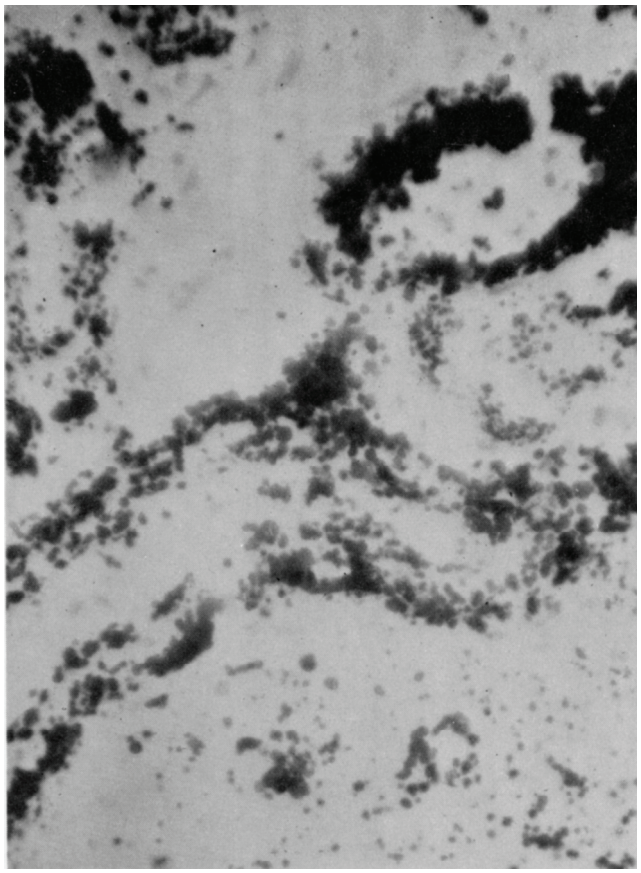

Fig. XI
Same as figure X with calcium stain showing peritubular calcifications, massive, little intratubular calcification. (Mag. 450, von Kossa's Stain.)

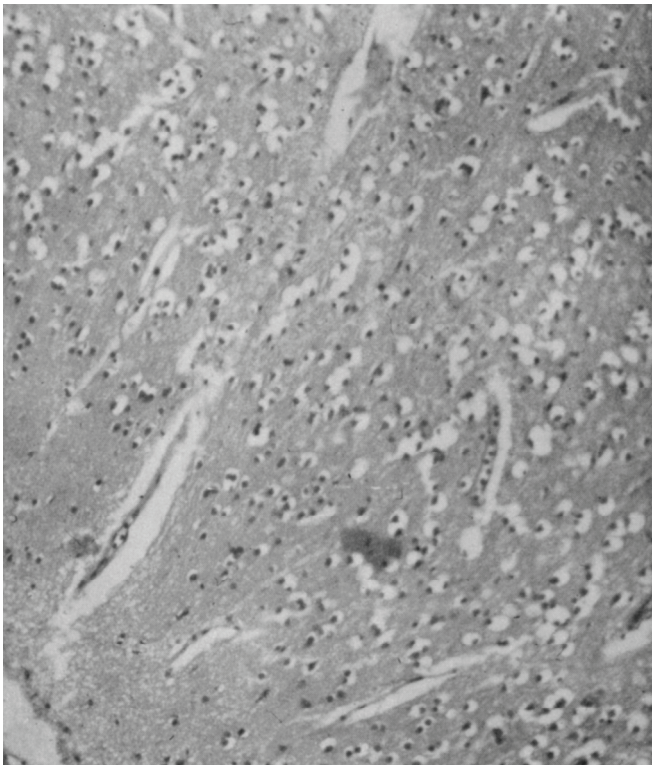

Fig. XII
Low-power magnification of brain showing conspicuous, diffuse, perinuclear edema and perivascular edema. (Mag. 100, H&E.)

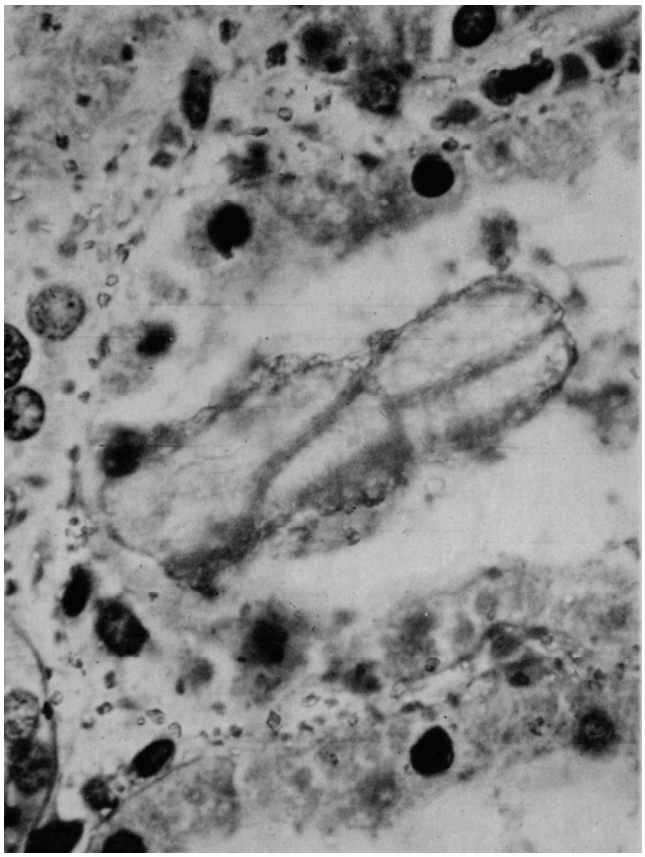

Fig. XIII
High-power magnification of renal tubule showing large calcium oxalate precipitate within tubules without associated inflammatory process in case of ethylene glycol poisoning. (Mag. 450, Naphalhydroxamic acid stain.)

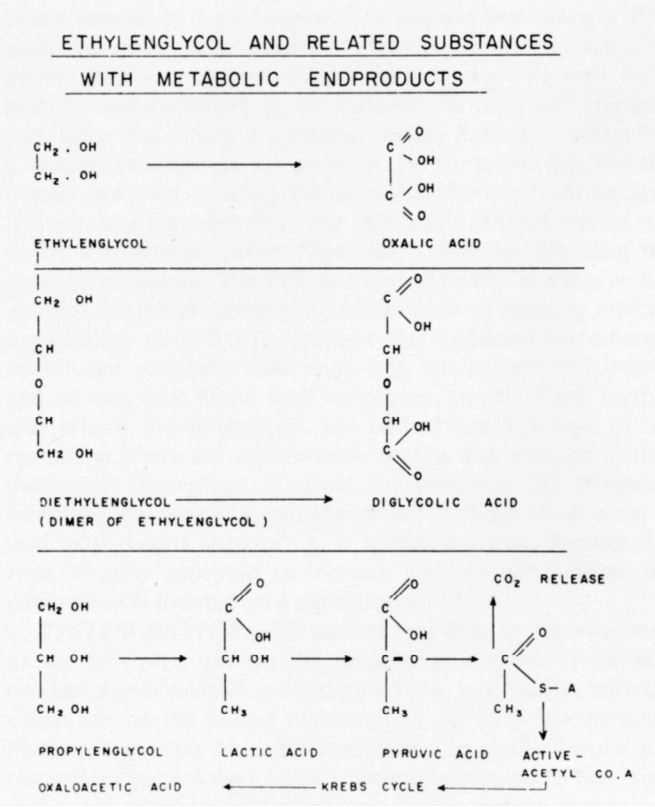

Table I. Schematic relationship of various glycols (ethylene glycol, diethylene glycol and its respective acids, oxalic acid, and diglycolic acid, including metabolic break-down).

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