EFFECTS OF CALCIUM CHLORIDE INGESTION IN SWINE

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ABSTRACT

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INGESTION IN SWINE

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Calcium chloride was administered to pigs in 4 experiments by various methods and under a variety of conditions in an effort to characterize its toxic properties. It was possible to produce acute harmful effects only by forced administration of concentrated solutions of calcium chloride. Large volumes of such solutions produced necrosis of the gastrointestinal mucosa and underlying structures. Smaller doses, administered repeatedly, caused less marked effects of gastrointestinal irritation, such as vomiting and ulcers of the stomach.

Animals fed dry rations containing calcium chloride did not gain weight at normal rates. This was probably mainly a result of reduced palatability of such rations. The results of Experiment I, in which calcium chloride was added to a swill, suggest a similar conclusion, but statistically cannot be considered significant because 1 of the control pigs gained less weight than did the pig receiving the calcium chloride in the ration. Pigs drenched repeatedly with calcium chloride solutions lost weight in contrast to controls, which made moderate gains despite water restriction.

Neither the clinical signs nor the pathological changes in any of the trials resembled those of sodium chloride poisoning.

It is highly improbable, considering the unpalatability of calcium chloride, that pigs would consume it in quantities or concentrations sufficient to be harmful.

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By

Robert L. Michel

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I. INTRODUCTION

The literature contains numerous references on the occurrence of sodium chloride poisoning in swine. This subject has been investigated by a number of workers, and a fairly complete characterization of the pathogenesis, clinical signs, and lesions is available. However, very little information is available on poisoning with calcium chloride.

This study was undertaken as a result of 2 outbreaks of poisoning in pigs which were brought to the attention of the personnel of the diagnostic service at Michigan State University during the winter and spring of 1963 and 1964. In both cases, clinical and pathological studies suggested sodium chloride poisoning. However, investigation into possible sources of the salt revealed that the pigs had apparently had access to calcium chloride rather than sodium chloride.

Calcium chloride is widely used to minimize highway ice in winter in the northern United States. It is conceivable that in the spring the combined effects of seasonal rains and melting snows might cause runoff from highways which could produce high levels of calcium chloride in water available to pigs.

The objectives of this study were as follows:

1. To determine the toxicity of calcium chloride for swine.

2. To characterize the clinical signs and lesions of such a toxicosis.

3. To determine if pigs would voluntarily ingest calcium chloride in quantities sufficient to cause poisoning.

4. To determine if calcium chloride can produce clinical signs and lesions in pigs similar to those seen in pigs with sodium chloride poisoning.

II. LITERATURE REVIEW

A. Toxicity of Calcium Chloride

References to the deleterious effects of calcium chloride are limited to the mention of its locally irritant properties and to its ability to produce arrythmia, heart block, and ventricular fibrillation when injected intravenously (Gleason et al., 1963). Smith (1957) failed in an attempt to poison pigs with a swill containing 2 kg. of feed, 6 liters of water, 130.0 Gm. potassium chloride (1.58%), and 95.0 Gm. calcium chloride (1.16%). It was necessary to add additional water and milk to induce the pigs to consume this ration.

B. Toxicity of Sodium Chloride

1. History

Poisoning of pigs by sodium salts has been recognized clinically for many years. Smith, writing in Diseases of Swine (1964, 2nd ed., edited by H. W. Dunne), cited Lepper (1856), Pyatt (1862), Borman and co-workers (1885), Junginger (1887), and Lamoureux (1890) among early writers on this condition. In this century, Kernkamp (1919) described the clinical features of field cases of sodium chloride poisoning. He mentioned 2 outbreaks. In the first, poisoning was associated with garbage feeding; in the second, poisoning was associated with excessive salting of the ration.

2. Experimental Sodium Salt Poisoning

Smith (1955) was among the first workers to associate eosinophilic meningoencephalitis in pigs with ingestion of sodium chloride. He demonstrated, in an extensive study at Cornell, that it is necessary to restrict water in order to produce poisoning with sodium chloride and that, when this is done, as little as 2.5% sodium chloride in the diet is toxic to pigs. His experiments also suggested that approximately 36 hours must elapse after ingestion of the toxic ration before the development of eosinophilic infiltration of the brain and meninges. In the same investigation, by feeding sodium proprionate, Smith succeeded in producing clinical signs and lesions indistinguishable from those of sodium chloride poisoning. However, as mentioned above, he failed to produce this response with a mixture of calcium and potassium chlorides. In several instances, Smith noted that pigs developed signs after the toxic ration had been removed and water was supplied ad libitum. Hjarre and Obel (1956) succeeded in producing signs and lesions typical of sodium chloride poisoning using sodium lactate. Dow and co-workers (1963) reported 2 field outbreaks of poisoning of pigs with sodium sulfate. They subsequently produced this condition experimentally and reported that the clinical signs and lesions were identical to those seen in sodium chloride poisoning.

Thus, these studies (Smith, 1955; Hjarre and Obel, 1956; and Dow and co-workers, 1963) seem to incriminate the sodium ion as the offender. However, Done and co-workers (1959) produced essentially the same clinical signs and pathological changes by adding urea to the ration at a concentration calculated to give the same osmotic effect

as 7% salt in the diet. Urea did not, however, excite an eosinophilic meningoencephalitis. In this study, pigs were poisoned with either urea or sodium chloride when the water was limited to a volume approximately equal to that of the feed. This represented about a 2.5:1 ratio of water to feed on a weight basis.

3. Pathogenesis of Sodium Salt Poisoning

Smith (1955) theorized that in pigs poisoned with sodium salts symptoms were initiated by edema, which occurred as a result of the sodium ion accumulating in the brain tissue and attracting fluid from the circulatory system. The resulting increased intracranial pressure caused a relative ischemia in the edematous tissue. In addition, sodium acted as a strong inhibitor of anaerobic glycolysis in the brain through stimulation of conversion of adenosine triphosphate to adenosine monophosphate and a decreased rate of removal of adenosine monophosphate by phosphorylation. The resulting accumulation of adenosine monophosphate inhibited glycolysis (Utter, 1950). The combined effect of (a) local anoxia from increased intracranial pressure and (b) inhibition of anaerobic glycolysis resulted in degeneration and death of the highly susceptible cerebral cortex. The eosinophilic infiltration of the meninges and Virchow-Robin spaces was not explained. Smith stated, however, that it is not simply a manifestation of isoallergic encephalitis and described an experiment which he conducted to support this claim.

Medway and Kare (1959) presented theories regarding the pathogenesis of the lesions of sodium chloride poisoning in swine based on their studies of electrolyte distribution in pigs. They suggested that an

increased concentration of sodium chloride in the cerebrospinal fluid and a low intracellular concentration of sodium resulted in the diffusion of sodium into the cells with resultant inhibition of glycolysis. This inhibition of glycolysis, coupled with a continuing increase in intracellular sodium, caused a breakdown in the normal selective permeability of the cell membranes with a loss of cell protein. This protein acted as a foreign protein stimulating an eosinophilic response.

4. Clinical Signs of Sodium Salt Poisoning in Swine

In Diseases of Swine (1964, 2nd ed., edited by H. W. Dunne), Smith separated the clinical signs of sodium chloride poisoning into peracute and acute syndromes. The peracute cases resulted from a massive dose and gave rise to signs such as weakness, tremors, running movements, coma, and death within 2 days. The acute syndrome was the type usually seen in field outbreaks and was characterized by thirst, pruritis, constipation, blindness, deafness, and apparent unawareness of environment. Affected pigs did not respond to external stimuli, wandered aimlessly, or exhibited retropulsion or epileptiform seizures. Mortality averaged 3% in 20 outbreaks.

5. Lesions of Sodium Salt Poisoning in Swine

Smith (1957) listed the following lesions in swine poisoned with sodium chloride: vacuolation of the cerebral gray matter, appearance of perineuronal and perivascular spaces, laminar cortical necrosis and malacia, and eosinophilic infiltration of the Virchow-Robin spaces and leptomeninges. In addition, he noted swelling and vesiculation of endothelial cells in the cerebral cortex and abundant capillary proliferation. There was increased cellularity in the affected areas

of the brain which was apparently the result of glial cell proliferation. Such proliferating elements often occurred in close relation to cyst-like cavities of malacia. Scavenger cells and mitotic figures were observed. Affected areas occurred most typically in the sulci of the cerebral cortex.

Sautter and co-workers (1957) noted in pigs poisoned with sodium chloride that there was thickening of the endothelium of brain capillaries almost to the point of occlusion. They also mentioned vacuolation of the gray and white matter, neuronal degeneration, neuronophagia, and edema of the Virchow-Robin spaces. Kidney epithelium was described as being fragmented and atrophic, and the tubules of the kidneys contained hyaline casts.

Rac and associates (1959) also observed eosinophilic meningoencephalitis, endothelial proliferation, laminar cortical vacuolation and malacia, and the appearance of gitter cells in the cerebral cortex.

Kernkamp (1919) and Hofferd (1939) described severe inflammatory reactions in the gastrointestinal tract as characteristic lesions of sodium chloride poisoning in swine. Other workers (Done and co-workers, 1959) attached little importance to this lesion in the diagnosis of salt poisoning. Smith (1955) stated that the gross lesions in cases of sodium chloride poisoning in pigs are nonspecific.

C. Occurrence of Sodium Salt Poisoning in Wildlife

Trainer and Karstad (1960) described poisoning of wildlife, including rabbits, pheasants, and pigeons, with sodium chloride used on highways in Wisconsin. They observed prominent leukocytic infiltrations in the brain stem, but cerebral lesions and eosinophilic infil-

trations were not as common as is the case in swine poisoned with sodium chloride.

Thus, it can be seen that, in contrast to poisoning with sodium salts, and especially sodium chloride, there is little information available regarding toxicity of calcium chloride in swine.

III. MATERIALS AND METHODS

A. Experimental Animals

The experimental animals used in this investigation were pigs approximately 8 weeks of age.

B. Ration

The pigs were fed a ration which was identical to the grower ration formulated by the Department of Animal Husbandry at Michigan State University for pigs of this age, with the exception that salt was excluded. The composition of the ration is given (TABLE 1).

C. Calcium Chloride

The calcium chloride used in these studies was anhydrous 8-mesh calcium chloride meeting American Chemical Society specifications, with a minimum assay of 96%.

D. Facilities and General Information

The pigs were divided into control and experimental groups and, in some experiments, were penned individually. Water was restricted or furnished ad libitum. Weights and temperatures were recorded at appropriate intervals during the course of the trials. Pigs were observed regularly for general health and behavior. Particular attention was given to their willingness to accept rations and water containing calcium chloride. At appropriate times, surviving pigs were killed by electrocution and necropsied.

TABLE 1. Ration formula.

Ground yellow corn	1554.0
Soybean meal (50% protein)	300.0
Meat scrap (50% protein)	60.0
Alfalfa leaf meal (17% protein)	50.0
Ground limestone ($CaCO_2$)	12.0
Dicalcium phosphate	4.0
Vitamin-mineral-antibiotic premix*	10.0

*Contains riboflavin, pantothenic acid, niacin, choline, vitamin B_{12}, Pro-strep (Merck Procaine penicillin-streptomycin), and zinc oxide.

E. Handling of Tissues

Tissues for histopathologic examination were fixed in 10% buffered formalin, trimmed, processed in an automatic tissue processing machine (Autotechnicon)* and embedded in Paraplast.** Sections were cut at 6 microns and routinely stained with hematoxylin and eosin. Oil red O stain was used on frozen sections to demonstrate fat content.

Brains were removed intact. The corpus callosum was then cut longitudinally and the septum pellucidum was cut in order to allow the fixative free passage into the ventricular system. Brains were fixed for at least 2 weeks, after which they were processed and sectioned. Toluidine blue was used for the demonstration of Nissl granules.

F. Experimental Procedures

1. Experiment I Procedure

Six Yorkshire crossbred litter mates were started on experiment at 7 weeks of age. The pigs were numbered 1 through 6 and identified by ear notching. Weights are given (TABLE 4). Pig 1, penned separately, received calcium chloride in his ration. Pigs 2 through 6 were penned and fed the control ration as a group. During the course of this experiment, feed and water were mixed as a swill. No other feed or water was provided. The experimental procedure is summarized (TABLE 2).

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* Autotechnicon, Technicon Company, Chauncy, New York.

**Paraplast, Aloe Scientific Division of Brunswick, St. Louis 3, Missouri.

TABLE 2. Experiment I. Experimental procedure.

Day	Pig No.	Amount of Feed (Gm.)	Approximate water:feed ratio by Vol.	by Wt.	$CaCl_2$ in Feed Weight (Gm.)	%
1	1	900.0	1.0:1.0	2.5:1.0	63.0	7
	2-6	4500.0	1.0:1.0	2.5:1.0	---	---
2	1	450.0	1.0:1.0	2.5:1.0	31.5	7
	2-6	2250.0	1.0:1.0	2.5:1.0	---	---
3	1	450.0	0.8:1.0	2:1.0	22.5	5
	2-6	2250.0	0.8:1.0	2:1.0	---	---
4	1	450.0	0.9:1.0	2.2:1.0	22.5	5
	2-6	2250.0	0.9:1.0	2.2:1.0	---	---
5	1	450.0	0.9:1.0	2.2:1.0	22.5	5
	2-6	2250.0	0.9:1.0	2.2:1.0	---	---
6	1	450.0	0.9:1.0	2.2:1.0	22.5	5
	2-6	2250.0	0.9:1.0	2.2:1.0	---	---
7	1	450.0	0.68:1.0	1.7:1.0	22.5	5
	2-6	2250.0	0.68:1.0	1.7:1.0	---	---
8 a.m.	1	450.0	0.9:1.0	2.2:1.0	22.5	5
8	2-6	2250.0	0.9:1.0	2.2:1.0	---	---
1 p.m.	1-6		Water ad libitum			

Discussion of Procedure of Experiment I. The amounts of feed and water were varied in attempts to find the maximum amount and concentration of calcium chloride that the pig would consume with a limited water allowance. However, the water-to-feed ratio did not at any time exceed 2.5:1 by weight. This was the mixture with which Done and coworkers (1959) had consistent success in producing sodium chloride poisoning.

Water was provided ad libitum on day 8 in an attempt to precipitate cerebral edema in the manner described by Smith (1955) in sodium chloride poisoning.

2. Experiment II Procedure

Pig 1 was returned to the control group. Pigs 5 and 6 were placed in a separate pen. Pigs 1 through 4 were penned as a group. Weights for pigs 1 through 6 were, respectively, 11.2, 14.8, 12.8, 15.4, 14.0, and 11.0 kg.

Pig 5 was intubated and drenched with 31.5 Gm. calcium chloride in 30 ml. water on the morning of day 1. The solution was permitted to cool to dissipate the heat of solvation before being administered. Pig 6 was similarly drenched with 40.5 Gm. in 40 ml. of water. Pigs 5 and 6 were then offered 418.5 Gm. and 409.5 Gm. of feed in 720 ml. and 710 ml. of water, respectively. Pigs 1 through 4 were given 1800 Gm. of feed in 3000 ml. of water.

Pig 5 was necropsied at 10 p.m. of day 1.

Discussion of Procedure of Experiment II. The failure to produce poisoning in Experiment I may have been due to the fact that the pig ate so sparingly of the calcium chloride-containing ration. Therefore,

poisoning by forced administration of calcium chloride was attempted using a syringe and stomach tube.

3. Experiment III Procedure

Pigs 2 and 3 were force-fed calcium chloride at a dose lower than that used in Experiment II and were fed the normal ration before drenching. These pigs were at first placed together in a pen. However, on day 2 they were separated in order to ensure equal division of feed and water. Rations for all pigs were prepared in the form of a swill. No other water was provided through day 6, except the small amount necessary to dissolve the calcium chloride.

Pigs 2 and 3 were given free access to water on the morning of day 7. Pig 2 was necropsied at 1:30 p.m. and pig 3 at 6:30 p.m. that same day. Pigs 1, 4, and 6 were given free access to water and necropsied the next day. The experimental procedure is summarized (TABLE 3). Weights are given (TABLE 5).

Discussion of Procedure of Experiment III. This experiment was an attempt to produce poisoning in pigs by forced administration of calcium chloride at a dose lower than that used in Experiment II in order to avoid some of its caustic action. Smaller doses were given over a period of several days in an effort to produce toxic effects different from those seen in Experiment II. The pigs were fed before drenching in a further effort to minimize gastrointestinal irritation.

After 4 days it was apparent that acute poisoning would not occur on the regimen being followed. Therefore, the dose was increased to 10 and 12 Gm. calcium chloride 3 times daily for pigs 2 and 3, respectively. The daily dose was divided into 3 parts to minimize the local irritant effect of the calcium chloride.

TABLE 3. Experiment III. Experimental procedure.

Day	Pig No.	Amount of Feed (Gm.)	Amount of Water (ml.)	$CaCl_2$ Drench
1	2,3	900.0	1500.0	7.0 Gm. in 30.0 ml. H_2O
				12.0 Gm. in 30.0 ml. H_2O
	1,4,6	1350.0	2250.0	---
2	2	500.0	750.0	7.0 Gm. in 30.0 ml. H_2O
	3	500.0	750.0	12.0 Gm. in 30.0 ml. H_2O
	1,4,6	1500.0	2250.0	---
3	2	500.0	750.0	7.0 Gm. in 30.0 ml. H_2O
	3	500.0	750.0	12.0 Gm. in 30.0 ml. H_2O
	1,4,6	1500.0	2250.0	---
4	2	500.0	750.0	7.0 Gm. in 30.0 ml. H_2O
	3	500.0	750.0	12.0 Gm. in 30.0 ml. H_2O
	1,4,6	1500.0	2250.0	---
9 a.m.	2	250.0	375.0	10.0 Gm. in 30.0 ml. H_2O
	3	250.0	375.0	12.0 Gm. in 30.0 ml. H_2O
	1,4,6	750.0	1125.0	---
5 1 p.m.	2	250.0	375.0	10.0 Gm. in 30.0 ml. H_2O
	3	250.0	375.0	12.0 Gm. in 30.0 ml. H_2O
	1,4,6	750.0	1125.0	---
5 p.m.	2	250.0	375.0	10.0 Gm. in 30.0 ml. H_2O
	3	250.0	375.0	12.0 Gm. in 30.0 ml. H_2O
	1,4,6	750.0	1125.0	---
9 a.m.	2	250.0	375.0	10.0 Gm. in 30.0 ml. H_2O
	3	250.0	375.0	12.0 Gm. in 30.0 ml. H_2O
	1,4,6	750.0	1125.0	---
1 p.m.	2	250.0	375.0	10.0 Gm. in 30.0 ml. H_2O with egg white and buttermilk
	3	250.0	375.0	12.0 Gm. in 30.0 ml. H_2O
6				with egg white and buttermilk
	1,4,6	750.0	1125.0	---
5 p.m.	2	250.0	375.0	5.0 Gm. in 30.0 ml. H_2O with egg white and buttermilk
	3	250.0	375.0	7.0 Gm. in 30.0 ml. H_2O with egg white and buttermilk
	1,4,6	750.0	1125.0	---

TABLE 3--continued

Day	Pig No.	Amount of Feed (Gm.)	Amount of Water (ml.)	$CaCl_2$ Drench
7 8 a.m.	2	---	free access	necropsied
	3	---	free access	necropsied
	1,4,6	750.0	1125.0	---
8	1,4,6	---	free access	necropsied

Pigs 2 and 3 were permitted to drink freely on the morning of day 7 in an effort to produce cerebral edema.

4. Experiment IV Procedure

Ten pigs were separated into 2 groups. Six of them, numbers 1, 2, 3, 5, 9, and 11, were penned together and fed the standard experimental ration with added calcium chloride. Pigs 4, 6, 7, and 10 were placed in another pen and fed the control ration. These pigs were from 2 litters which had been affected with polyserositis. They had been treated with antibiotics and were clinically normal. They were kept on the experimental ration a total of 24 days. During this period the experimental group was induced to consume the maximum amount of calcium chloride by mixing it in the ration at the highest level which they would accept and by allowing them all the feed they would eat. The concentration of calcium chloride mixed into the ration varied from 1.96% to 2.7%. The total amount mixed into the ration varied from 82.0 Gm. to 250.0 Gm. daily for the 6 pigs.

Weights are given (TABLE 6).

At the conclusion of the trial, all pigs were killed by electrocution and necropsied. Tissue specimens were collected for histopathologic examination.

IV. RESULTS

A. Experiment I

1. Clinical Signs

The addition of calcium chloride to the ration of pig 1 at levels of 5 to 7% apparently rendered the ration so unpalatable that the pig ate it sparingly. Under this regimen, no signs of acute toxicity were produced. All pigs exhibited signs of thirst on the restricted water allowance, and pig 1 became constipated. Pigs 2 through 6 consumed all their feed every day, despite restriction of water.

2. Growth

Weights at the termination of Experiment I, with gains and percentage gains, are given (TABLE 4).

B. Experiment II

1. Clinical Signs

Within 15 minutes after drenching with calcium chloride solution, the 2 experimental pigs vomited, and subsequently refused feed and exhibited depression and signs of posterior weakness. Eight hours after drenching pig 5 was unable to rise; pig 6 was up and alert but would not eat. There was evidence of a watery, blood-tinged diarrhea in the pen of pig 6.

Pig 5 died 13 hours after drenching. Twenty-four hours after drenching, pig 6 was gaunt but otherwise appeared normal.

TABLE 4. Experiment I. Weights and weight changes.

Pig No.	Initial Wt. (kg.)	Final Wt. (kg.)	Total Gain (kg.)	% Gain	Average Daily Gain (Gm.)
Experimental					
1	10.0	11.1	1.1	11.0	138
Controls					
2	11.9	14.8	2.9	24.0	356
3	10.3	12.8	2.5	24.3	313
4	12.3	15.7	3.4	27.6	425
5	12.3	14.0	1.7	13.8	213
6	10.2	10.9	0.7	6.85	87.5

2. Necropsy Findings

a). Gross examination.

Pig 5. The pig was in good flesh. There was a generalized, acute peritonitis. The liver appeared pale and was covered with a granular, light-colored deposit of fibrin. The serosae of the stomach and small intestine were extremely congested and hemorrhagic. The mucosae of the stomach, duodenum, first part of the jejunum, and the ileum were hemorrhagic. The mucosae of the large intestine and cecum were relatively free of inflammation. The wall of the stomach was edematous.

b). Microscopic examination.

Pig 5. There was widespread, deep necrosis of the mucosa of all regions of the stomach. There was a pronounced edema in the submucosa (Figure 1). Necrosis of the epithelium and congestion of mucosa and submucosa were marked in all sections of the small intestine. In some areas of the jejunum and ileum there was infiltration of the lamina propria by large numbers of eosinophils. The cecum and colon were hyperemic. A section of a mesenteric lymph node was hyperemic. The spleen was extremely congested. There was pyknosis in some of the epithelial cells lining the proximal convoluted tubules of the kidneys.

There were no lesions in any of 4 sections taken from different regions of the cerebrum.

C. Experiment III

1. Clinical Signs

Daily doses of 7 and 12 Gm. of calcium chloride failed to produce signs of acute toxicity in pigs 2 and 3, the only noticeable effects being

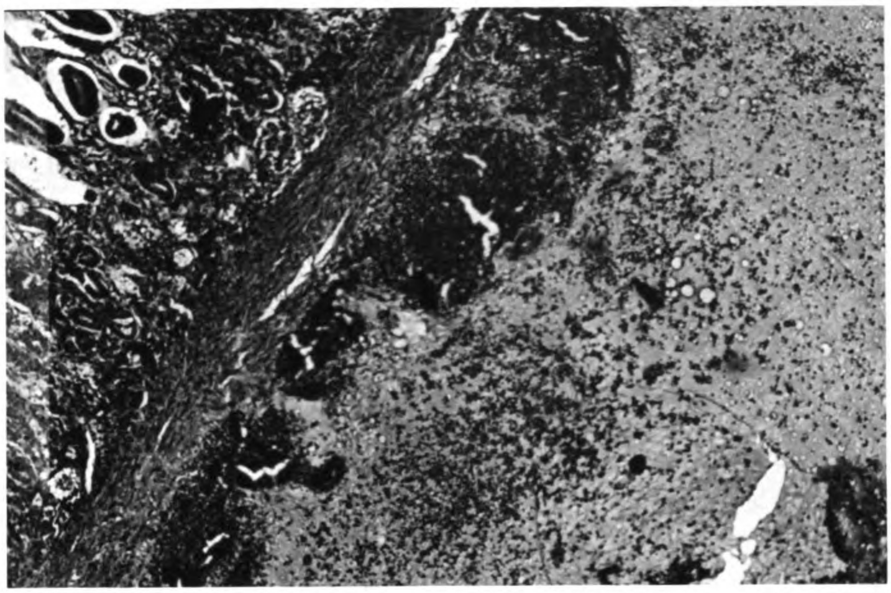

Figure 1. Photomicrograph of stomach of pig 5. Experiment II. Necrotic epithelium is at upper left. Congestion, hemorrhage, and edema evident in deeper structures. Hematoxylin and eosin. x 75.

constipation and diminished appetite. Experimental and control groups both exhibited signs of thirst on the restricted water allowance.

Increasing the doses to 10 and 12 Gm. 3 times daily, along with a 50% increase in feed and water, resulted in prompt vomition of the solution after drenching. The addition of demulcent agents to the calcium chloride and the reduction of the doses of calcium chloride to 5 and 7 Gm., respectively, 3 times daily, failed to control the vomiting.

By day 7, pigs 2 and 3 were depressed, were consuming very little feed, and were exhibiting signs of extreme thirst. It was apparent that acute poisoning would not develop in pigs on this regimen. Therefore, all pigs were given water ad libitum in an attempt to precipitate cerebral edema in pigs 2 and 3. All animals drank greedily. No deleterious effects were observed.

2. Growth

Final weights, gains or losses, and percentages gained or lost are given (TABLE 5). Control pigs 1 and 4 made moderate gains despite restricted feed and water. Pig 6, which had received a single large dose of calcium chloride by stomach tube in Experiment II, failed to gain. Pigs 2 and 3 each lost considerable weight.

3. Necropsy Findings

a). Gross examination.

Pigs 2 and 3. The only significant findings were ulcers on the mucosal surfaces of the stomachs of both pigs. Pig 2 had a single ulcer, approximately 2 cm. in diameter, in the lower part of the fundic region on the greater curvature. Pig 3 had a raised, firm, reddish-brown

TABLE 5. Experiment III. Weights and weight changes.

Pig No.	Initial Wt.(kg.)	Wt. when 3-times-daily feeding and drenching begun (kg.)	Final Wt. (kg.)	Total Change +or-(kg.)	% Change +or-	Avg. Daily Gain or Loss + or - (Gm.)
Experimental						
2	14.9	15.4	12.7	-2.2	-14.8	-314.0
3	12.9	11.3	9.8	-3.1	-24.0	-443.0
Controls						
1	11.1	13.2	13.6	+2.5	+22.5	+357.0
4	16.0	18.5	20.0	+4.0	+25.0	+571.0
6	9.8	9.7	9.8	---	---	---

ulcer approximately 2.5 cm. in diameter in the fundic region about 2 cm. from the pyloric region. Another ulcer was located at the edge of the cardiac region adjacent to the esophageal region. This latter ulcer was irregularly shaped, approximately 3 cm. across at its greatest dimension, and was covered with a yellowish material.

Pig 6. This pig was in poor condition. There were extensive adhesions involving the visceral peritoneum, parietal peritoneum, and omentum. There was necrosis of the entire mucosa of the fundic region of the stomach. The mucosa was thickened, firm, wrinkled, and had a dirty, grayish-yellow color. There was a sharp demarcation between necrotic and viable tissue (Figure 2).

Pigs 1 and 4. These pigs had no significant gross lesions.

b). Microscopic examination.

Pigs 1, 2, and 3. There were numerous prominent vacuoles in the epithelium of the proximal convoluted tubules of the kidneys of pigs 1, 2, and 3. These vacuoles proved to be fat upon staining with oil red O. There were eosinophils in the connective tissue adjacent to the renal papillae in pigs 1 and 2. Pig 1 also had foci of lymphocytes and macrophages in this region..

Several of the pigs had moderate, localized areas of enteritis, as well as interstitial pneumonitis. These lesions occurred irrespective of whether the pigs had received calcium chloride or not. However, evidence of gastrointestinal inflammation was usually more pronounced in those which had received the compound. Microscopic manifestations of inflammation in these cases included increased mucus production and

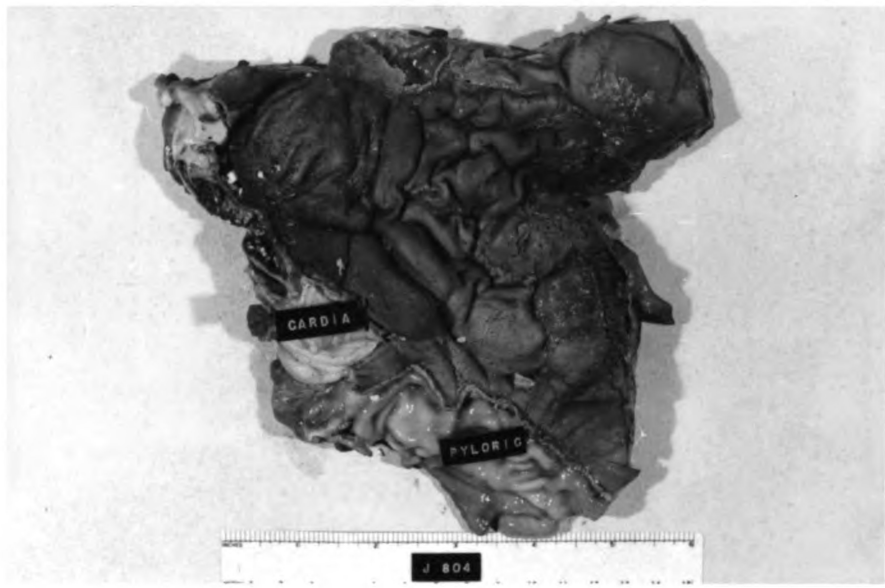

Figure 2. Necrotic mucosa of stomach of pig 6 as a result of calcium chloride drench administered in Experiment II. Note sharp line of demarcation between necrotic and viable tissue.

infiltration of the laminae propriae by large numbers of plasma cells. Some of the gastric and intestinal glands in these animals were dilated and lined with a flattened epithelium.

Changes at the sites of the stomach ulcers seen in pigs 2 and 3 included loss of epithelium with an inflammatory cellular infiltrate consisting mainly of neutrophils. Thrombosis had occurred in some of the smaller vessels in the mucosa and submucosa, and there was active fibroblastic proliferation at the bases of the ulcers (Figures 3 and 4).

Pig 4. This pig, the only one of the 6 which had not at any time received calcium chloride, had a small amount of fat in the convoluted tubules of the kidneys.

Pig 6. There was a localized thickening of the capsule of the left kidney accompanied by an infiltration of macrophages and many giant cells. Normal tubular architecture was not discernible in this area (Figures 5 and 6). There were vacuoles in many of the epithelial cells of the proximal convoluted tubules and in some of the tubules of the medullary rays. The right kidney had similar, but less marked, lesions.

In the pyloric region of the stomach there was a loss of surface epithelium and markedly increased mucous secretion. The mucosa of the fundic region was completely destroyed by a coagulative type of necrosis (Figures 7 and 8). The underlying submucosa was extremely edematous (Figure 9). A zone of caseation necrosis was observed in the submucosa near the muscularis. In the muscularis there were necrosis, active fibroblastic proliferation, and infiltration by neutrophils, macrophages, and foreign body giant cells. Many bacterial colonies

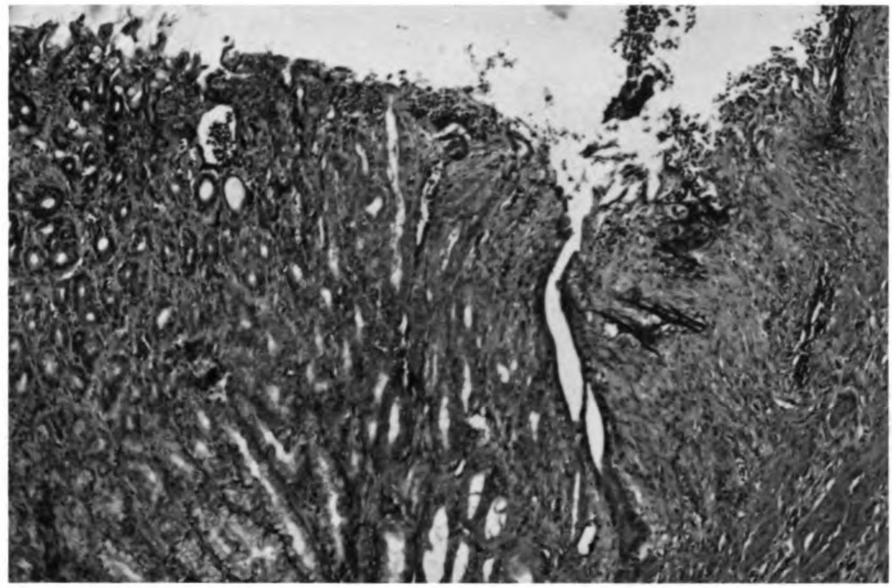

Figure 3. Edge of ulcer in fundic region of the stomach of pig 3. Experiment III. Ulcerated area to the right. Hematoxylin and eosin. x 75.

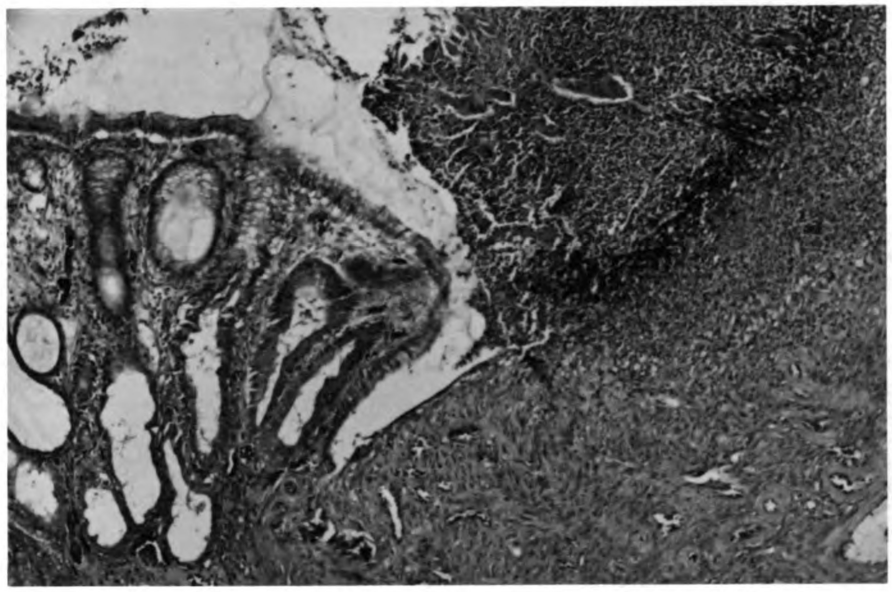

Figure 4. Ulcer at the edge of the cardiac region of the stomach of pig 3. Experiment III. Epithelium completely destroyed at the right. Cardiac glands to the left are cystic. Hematoxylin and eosin. x 75.

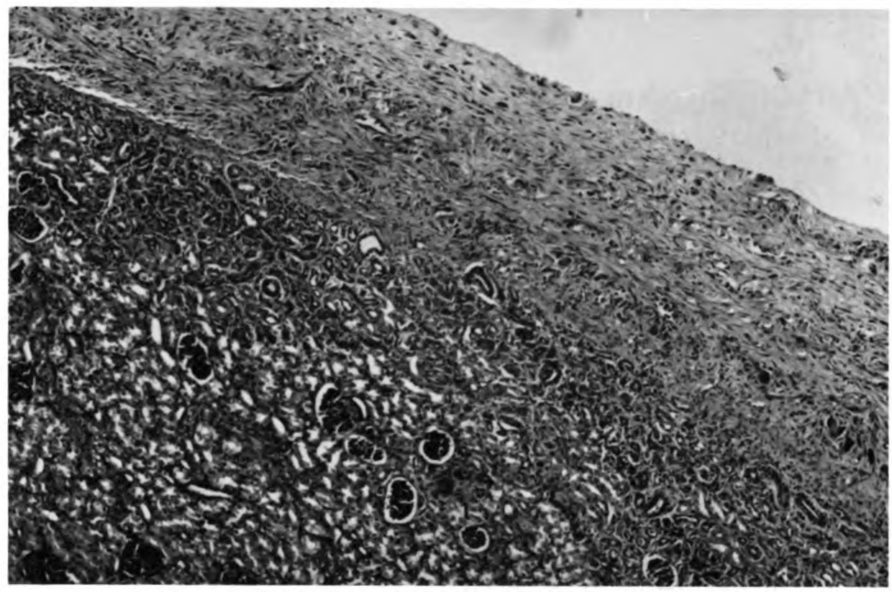

Figure 5. Photomicrograph of surface of left kidney of pig 6, Experiments II and III, showing chronic effects of peritonitis. Note thickened capsule and disrupted architecture of subcapsular cortex. Hematoxylin and eosin. x 75.

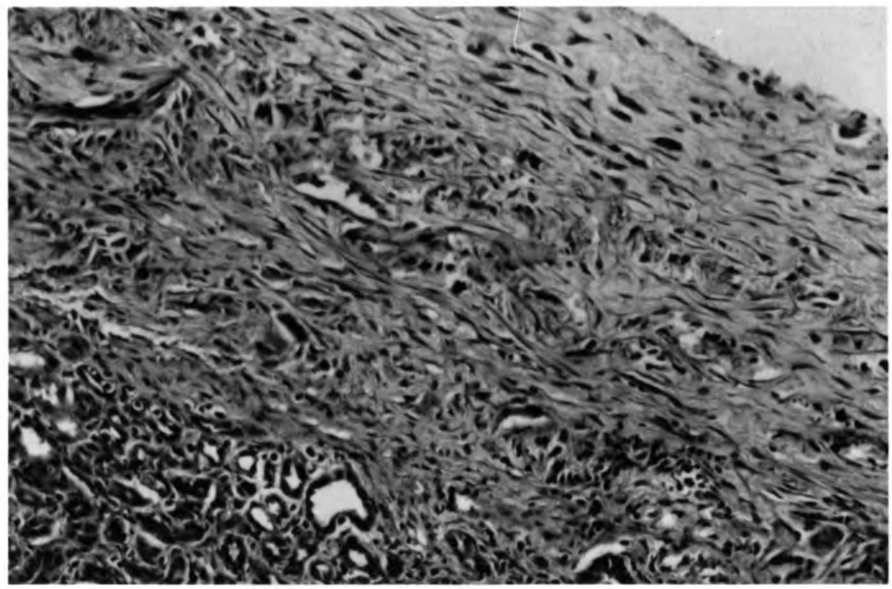

Figure 6. Higher power of section shown in Figure 5. Note typical appearance of chronic inflammatory process. Hematoxylin and eosin. x 187.

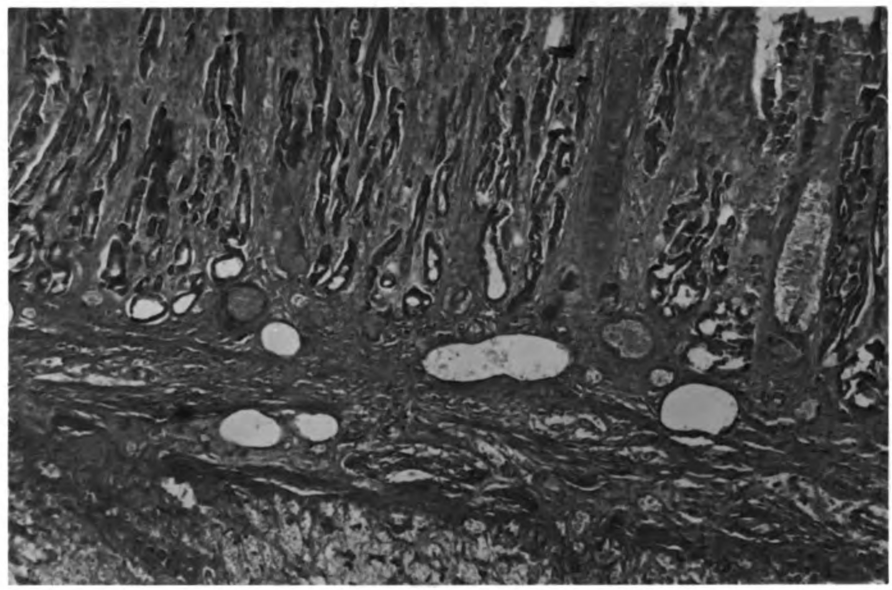

Figure 7. Mucosa and part of submucosa of fundic region of stomach of pig 6. Experiments II and III. Note coagulative necrosis of mucosa and edema of submucosa. Hematoxylin and eosin. x 75.

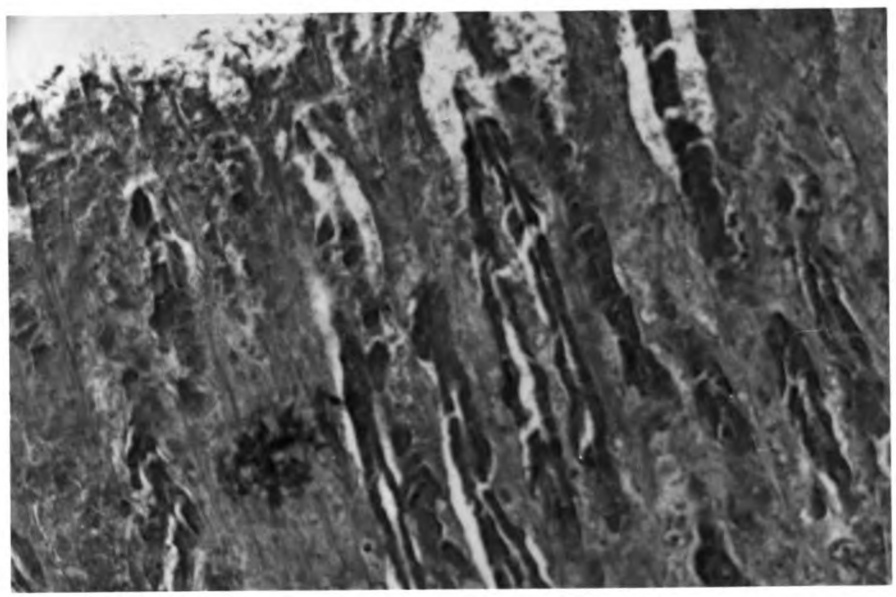

Figure 8. Photomicrograph showing coagulative necrosis of mucosa of fundic region of stomach of pig 6. Experiments II and III. Hematoxylin and eosin. x 187.

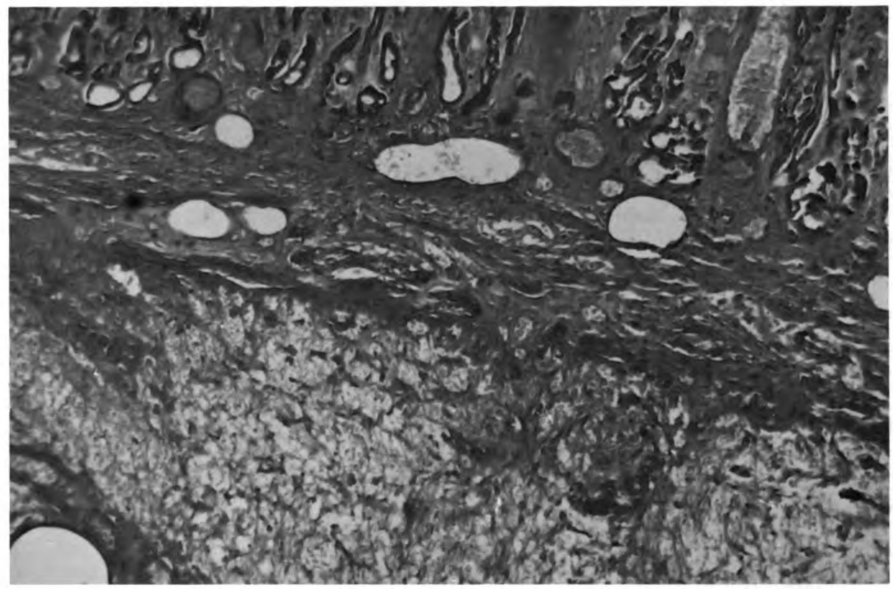

Figure 9. Photomicrograph showing edema in submucosa of stomach of pig 6. Experiments II and III. Hematoxylin and eosin. x 75.

were observed in the necrotic mucosa and in the submucosa. There were aggregates of lymphocytes around some of the smaller blood vessels of the muscularis. The serosa was thickened with connective tissue.

None of the animals had significant lesions of the central nervous system.

D. Experiment IV

1. Clinical Signs

Pigs did not eat well if their rations contained more than 2% calcium chloride. Even at the 2% level, the experimental group frequently did not eat as well as the controls. Trituration of the calcium chloride to a fine powder before mixing it into the feed did not make it any more acceptable to the pigs.

The only clinical manifestation of disease which appeared during the trial was rather persistent diarrhea among those receiving calcium chloride. This did not involve all of the experimental group simultaneously. Pig 5 was affected most consistently.

2. Growth

Effects on growth are summarized (TABLE 6). The pigs in the control group made significantly greater gains than those on the ration containing calcium chloride. The average percentage gain among the controls was more than twice that for the experimental group.

3. Necropsy Findings

There were no lesions, macroscopic or microscopic, which could be associated with consumption of calcium chloride in the feed. Notwithstanding the fact that the pigs of the experimental group showed a

TABLE 6. Experiment IV. Weights and weight changes.

Pig No.	Initial Wt.(kg.)	Final Wt. (kg.)	Total Gain(kg.)	% Gain	Avg. % Gain	Avg. Daily Gain (Gm.)
Experimental						
1	15.0	20.4	5.4	36.0		225.0
2	17.7	22.7	5.0	28.2		208.0
3	20.5	26.8	6.3	30.8		262.0
5	15.9	17.3	1.4	8.8	24.0	5.9
9	15.9	20.4	4.5	28.3		187.0
11	19.1	21.4	2.3	12.0		96.0
Controls						
7	17.3	26.8	9.5	55.0		396.0
4	20.0	34.0	14.0	70.0		585.0
10	15.4	24.6	9.2	59.8	59.2	384.0
6	18.6	28.2	9.6	51.6		400.0

greater tendency toward diarrhea, no gross or microscopic lesions suggestive of gastrointestinal irritation were observed.

V. DISCUSSION AND CONCLUSIONS

The caustic properties of calcium chloride were demonstrated in Experiment II. Pig 5 died of the acute effects of calcium chloride drench. Pig 6 survived the acute effects but had a severely damaged gastric mucosa and grew poorly.

In Experiment III smaller doses of calcium chloride consistently produced vomiting and resulted in gastric ulcers in pigs 2 and 3.

Experiments I and IV were dependent on voluntary ingestion of calcium chloride in the ration. In Experiment I, the compound was added to a swill and water was restricted. In Experiment IV, calcium chloride was mixed with the dry ration, and water was not limited. It was obvious in both Experiment I and Experiment IV that pigs would not voluntarily eat such rations well if they contained large amounts of calcium chloride. When calcium chloride was added to dry rations at levels greater than 2%, palatability apparently was markedly affected, and pigs ate such rations sparingly. Trituration of the compound to a fine state of division did not enhance its acceptability to the pigs. It is probable that this lack of palatability was the main factor accounting for the great difference in percentage of weight gains between the experimental and control groups in Experiment IV.

The diarrhea which occurred consistently among the experimental group in Experiment IV may have been the result of an osmotic effect of the relatively slowly absorbed calcium ion in the gut or possibly the result of increased water consumption among this group. Necropsy and histopathologic examination did not reveal any lesions which would account for disturbances of gastrointestinal function.

Sodium chloride produces its toxic effects in pigs after absorption apparently by the passage of sodium across the blood-brain barrier and its accumulation in the cerebral tissue. Resultant fluid and electrolyte imbalance leads to edema, neuronal degeneration, and malacia (Smith, 1955).

None of the methods used in this study produced clinical signs or lesions like those of sodium chloride poisoning in swine. There was no evidence to indicate that calcium tends to accumulate in the brain tissue to produce cerebral edema.

It appears that, due to its extreme unpalatability, calcium chloride would not be the cause of naturally occurring cases of poisoning in swine. If, in extraordinary circumstances (for example, prolonged water deprivation and subsequent access to solutions of calcium chloride), pigs did consume toxic amounts of this compound, effects would be limited to manifestations of local irritation of the gastrointestinal tract. Effects would not resemble sodium chloride poisoning.

VI. SUMMARY

Calcium chloride was administered to pigs in 4 experiments by various methods and under a variety of conditions in an effort to characterize its toxic properties. It was possible to produce acute harmful effects only by forced administration of concentrated solutions of calcium chloride. Large volumes of such solutions produced necrosis of the gastrointestinal mucosa and underlying structures. Smaller doses, administered repeatedly, caused less marked effects of gastrointestinal irritation, such as vomiting and ulcers of the stomach.

Animals fed dry rations containing calcium chloride did not gain weight at normal rates. This was probably mainly a result of reduced palatability of such rations. The results of Experiment I, in which calcium chloride was added to a swill, suggest a similar conclusion, but statistically cannot be considered significant because 1 of the control pigs gained less weight than did the pig receiving the calcium chloride in the ration. Pigs drenched repeatedly with calcium chloride solutions lost weight in contrast to controls, which made moderate gains despite water restriction.

Neither the clinical signs nor the pathological changes in any of the trials resembled those of sodium chloride poisoning.

It is highly improbable, considering the unpalatability of calcium chloride, that pigs would consume it in quantities or concentrations sufficient to be harmful.

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