MERCURY TOXICOSIS IN THE PIG

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ABSTRACT

MERCURY TOXICOSIS IN THE PIG

by William J. C. Donnelly

Research was conducted using 12 pigs assigned in pairs to the following groups: (1) control, (2) 2 mg. mercuric chloride ($HgCl_2$) per kilogram ration, (3) 20 mg. $HgCl_2$ per kilogram ration, (4) 100 mg. $HgCl_2$ per kilogram ration, (5) 200 mg. $HgCl_2$ per kilogram ration, and (6) 2 Gm. $HgCl_2$ per kilogram ration.

Signs of clinical disturbance developed on the 5th day in both animals fed the high level of $HgCl_2$. One of the pigs fed 200 mg. per kilogram ration had signs of acute illness on day 19 and died. Clinical signs included anorexia, staggering gait, emaciation, and diarrhea. None of the remaining pigs became clinically ill.

Gross lesions noted in the clinically affected pigs included a paleness of the renal cortex, generalized hemorrhages, and a pseudomembrane formation in the colon. Microscopic lesions included neuronal necrosis and vacuolation, necrosis and regeneration of renal parenchymal tissue, and focal hepatic coagulation necrosis.

Individual susceptibility appeared to be an important factor in mercuric chloride toxicosis in the pig, since there was little correlation between the amount of mercuric chloride ingestion per unit of body weight and the degree of toxicosis.

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By

William J. C. Donnelly

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The writer wishes to acknowledge his gratitude to the Department of Pathology, Michigan State University, for the many favors, courtesies, technical assistance, and financial support in conducting this research and making my visit to Michigan such a worth-while experience.

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INTRODUCTION

The treatment of seed grains by mercurial fungicides has resulted in the exposure of livestock to a possible source of mercury poisoning. Animals may fortuitously gain access to the treated grain; or the farmer, in the interests of economy, may use it for the compounding of a ration. Naturally occurring episodes of mercurialism have been recorded in swine following the ingestion of treated grain.

Variability in the biological activity of mercurial compounds is known to depend not only on their mercury content but also on their molecular structure (Hughes, 1957, and Garner, 1961). Nevertheless, characterization of the clinical and pathologic aberrations produced by the inclusion of a simple inorganic mercurial compound at varying concentrations in the ration of swine would provide information hitherto unavailable in this species.

This project was designed to furnish such information with particular reference to toxic levels of mercuric chloride and the clinical signs and pathologic changes induced by this compound in growing swine.

REVIEW OF THE LITERATURE

King (1957), in a brief resumé of the history of mercury in chemistry and medicine, stated that mercury compounds were used as drugs in Greece by Hippocrates around 400 B.C. Occupational mercury poisoning in man was described by Jean Fernel in 1557 (Goldwater, 1957). At this time Paracelsus advocated the use of mercury as a treatment for syphilis, for which condition it became regarded as a specific remedy; and it continued in this role as a therapeutic agent until the introduction of the organic arsenical Salvarsan by Ehrlich in 1912 (Haggard, 1929). Haggard stated,

> "Patients with syphilis were dosed with mercury internally and rubbed with it externally until the saliva flowed from their mouths in a steady stream, their teeth were loosened and their health permanently impaired by mercury poisoning."

Thus, in human medicine the disease entity was early recognized and the clinical changes documented.

Early reports of toxicosis in domestic animals are rare. Cases, presumably as a result of ingestion, have been reported in dogs (Green et al., 1938) and cats (Gorton, 1924). Two reports of poisoning in cattle subsequent to the application of mercurial ointment to the skin illustrate the susceptibility of ruminants to the toxic action of the element. Stevens (1938) recorded a case of dermal necrosis in a calf. A young bull was also poisoned after licking the mercurial ointment which had been applied to the back of the calf. Petrelius (1953) experimentally demonstrated the susceptibility of the bovine and ovine species to inhalation of mercury vapor generated after the application of ointments to the skin of the horse.

McNew (1959) traced the development of mercurial compounds as fungicidal cereal seed dressings. Corrosive sublimate was used in the late 18th century for this purpose, and this was later supplanted by organic mercurial compounds. McNew attributed the development of these preparations to Riehms in 1913 following Ehrlich's success with organic arsenicals. Within 3 years, organic mercurials were introduced into the United States, and as much as 512,000 pounds of mercury equivalent went into this use each year.

Edwards (1942), in England, reported the death of a 9-year-old horse following ingestion of grain treated with mercury. Boley et al. (1941) and Herberg (1954) reported cases in feeder calves and dairy cattle, respectively, in the United States. Sonoda et al. (1956), in Japan, investigated the clinical manifestations in 29 cattle fed treated seed grain, and the pathologic changes in these animals were documented by Fujimoto et al. (1956). Experimental work on the pharmacologic action of an organic mercurial in 6-month-old calves was described by Oliver and Platonow (1960). Palmer (1963) reported the toxicity of the same compound (ethyl mercury p-toluene sulfonanilide) for sheep and chickens.

Toxicosis was first reported in swine by Taylor (1947), who described sickness and death of a sow and 8 shoats following feeding of seed grain treated with a fungicidal mercurial preparation containing 1% ethyl mercury phosphate. One ounce of the preparation was added to each bushel of corn, and 1.5 gallons of this treated corn was added to 3.5 gallons of untreated corn to comprise the daily ration. The ration was fed for about 2 months before the onset of signs. Signs of toxicosis were observed over a period of almost 3 weeks. These included anorexia, weakness, paralysis, convulsions, blindness, and loss of condition.

There were no gross pathologic changes. There was an "appreciable" quantity" of mercury in the liver. Kernkamp (1963), in referring to the work of Ferris et al. (1949), described a controlled study in pigs fed undiluted treated grain. The pigs fed the treated grain for over 20 days had signs of illness and died after an additional 5 to 10 days. When pigs were fed the treated grain for only 10 days, no disorders developed and they reached market weight. In a case report, McEntee (1950) described the clinical signs and microscopic lesions associated with mercurial poisoning in 2 droves of swine after prolonged feeding with seed oats treated with a mercurial fungicide. Signs included inappetance, vomiting, paralysis, blindness, locomotor disturbance, and a possible glossopharyngeal paralysis. Characteristic gross lesions were not described. Histopathologically, there was coagulation necrosis of epithelial cells lining the convoluted tubules of the kidney and neuronal degeneration in the brain.

In summary, toxicoses arising from the absorption of mercury occur in a number of species. Those publications which described mercurialism in swine pertained, in general, to naturally occurring episodes and provided only limited information on toxic levels and on the clinical signs and pathologic lesions.

MATERIALS AND METHODS

Experimental Animals, Housing, and Care

One litter of 12 Yorkshire-Hampshire crossbred 4-week-old pigs was purchased from a local swine farm, and each pig was placed in an individual galvanized metabolism cage. Twelve days of acclimatization elapsed before commencement of the experimental regimen. Observation of the piglets during this period revealed no clinical abnormalities.

Each piglet was identified and the group was divided into 6 pairs by random numbers according to Goulden (1956). Pigs were fed once daily in troughs attached to each cage. Water was given *ad libitum*. Records were kept of food consumption. Clinical signs of disease were observed and recorded. The animals were weighed at the beginning of the experiment and weekly thereafter.

Ration. The pigs were fed the standard Michigan State University, Animal Husbandry Department, grower ration. For the period of acclimatization, each pig was fed 400 Gm. daily of this feed. Mercuric chloride ($HgCl_2$) was added to the ration at the levels indicated (TABLE 1). Pair I (controls) received no mercuric chloride. The concentrations of $HgCl_2$ ranged from 2 mg./kg. basic ration in Pair II to 2 Gm./kg. basic ration in Pair VI. The ration for each animal was increased to 500 Gm. daily on day 6, with the exception of Pair VI, whose food consumption had decreased by this time. The ration was again increased to approximately 600 Gm. daily on day 18 and continued at this level until termination

TABLE 1. Identification of pigs assigned to each pair, initial and final weights and concentration of mercuric chloride ($HgCl_2$) in ration.

Pair No.	Pig No.	Sex	Weights		Avg. Daily Gain (Gm.)	Concentration of $HgCl_2$ (mg./kg. ration)
			Initial (kg.)	Final (kg.)		
I	5	M	8.2	24.1	468	control
	10	F	10.0	25.5	456	control
II	3	F	10.0	24.5	453	2
	11	M	11.8	22.7	373	2
III	1	M	6.8	18.6	600	20
	8	F	9.1	18.6	327	20
IV	6	F	9.5	25.5	500	100
	12	M	7.3	18.2	376	100
V	2	M	8.2	20.9	410	200
	9	M	6.8	13.6	358	200
VI	4	F	8.2	10.9	90	2000
	7	F	6.4	7.3	33	2000

of the experiment. Pigs were fed the experimental ration for 28 to 34 days and necropsied on the days indicated (TABLE 2).

Mercury. The mercury was in the form of the inorganic salt, mercuric chloride ($HgCl_2$). The requisite amounts of the salt were measured on a Mettler balance. Four kilograms of the salt-meal mixture for each pair of experimental animals were prepared at one time. The dry preparation was mixed at a slow speed for 5 minutes in an electric feed mixer. At a later date, when 8 kilograms of mixture were prepared, the time of mixing was increased to 10 minutes.

On day 14 molasses was added to the ration of those pigs in Pair VI in an attempt to increase palatability. Eight Grams of $HgCl_2$ were dissolved in 1200 ml. of molasses. One hundred fifty milliliters of this solution (containing 1 Gm. $HgCl_2$) was mixed with 500 Gm. of feed, the final weight of the mixture being 670 Gm. Fresh feed was prepared as required. Unconsumed food was weighed at 3-day intervals.

Urine Analyses. Urine was examined at weekly intervals during the course of the experiment and collected aseptically from the urinary bladder at necropsy. All urine samples were screened for glucose, protein, and pH using proprietary indicator strips.* Specific gravity was routinely recorded on all samples.

Blood Analyses. Blood samples were collected from the anterior vena cava, as described by Carle and Dewhirst (1942), using 10-ml. syringes

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*Combistix, Ames Company, Incorporated, Indiana.

TABLE 2. Total amount of mercury consumed to date of necropsy and organ weights at necropsy.

Pig No.	Day of Necropsy	Total $HgCl_2$ Consumed (mg.)	Organ Wts. at Necropsy (Gm. and % B. Wt.)			
			Liver	Right Kidney	Left Kidney	Spleen
5	34	control	727(3)*	62(.26)	68(.28)	55(.23)
10	34	control	761(2.9)	60(.24)	59(.23)	51(.20)
3	32	33.0	459(1.9)	45(.18)	41(.17)	31(.13)
11	30	29.6	459(2.0)	45(.19)	41(.18)	26(.11)
1	31	310.8	391(2.1)	40(.22)	34(.18)	35(.19)
8	29	280.0	460(2.5)	42(.23)	38(.20)	22(.12)
6	32	1670.0	609(2.4)	60(.24)	61(.24)	28(.11)
12	29	1440.0	401(2.2)	42(.23)	43(.24)	15(.08)
2	31	3100.0	425(3.0)	63(.30)	61(.29)	30(.14)
9	19	1580.0	525(3.9)	60(.44)	65(.48)	50(.37)
4	30	8270.0	317(2.9)	68(.62)	67(.62)	21(.19)
7	28	6550.0	348(4.8)	35(.48)	40(.55)	8(.11)

*( ) = % body wt.

with 1½-inch, 20-gauge needles. Five milliliters each of clotted and whole blood were collected. The anticoagulant was potassium ethylene diaminotetraacetic acid (EDTA). Smears for total and differential white cell counts were prepared immediately and stained with Wright's stain as described by Benjamin (1964). The cyanmethemoglobin method was used for the estimation of hemoglobin (Benjamin, 1964).

Serum samples collected on days 1, 21, and terminally were examined for blood urea nitrogen (BUN) levels using a modification of the direct chemical method of Friedman (1953) as recommended by the manufacturers of the reagents used.*

A bilirubin estimation was carried out on the serum collected from pig number 4 using a spectrophotometric method (Giordano-Pestrud, Modified) as described by Levinson and MacFate (1961).

Necropsy Procedure. With the exception of pig 9, which died on day 19, all the experimental animals were electrocuted and necropsies performed. Prior to death the animals were weighed and terminal blood samples and rectal temperatures taken. The liver, spleen, and both kidneys were removed and weighed. Tissue sections were prepared from the following: cerebrum, cerebellum, medulla oblongata, thoracic and lumbar spinal cord, liver, kidneys, spleen, heart muscle, salivary gland, urinary bladder, skin, duodenum, jejunum, ileum, and colon. Skeletal muscle, lymph nodes, and stomach were taken from selected cases. The tissues were placed in 10% neutral formalin for fixation. Sections were cut at 5 microns and stained with Harris' hematoxylin and eosin. All histopathologic methods used are described in the Manual of Histologic and Special Staining Technics of the Armed Forces Institute of Pathology, Washington, D.C. (1957).

*Hycel, Incorporated, Texas.

RESULTS

General Observations

Pig 9 died on day 19 of the experiment, manifesting an acute terminal syndrome. Pigs 7 and 4 were euthanatized on days 28 and 30, respectively, having manifested signs commonly associated with chronic disease of enteric origin. Definitive clinical signs of disease or gross pathologic changes were not demonstrable in the other animals. The total amount of $HgCl_2$ consumed by each animal throughout the experimental period and organ weights are given (TABLE 2). An increase in kidney weight is evident in pig 4.

Clinical Signs

Acute. On day 13, pig 9, having consumed a total of approximately 1.05 Gm. $HgCl_2$, had slight but noticeable petechiation of the skin of the base and outer surface of the ears. There was marked petechiation the following day on the skin of the back, shoulders, sides, and medial surface of the thighs. In some areas these hemorrhages were ecchymotic and purple. There was a large ecchymotic hemorrhage on the sclera towards the medial canthus of the right eye, and there were many petechiae on the skin of the snout. Skin irritation was not manifested. On day 16 the nictitating membrane of the left eye had protruded and was hemorrhagic. The central areas of many of the larger petechiae and ecchymoses of the skin were black and necrotic. On day 18 the pig was reluctant to rise but had no signs of incoordination. At 7 a.m. on day 19, it was very weak, and the

rectal temperature was 103 F. It was found dead at 12:30 p.m. on day 19. Total $HgCl_2$ consumed up to this time was 3.1 Gm.

Chronic. There were signs of chronic toxicosis in both animals (numbers 7 and 4) of Pair VI. On day 5, there was partial anorexia and a slight diarrhea, and it was estimated that each pig had consumed about 3.5 Gm. $HgCl_2$. Food consumption was markedly reduced, and there was weakness of the posterior limbs by day 8. Diarrheic, dark-colored, fetid feces were passed. Deterioration in condition occurred more rapidly in pig 7. On day 21, pig 7 had jaundice which persisted until necropsy. Weight gains in both animals were negligible (TABLE 1). There was almost total inappetance in both animals from day 21 until necropsy. The addition of molasses did not increase food consumption. The water intake of pig 7 was reduced. Signs of illness included hind leg weakness, swaying motion when walking, crossing of the hind legs, and collapse. The hind legs were drawn forward when standing and during forward progression were moved stiffly, without free joint action. The only evidence of abdominal pain was intermittent grinding of the teeth during the last 2 weeks of the experiment. The hindquarters were stained with fecal material (Figure 1).

Pathology

The most marked gross and microscopic changes were in pigs 4, 7, and 9. These are described in detail.

Brain and Spinal Cord

Gross Lesions.

Pig 9. A large submeningeal hemorrhage obscured the surface of the

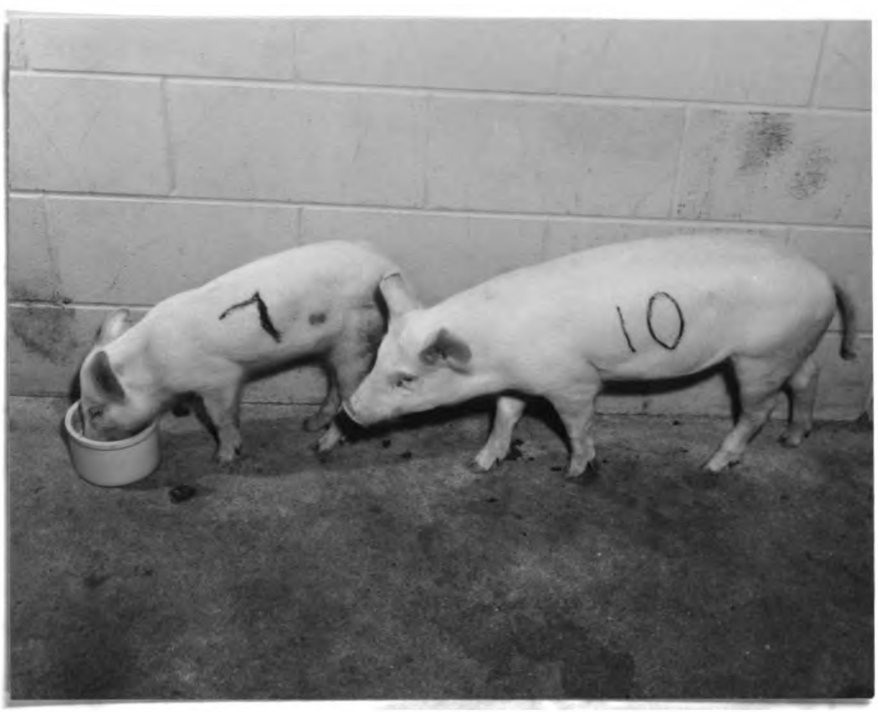

Figure 1. Pigs 7 (2 Gm. $HgCl_2$/kg. ration) and 10 (control) on day 22. Pig 7 has a retardation of growth and fecal material adhering to the rear quarters.

right frontal lobe of the cerebrum. There were many petechiae on the superficial and cut surfaces of the brain. The spinal cord was normal.

Pigs 4 and 7. The only gross change was congestion of the meningeal blood vessels.

Histopathologic Examination.

Pig 9. Hemorrhage, as reported under gross lesions, was present. There was no evidence of a breakdown of the extravasated red blood cells. Edema in the meninges and in the Virchow-Robin spaces was evident. There was vacuolation, swelling, and loss of Nissl's substance in the neurons of the gray matter of the thoracic spinal cord (Figure 2). Hemorrhage and accumulation of macrophages and lymphocytes were adjacent to the central canal of the thoracic spinal cord.

Pigs 4 and 7. Focal glial proliferations, hemorrhages, and edema were in the proximity of blood vessels in the cerebrum (Figures 3 and 4). The meninges were edematous and contained focal petechial hemorrhages. There was neuronal degeneration in thoracic and lumbar portions of the spinal cord.

Kidney

Gross Lesions.

Pig 9. The kidneys were pale gray and stippled with a few petechiae (Figure 5). The pale coloration was localized in the cortex. There was an area of reddening at the corticomedullary junction. Petechial hemorrhages were present throughout the cortex, and there were ecchymotic hemorrhages in the pelvic area which extended into the medulla.

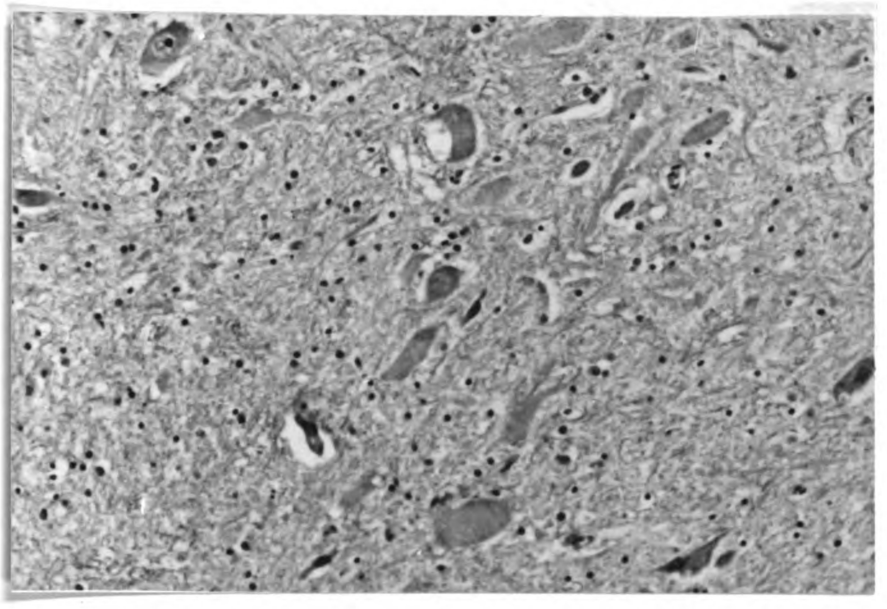

Figure 2. Thoracic spinal cord from pig 9 on day 19. Neuronal vacuolation and swelling with loss of Nissl's granules. Hematoxylin and eosin. x 187.5.

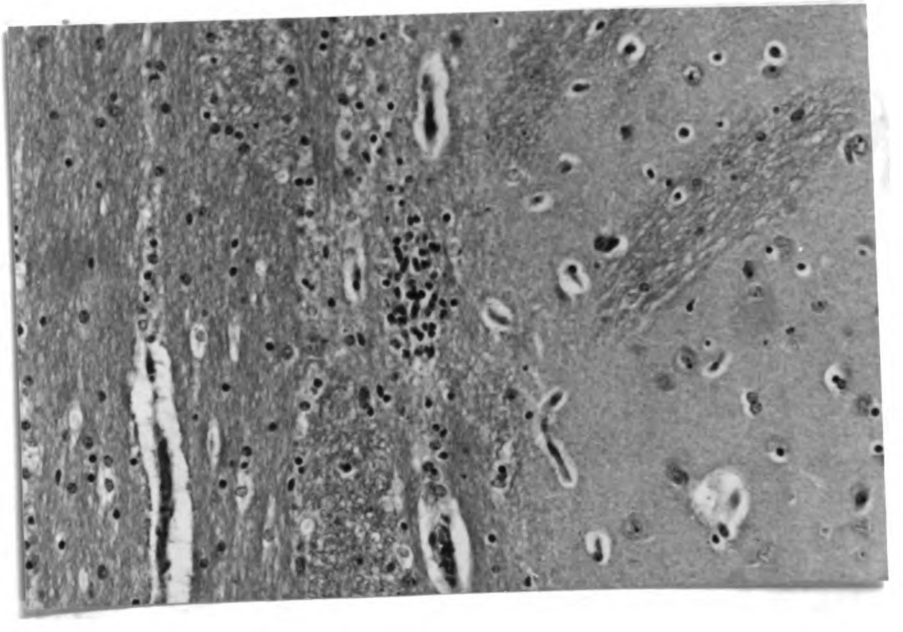

Figure 3. Cerebrum from pig 7 on day 27. Focal glial proliferation. Hematoxylin and eosin. x 75.

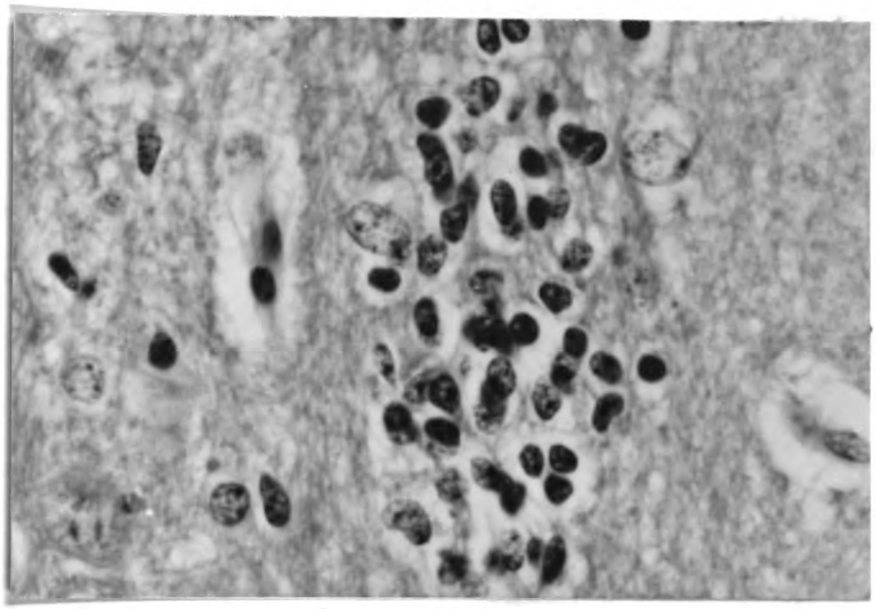

Figure 4. Cerebrum from pig 7 on day 27. Detail of glial proliferation in Figure 3. Hematoxylin and eosin. x 750.

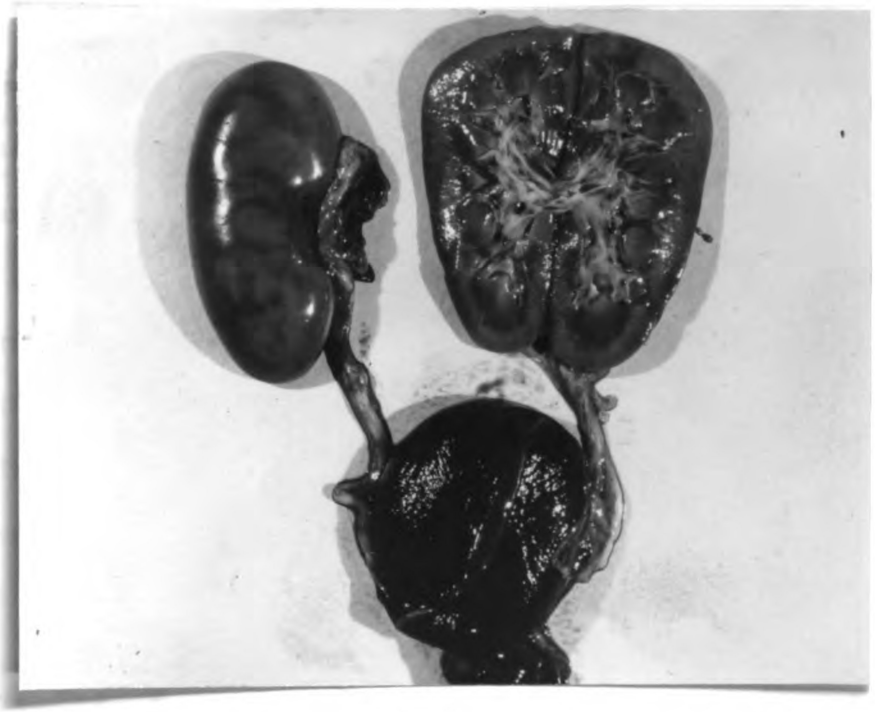

Figure 5. Kidneys, ureters, and urinary bladder from pig 9 on day 19. Dark hemorrhagic bladder and diffuse surface petechiation on kidney.

Pigs 4 and 7. The renal cortex was pale.

Histopathologic Examination.

Pig 9. There were hemorrhages and edema in the capsule. Many of the glomeruli were atrophic with pyknotic nuclei and vacuolation of the cytoplasm. Some of the epithelial cells lining the convoluted tubules were pyknotic and some had cloudy swelling. Many of these cells were desquamated into the lumens (Figure 6). There were scattered interstitial hemorrhages in the cortex and medulla. Margination of the chromatin in the nuclei of the transitional epithelium lining the pelvis was observed (Figure 7).

Pigs 4 and 7. Many glomeruli were atrophic. There was cloudy swelling of many of the epithelial cells lining the convoluted tubules, with some pyknosis and desquamation of epithelium (Figure 8). Regenerative processes were widespread throughout the tissue. In these areas the cellular cytoplasm was more basophilic and the nuclei were large, vesicular, and contained prominent nucleoli (Figure 9). A few mitotic figures were seen. There were scattered dilated tubules with flattened lining epithelium, some containing desquamated cells and albuminous material (Figure 10). There was an interstitial fibroblastic reaction and occasional foci of lymphocytes. Perivascular edema was demonstrable.

Urinary Bladder

Gross Lesions.

Pig 9. The organ was dark red and contained approximately 40 ml. of orange-colored urine (Figure 5). The redness was the result of severe

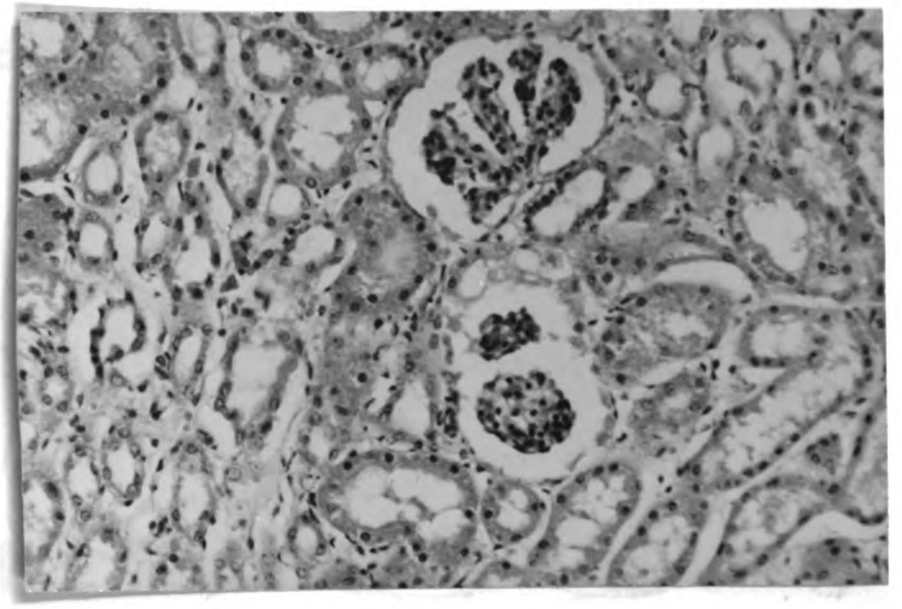

Figure 6. Kidney from pig 9 on day 19. Atrophic glomeruli, pyknotic nuclei, and desquamation of cells of the convoluted tubules. Hematoxylin and eosin. x 187.5.

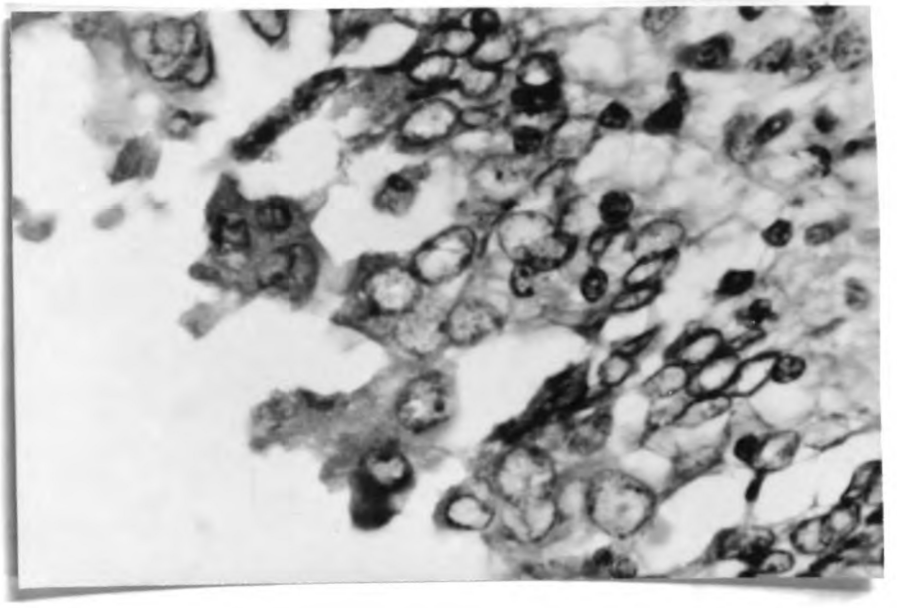

Figure 7. Kidney from pig 9. Degeneration of transitional epithelium of renal pelvis with margination of nuclear chromatin. Hematoxylin and eosin. x 187.5.

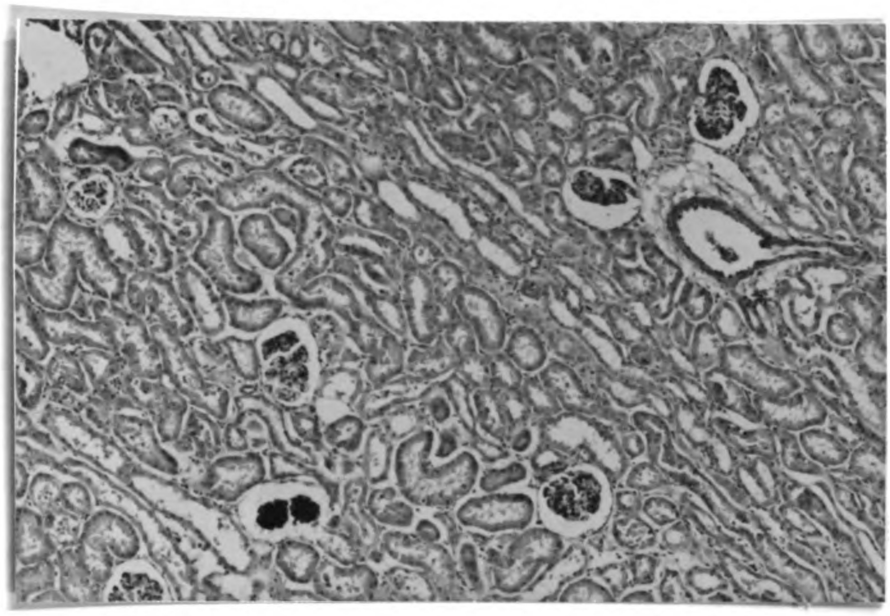

Figure 8. Kidney from pig 7. Atrophic glomeruli, desquamation of tubular epithelium, and perivascular edema. Hematoxylin and eosin. x 75.

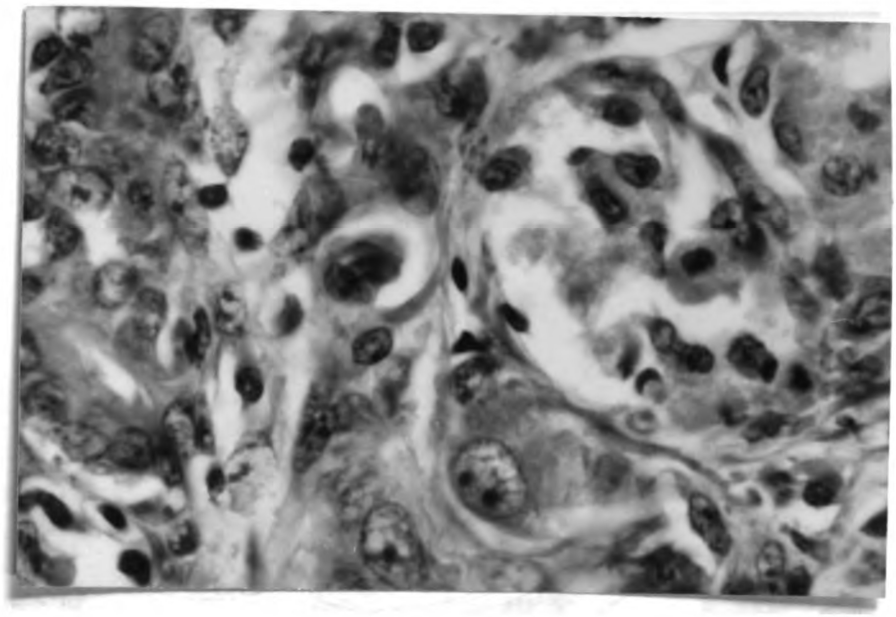

Figure 9. Kidney from pig 4. Desquamated epithelial cells with pyknotic nuclei and proliferating cells with large vesicular nuclei and prominent nucleoli. Hematoxylin and eosin. x 187.5.

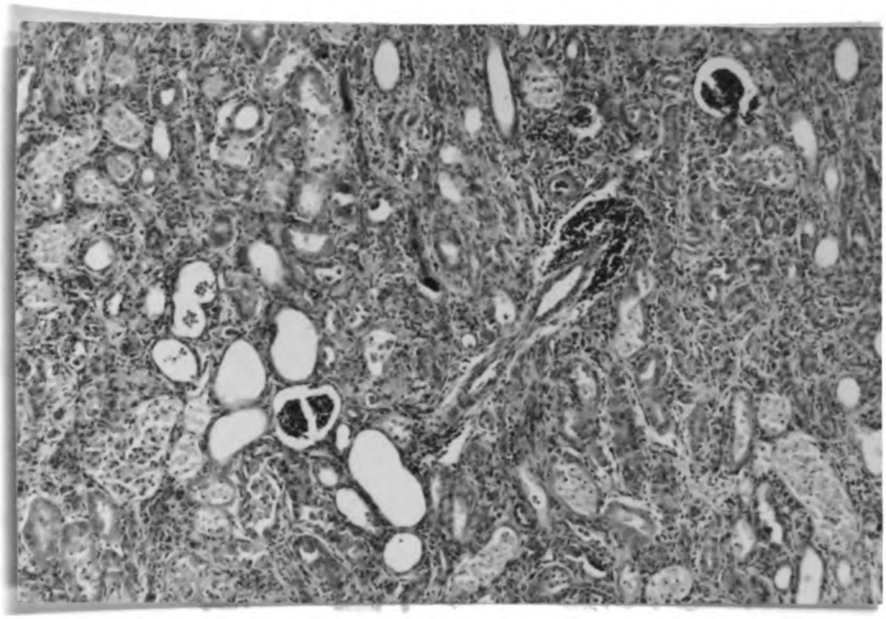

Figure 10. Kidney from pig 7. Necrotic dilated tubules and foci of lymphocytic infiltration. Hematoxylin and eosin. x 75.

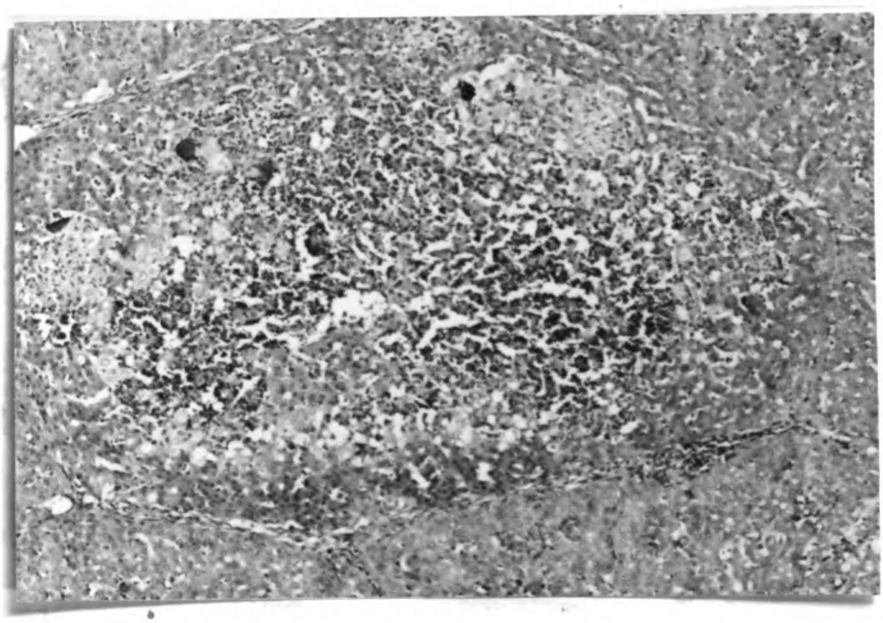

Figure 11. Liver from pig 7. Centrolobular coagulation necrosis. Hematoxylin and eosin. x 75.

hemorrhage in the muscularis. The mucosal surface had irregular dark red areas which were most numerous in the fundus and abated towards the urethral outlet. There was an abrupt change to normal epithelium on the urethral side of the sphincter.

Pigs 4 and 7. No gross lesions were observed.

Histopathologic Examination.

Pig 9. There was a hemorrhagic infiltration of the urinary bladder wall from the mucosal to the serosal surfaces. Atrophy and pyknosis of the smooth muscle cells were prominent. The atrophy in places was advanced, leaving areas almost devoid of musculature. Much of the transitional epithelium was desquamated, and the remaining cells were atrophic.

Pigs 4 and 7. There was coagulation necrosis of the transitional epithelium with pyknosis and loss of cellular integrity.

Liver

Gross Lesions.

Pig 9. The organ was pale yellow-brown with a well demarcated lobular structure.

Pigs 4 and 7. The liver of pig 7 was brownish-red and had well demarcated lobules. The peripheral zone of the hepatic lymph node was bile stained. No changes were observed in pig 4.

Histopathologic Examination.

Pig 9. There were focal discrete areas of coagulation necrosis of

irregular intralobular distribution, and these were lightly infiltrated with neutrophils, fibrin, and red blood cells. The remaining hepatic cells had cloudy swelling and cytoplasmic vacuolations. The degenerative changes were most pronounced in the centrolobular regions. There was a slight increase of fibrous connective tissue and edema in the regions of the portal triads, with moderate increases in numbers of lymphocytes, neutrophils, and eosinophils.

Pigs 4 and 7. Widespread parenchymal degeneration was demonstrable in pig 7 (Figure 11). There were irregularly distributed areas of focal coagulative necrosis similar to that reported in pig 9. In association with these areas, there were small, irregular "bile lakes" (Obel, 1953) (Figure 12). There was sinusoidal dilatation and many Kupffer cells contained pigment similar to hemosiderin. The severity of the centrolobular necrosis was again a notable feature. In pig 4, in which there was no discernible gross change, there was edema of the portal triads, sinusoidal dilatation, and degeneration of the parenchymal cells. The Kupffer cells again contained pigment resembling hemosiderin, but they were less affected.

Heart

Gross Lesions.

Pig 9. The cardiac musculature was diffusely affected by hemorrhage. Ecchymotic hemorrhages extended from the subepicardial and subendocardial regions deep into the musculature of the left ventricle. The entire musculature of the right ventricle was hemorrhagic and dark red (Figure 13). There were subepicardial and subendocardial petechiae of both atria.

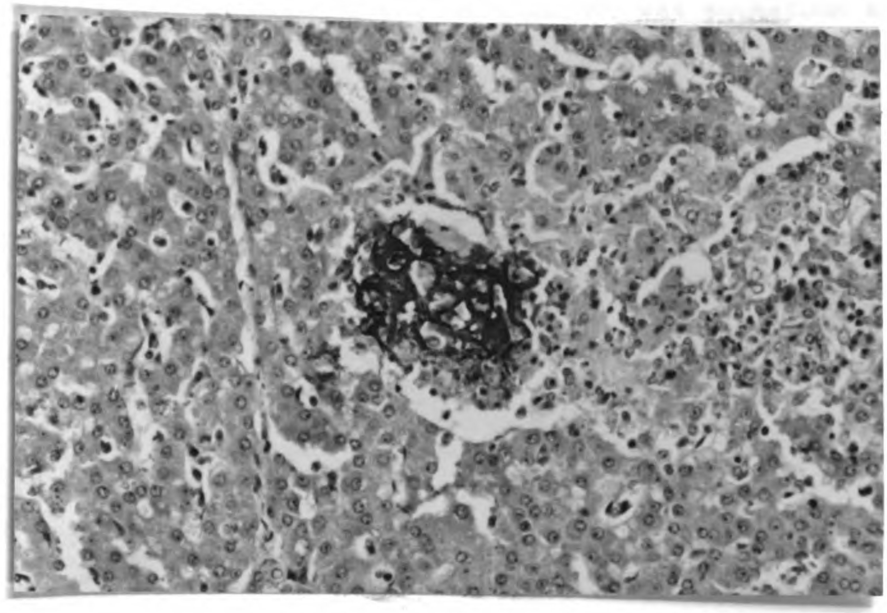

Figure 12. Liver of pig 7. "Bile lake" with adjacent necrotic hepatic cells and a mild neutrophilic infiltration. Hematoxylin and eosin. x 187.5

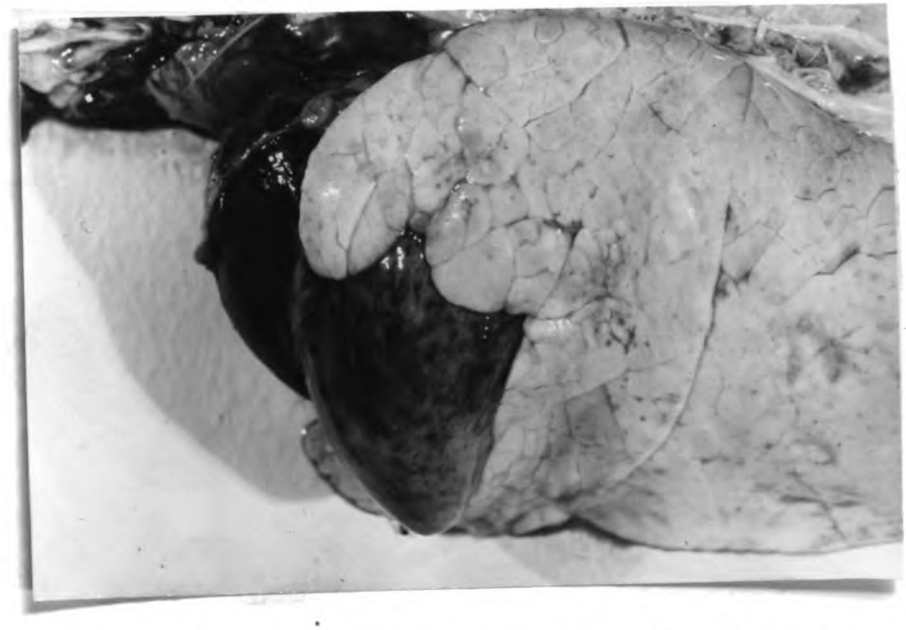

Figure 13. Heart and lung from pig 9 on day 19. Subepicardial hemorrhage with total involvement of the right ventricle.

Pigs 4 and 7. No gross changes were detectable in the muscular tissue. In pig 7 the fat of the coronary groove was edematous and appeared similar to serous atrophy.

Histopathologic Examination.

Pig 9. There were many hemorrhages in the myocardium, which were often infiltrated with neutrophils and lymphocytes (Figures 14 and 15). There was an interstitial and perivascular edema. A wide variation in the size, shape, and density of the myocardial nuclei was noted. Anitschkow myocytes were present (Figure 16). Small foci of coagulation necrosis were detectable, and these were often associated with hemorrhagic areas.

Pigs 4 and 7. Hemorrhage, though present to some degree, was not a noticeable feature. There were numerous Anitschkow myocytes.

Colon

Gross Lesions.

Pig 9. There were hemorrhages on the serosal and mucosal surfaces. No gross mucosal ulceration was detectable. The contents of the organ were bright yellow and of normal consistency.

Pigs 4 and 7. The mucosal surface was covered by a yellowish-white, thick, necrotic material which was easily detached. In some areas the mucosa was speckled with small points of black discoloration. These may have represented petechial hemorrhages with digestion of the blood. The contents of the organ were sparse, fluid, and yellow. The terminal

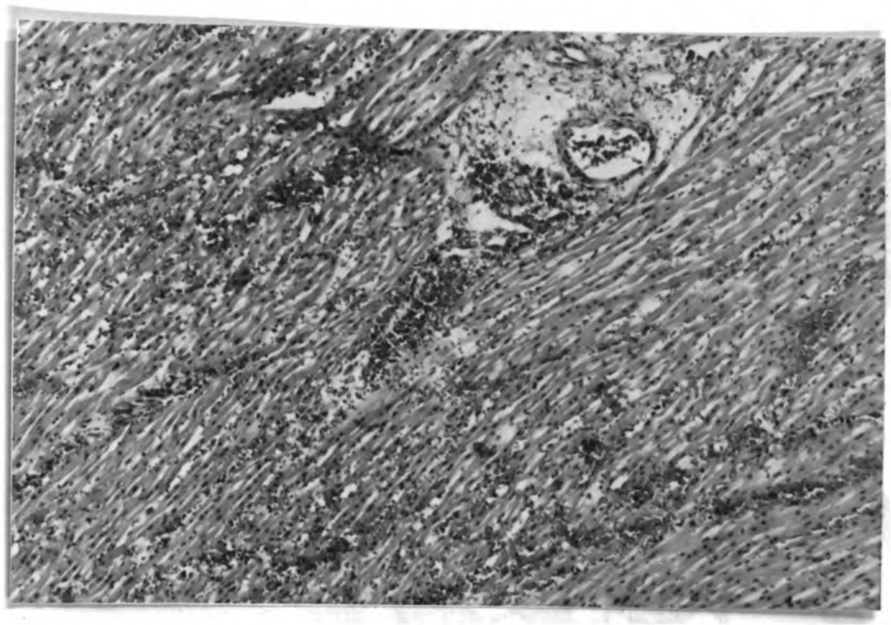

Figure 14. Heart from pig 9. Areas of hemorrhage and perivascular edema. Hematoxylin and eosin. x 75.

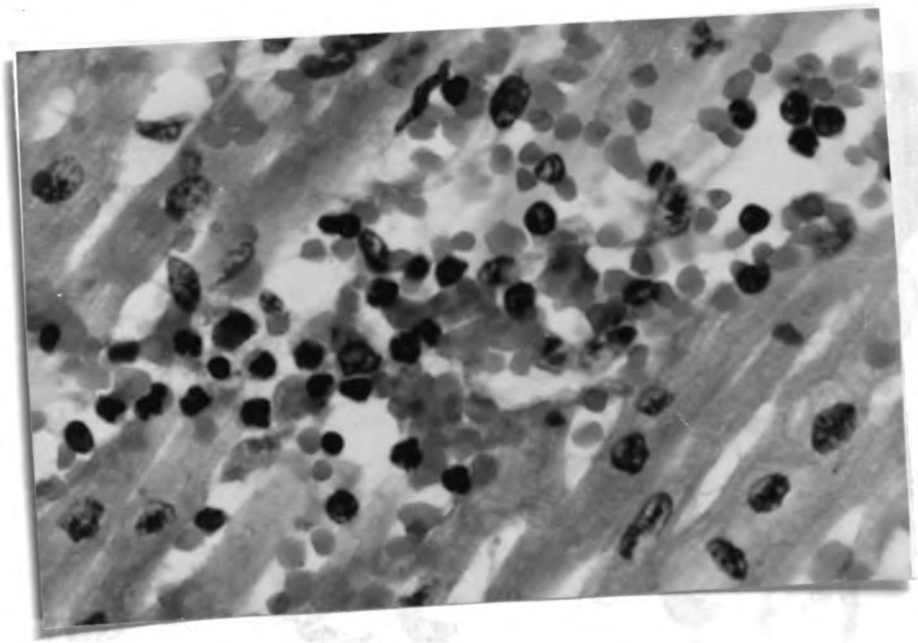

Figure 15. Heart from pig 9. Hemorrhage with infiltration of neutrophils and lymphocytes. Hematoxylin and eosin. x 750.

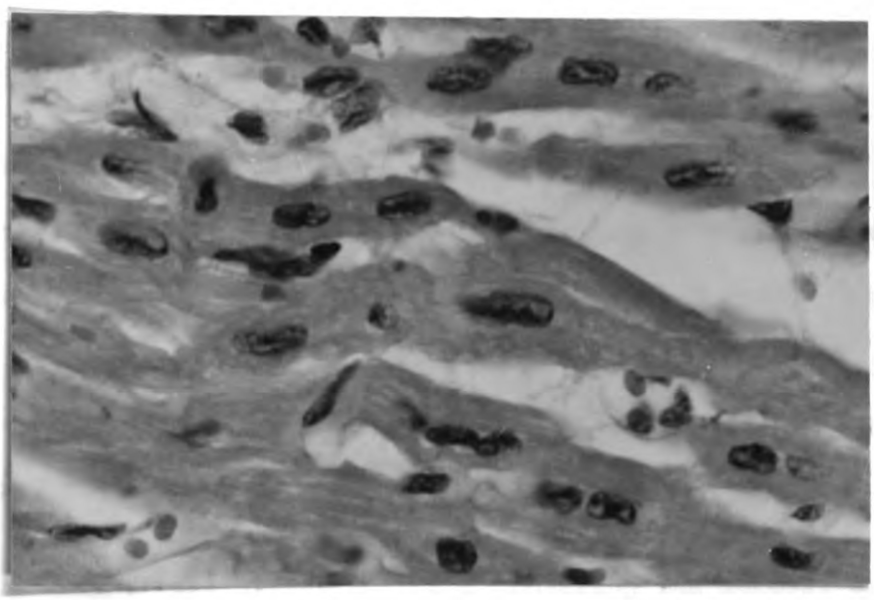

Figure 16. Heart from pig 9. Anitschkow myocytes. Hematoxylin and eosin. x 750.

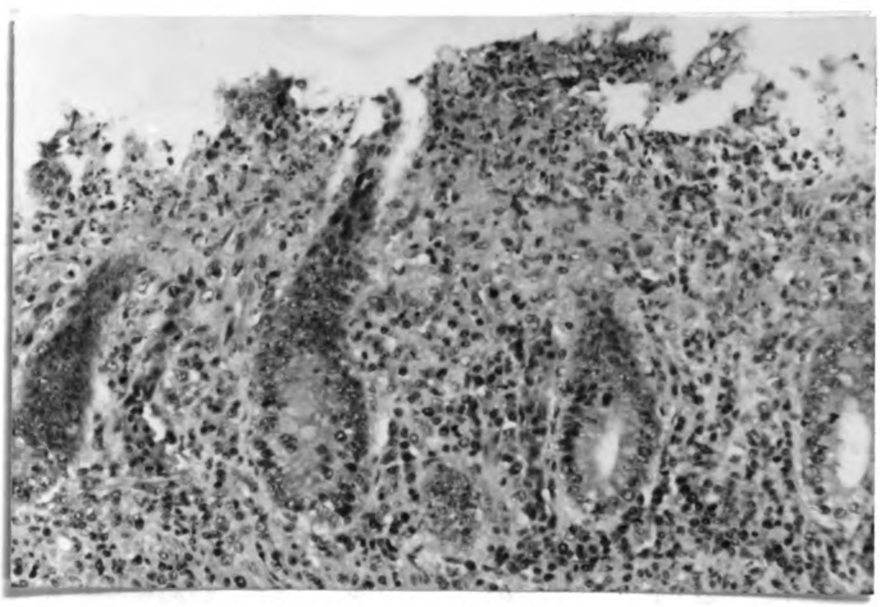

Figure 17. Colon from pig 7. Necrosis and degeneration of mucosa with leukocytic infiltration and surface debris. Hematoxylin and eosin. x 187.5.

24 inches of the mucosal surface of the ileum in pig 4 were also necrotic.

Histopathologic Examination.

Pig 9. There was coagulation necrosis of cells within the crypts of Lieberkühn. Individualization, opaque eosinophilic cytoplasm, and nuclear margination of chromatin were common to these necrotic cells. There was swelling of the cells at the base of the crypts. Large areas of hemorrhage dissected the muscular layers and in some locations involved the submucosa.

Pigs 4 and 7. The "false membrane" covering the mucosal surface consisted of a thick layer of necrotic debris containing the degenerative nuclei of many neutrophils and lymphocytes (Figure 17). The necrosis extended into the submucosa and in many areas obliterated the muscularis mucosae. Granulation tissue infiltrated by macrophages and a few other inflammatory cells represented the reparative process in the area. The villi in the ileum of pig 4 were necrotic and structurally indiscernible. Recognizable cells at the base of the crypts were pyknotic. A band of cellular reaction beneath the necrotic debris was composed mainly of neutrophils and lymphocytes. There was congestion of submucosal blood vessels.

Hematology

The results of hemoglobin, hematocrit, and total and absolute differential leukocyte counts are given (TABLE 3). Pig 4 had a neutrophilia with a shift to the left. Pig 7 had similar changes in the white cell count and a fall in the hemoglobin content to 8.6 mg./100 ml. The BUN level in pig 4 at death was elevated to 200 mg./100 ml. The result of a total serum bilirubin analysis on pig 7 before death was 6.5 mg./100 ml.

TABLE 3. Hemoglobin, hematocrit, and total and absolute and differential leukocyte counts of pigs fed mercuric chloride.

Pair No.	Ear No.	Expt. Day	Hb. (mg./100 ml.)	Hct. (%)	Total WBC	Absolute Differential Leukocyte Count					
						PMN	Stab.	Lymph.	Mono.	Baso.	Eosin.
		-1	10.7	34	17,300	4498	865	9,861	2076	---	---
	5	23	11.3	37	16,200	6480	972	7,452	1134	---	162
		34	11.8	36	12,400	4464	124	6,968	744	---	---
I											
		-1	11.3	37	16,000	2240	320	11,520	1440	160	320
	10	23	11.6	38	18,300	3477	1098	12,444	732	366	183
		34	13.0	40	18,000	5220	180	11,880	720	---	---
		-1	11.5	38	16,200	2430	1782	10,530	1134	---	324
	3	23	12.5	41	21,100	5064	211	13,926	422	844	633
		31	12.3	39	24,300	9963	---	13,365	243	---	729
II											
		-1	10.8	34	19,300	4632	579	15,703	386	---	---
	11	23	11.5	38	15,100	3926	453	10,268	---	---	453
		30	11.3	37	28,700	10905	861	15,785	861	---	287
		-1	11.3	35	20,300	3451	812	14,210	812	---	1015
	1	23	12.6	41	25,300	7084	253	17,457	253	---	253
		31	13.0	40	23,400	3276	---	18,486	1170	---	468
III											
		-1	clotted	---	---	---	---	---	---	---	---
	8	23	12.2	40	19,400	3104	---	15,520	582	---	194
		28	12.1	38	21,000	6090	---	14,280	---	---	630

TABLE 3--continued

Pair No.	Ear No.	Expt. Day	Hb. (mg./100 ml.)	Hct. (%)	Total WBC	Absolute Differential Leukocyte Count					
						PMN	Stab.	Lymph.	Mono.	Baso.	Eosin.
		-1	9.6	32	29,200	11,388	3796	11,096	2336	---	584
	6	23	11.8	39	20,400	5,916	1224	13,260	---	---	---
		31	11.2	36	22,600	6,102	---	14,238	1808	226	226
IV											
		-1	clotted	---	---	---	---	---	---	---	---
		23	12.2	40	14,500	3,480	435	9,135	725	435	290
		28	12.0	40	18,000	7,380	900	9,000	360	180	180
		-1	clotted	---	---	---	---	---	---	---	---
	2	23	13.0	42	21,000	9,240	---	10,710	420	420	420
		31	13.2	44	24,400	5,368	---	17,812	488	244	488
V											
		-1	11.3	34	19,700	7,289	985	7,683	2955	---	788
	4	23	12.6	43	34,600	8,650	4844	16,608	4498	346	346
		30	10.0	36	34,500	17,595	3795	12,075	1035	---	---
VI											
		-1	10.4	34	20,900	8,360	627	8,569	1881	209	1254
	7	23	9.6	33	41,000	16,810	15,170	4,510	4510	---	---
		28	8.6	30	36,200	11,584	10,498	3,620	10,498	---	---

Changes in Remaining Pigs

Changes in the parenchyma of the liver, kidney, and heart were discernible in 5 other pigs (numbers 1, 8, 6, 12, and 2) fed $HgCl_2$. These same pigs had no clinical signs or gross lesions. The changes were minimal in the 4 pigs in Pairs III and IV. Pig 2, from Pair V, had cloudy swelling of the renal convoluted tubules, and this was limited to a comparatively small number of nephrons. The pigs in Pair II and the control animals in Pair V were normal.

DISCUSSION

Clinical

This research using a highly soluble inorganic mercury salt gave results suggestive of individual variation in susceptibility to the toxicosis. Signs developed in pig 9 after a total of 1.58 Gm. $HgCl_2$ had been consumed; however, in pig 2, 3.1 Gm. $HgCl_2$ was consumed without any clinically detectable changes.

Both animals in Pair VI, fed 2 Gm. of $HgCl_2$ per kilogram basic ration, gave early indications of toxicosis. The acute form of mercury poisoning, as described by Kernkamp (1964), was not observed. Clinical disturbance did not appear until experimental day 5, when the estimated amount of ingested mercuric chloride was 3.5 Gm. per pig. Approximately 0.1 Gm./kg. body weight was consumed by these pigs up to this time. Figures quoted by other authors on the toxicity of organic mercurial compounds for species other than swine demonstrate that much smaller amounts of these compounds are required to produce clinical signs and death (Boley, et al., 1941, and Palmer, 1963). Death did not occur in the pigs in Pair VI of this experiment. Signs of the chronic toxicosis increased in severity in the 2 pigs as the experiment progressed. The sudden rise in BUN level in pig 4 on experimental day 30 may have been an indication of approaching death. A rapid terminal rise in BUN levels was noted by Oliver and Platonow (1960) in experimentally induced toxicosis in 6-month-old calves. They attributed it to an acute renal failure.

Clinical variation in the individual response of pigs 4 and 7 was found. The rise in BUN level in pig 4 has already been mentioned. No significant change in BUN levels was demonstrable in pig 7. In this animal, however, jaundice was clinically detectable on experimental day 21. The serum in blood samples taken from this pig after the development of clinical jaundice was yellow. A serum bilirubin estimation was carried out on a blood sample taken immediately prior to euthanasia. The total serum bilirubin concentration was 6.5 mg./100 ml. These clinical indications of extensive hepatic damage were confirmed histologically.

Taylor (1947) and McEntee (1950) have described naturally occurring outbreaks in which definite neurologic disturbances were noted. There was some difficulty in assessing the clinical manifestations of incoordination and staggering gait occurring in the pigs in Group VI of this experiment, since deterioration in condition produced lassitude and weakness. No disturbance in vision or convulsions were detectable.

There was no laboratory evidence of kidney damage until the rise of the BUN level in pig 4 described earlier. Goldwater (1957) has pointed out that there is uncertainty as to whether or not occupational mercury poisoning in man due to inorganic compounds produces such laboratory evidence.

Pathological

In the present investigation the 3 pigs (numbers 4, 7, and 9) which were clinically affected also had grossly demonstrable lesions. There was evident paleness of the renal cortex in all 3 cases. This was the only lesion common to all pigs. Hughes (1957) stated that the pathologic

effects of mercury on human tissues are the result of real concentrations of the element in the affected organ. Most analytical data on tissue concentrations of mercury both in man and the domestic animals indicate that mercury is found in highest concentration in the kidneys (Boley et al., 1941; Drill, 1958; Fujimoto et al., 1956). It is to be expected, therefore, that these organs would be abnormal in appearance if sufficient time had elapsed from primary contact with mercury. Glomerular changes have not been previously reported in the pig. Atrophic changes in the glomeruli were observed in pigs 4, 7, and 9. The necrosis and regeneration of the tubular epithelium corresponded to that described by McEntee (1950).

The histologic changes in the brain and spinal cord were similar to those described by McEntee (1950) but also included neuronal vacuolation and focal glial proliferation. Drill (1958) stated that the prolonged systemic action from mercuric salts is manifested by damage to the capillary bed and at sites of excretion. The neuronal damage in the pigs of this series could thus be due to anoxia. Both Taylor (1947) and McEntee (1950) reported blindness and paralysis in pigs fed organic mercurials. Certain organic mercurials, for example the methyl mercury halides, are 100 times more soluble in lipids than in water (Hughes, 1957), and their action could be attributed to selective deposition in nervous tissue. It would seem that the comparative lack of definitive nervous symptoms and lesions in this experiment may be due to the nature of the compound administered.

Hepatic damage was found in the 3 clinically affected cases in this series. It was most evident in pig 7, which had a clinical icterus and gross evidence of liver change. The distribution of the intralobular

focal necrosis was difficult to explain. Few normal liver cells were found. Taylor (1957) stated that mercury was found in appreciable quantities in the liver in those pigs dying after eating seed grain treated with 1% ethyl mercury phosphate. Ogilvie (1932) described a cloudy swelling of the liver in rabbits given $HgCl_2$. Fujimoto *et al.* (1956) also described focal hepatic necrosis in cases of mercury poisoning in cattle due to "Ceresan", an organo-mercuric fungicide.

The necrosis of the mucosa of the colon in pigs 4 and 7 may be explained on the basis of partial excretion of mercury through the mucosal surface. Ogilvie (1932), using rabbits, demonstrated that intravenous as well as oral administration of $HgCl_2$ resulted in mucosal degeneration in the colon and postulated that the mercury is partially excreted by this route.

Drill (1958) indicated that the mercuric ion produced a circulatory collapse as a result of arrhythmia and ventricular fibrillation. The changes found in cardiac musculature of pig 9 in this experiment appeared to be the result of prolonged tissue damage and not acute circulatory collapse.

SUMMARY

Research was conducted using 12 pigs assigned in pairs to the following groups: (1) control, (2) 2 mg. mercuric chloride ($HgCl_2$) per kilogram ration, (3) 20 mg. $HgCl_2$ per kilogram ration, (4) 100 mg. $HgCl_2$ per kilogram ration, (5) 200 mg. $HgCl_2$ per kilogram ration, and (6) 2 Gm. $HgCl_2$ per kilogram ration.

Signs of clinical disturbance developed on the 5th day in both animals fed the high level of $HgCl_2$. One of the pigs fed 200 mg. per kilogram ration had signs of acute illness on day 19 and died. Clinical signs included anorexia, staggering gait, emaciation, and diarrhea. None of the remaining pigs became clinically ill.

Gross lesions noted in the clinically affected pigs included a paleness of the renal cortex, generalized hemorrhages, and a pseudomembrane formation in the colon. Microscopic lesions included neuronal necrosis and vacuolation, necrosis and regeneration of renal parenchymal tissue, and focal hepatic coagulation necrosis.

Individual susceptibility appeared to be an important factor in mercuric chloride toxicosis in the pig, since there was little correlation between the amount of mercuric chloride ingestion per unit of body weight and the degree of toxicosis.

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