

# MINIMUM LETHAL DOSE OF SELENIUM, AS SODIUM SELENITE, FOR HORSES, MULES, CATTLE, AND SWINE<sup>1</sup>

By W. T. MILLER, *associate veterinarian, Animal Disease Station, Bureau of Animal Industry*, and K. T. WILLIAMS, *formerly associate chemist, Division of Soil Chemistry and Physics, Bureau of Plant Industry, United States Department of Agriculture*<sup>2</sup>

## INTRODUCTION

Following the discovery of selenium in numerous plants grown in certain areas of the north-central Great Plains and its identification as the cause of so-called alkali disease of livestock in those areas, a number of experiments have been undertaken to test its toxicity. Most of this work was designed to study the effect of continued feeding of small doses of selenium in various forms to small experimental animals. The disease produced in this way was of the subacute or chronic type. In a few studies, however, large single doses of selenium have been administered, resulting in the acute type of poisoning. It appears that only small laboratory animals have previously been used for this work. Franke and Moxon,<sup>3</sup> using rats, found that the minimum fatal dose (smallest dose that killed 75 percent or more of the animals in 48 hours) of selenium, in the form of sodium selenite, injected intraperitoneally was 1.5 mg. per pound of body weight. Of sodium selenate, the minimum fatal dose was found to be 2.5 mg. per pound of body weight. Smith, Stohلمان, and Lillie,<sup>4</sup> using rabbits, found that the fatal dose of selenium, in the form of sodium selenite or selenate, when administered orally was 1.5 to 2.0 mg. per pound of body weight. No reference has been found of any such experimentation with the larger domestic animals.

In order to obtain information on this point, experiments were carried on in 1934 and 1938 at the Animal Disease Station, Beltsville, Md., to determine the minimum lethal dose of selenium for horses, mules, cattle, and swine. This work also afforded an opportunity to observe any symptoms and gross pathological changes which might result from acute selenium poisoning and how the element was distributed in the body tissues. The results of the experiments are reported in this paper.

## EXPERIMENTAL PROCEDURE

The number and weights of the different species of animals used in the experiments, the dosages given, and the methods of administration appear in table 1. The animals were normal as far as could be ascertained by clinical examination. Some of the horses and mules, however, had been included in infectious-disease experiments before being used in this work. Horse 775 had been given 5 cc. of a 24-hour culture of *Pasteurella bubaliseptica* a few weeks before it received sele-

<sup>1</sup> Received for publication October 30, 1939.

<sup>2</sup> The writers are indebted to H. C. Dudley, formerly of the Bureau of Chemistry and Soils, for chemical analyses, for selenium, of the tissues, milk, and urine of several experimental animals. Acknowledgment is also made to G. T. Creech of the Bureau of Animal Industry for histopathological examinations.

<sup>3</sup> FRANKE, K. W., and MOXON, A. L. A COMPARISON OF THE MINIMUM FATAL DOSE OF SELENIUM, TELLURIUM, ARSENIC, AND VANADIUM. *Jour. Pharmacol. and Expt. Ther.* 58: 454-459. 1936.

<sup>4</sup> SMITH, M. I., STOHLMAN, E. F., and LILLIE, R. D. THE TOXICITY AND PATHOLOGY OF SELENIUM. *Jour. Pharmacol. and Expt. Ther.* 60: 449-470. 1937.

mium. Horses 875 and 1003 and mules 991 and 1033 had been exposed to infectious anemia virus. Horse 1009 had been used in several infectious-disease experiments, whereas no previous experimentation had been done on horse 764 or on mule 1035. Although no records were available concerning the ages of the horses and mules, it was evident that they were 8 years of age or more.

TABLE 1.—Summary of experiments to determine the toxicity of single doses of selenium in the form of sodium selenite administered orally to horses, mules, cattle, and swine

Species and No.	Live weight	Dosage of		Method of administration	Selenium as sodium selenite per pound of body weight	Result
		Sodium selenite	Water			
Horse:	<i>Pounds</i>	<i>Grams</i>	<i>Cubic centimeters</i>		<i>Milligrams</i>	
775.....	1, 185	14. 22	100	Drench.....	5. 50	Death in 24 hours.
764.....	970	9. 70	500	Stomach tube.	4. 60	Death in less than 24 hours.
875.....	1, 435	11. 48	500	do.....	3. 65	Do.
1009.....	1, 450	6. 34	500	do.....	2. 00	Death in 26 hours.
Mule:						
1033.....	1, 227	4. 02	500	do.....	1. 50	Death in 36 hours.
1035.....	925	3. 03	500	do.....	1. 46	Death in about 36 hours.
991.....	850	2. 79	500	do.....	1. 50	Very sick.
Horse 1003.....	1, 110	2. 98	500	do.....	1. 23	Sick.
Calf 1.....	66	1. 32	50	Drench.....	9. 15	Death in 6 hours.
Cow:						
1729.....	1, 050	14. 71	85	do.....	6. 40	Death in about 48 hours.
1912.....	1, 360	16. 32	95	do.....	5. 10	Death in about 30 hours.
1914.....	705	7. 05	75	do.....	4. 57	Very sick.
1839.....	710	5. 00	50	do.....	3. 20	No effect.
Pig:						
4282.....	53	1. 20		Feed.....	10. 30	Death in 72 hours.
4754.....	130	2. 28	35	Drench.....	7. 90	Paralyzed; killed after 18 days.
4737.....	100	1. 31	35	do.....	6. 00	Sick.
4730.....	120	1. 57	20	do.....	6. 00	Do.
4683.....	120	1. 05	20	do.....	4. 00	Do.
4703.....	120	. 52	15	do.....	2. 00	Slightly sick.
4746.....	150	. 33	15	do.....	1. 00	No effect.

Two of the cows, Nos. 1914 and 1839, were in the first lactation period and were between 3 and 4 years old, whereas the other two were several years older. The calf was 5 days old. The pigs ranged in age from 4 to 6 months. None of these animals had been exposed directly to any known sources of infectious disease.

Selenium was given orally to each animal, in the form of sodium selenite, in the feed, as a drench, or by stomach tube. All the dosages were calculated on the basis of body weight. Since no information was available on what constituted a toxic or lethal dose for large animals, a fairly large quantity was given in the beginning and was reduced progressively in subsequent tests on other animals until symptoms of acute poisoning were obtained. The animals of each species (horses and mules being grouped together) are listed in table 1 according to size of the dose, with one exception.

## EXPERIMENTAL RESULTS

### HORSE 775

Horse 775, which was dosed in the afternoon, was depressed, weak, and trembling on the following morning, and its breath had a distinct odor resembling that of garlic. Death occurred in the afternoon of the same day.

On post mortem few lesions were found. The lungs were expanded and marked with the outline of the ribs, and although the interlobular

connective tissue was easily observed no emphysema was present. The heart contained black, coagulated blood. Black hemorrhages about 1 cm. in diameter were found along the coronary groove and in the ventricles. The intestinal tract was reddened and filled with bloody fluid.

## HORSE 764

Horse 764 was treated about 1:30 p. m., at which time it appeared normal in all respects and its temperature was 99.2° F. About 10 a. m. on the following day the temperature had risen to 102°. At this time there were slight spasms of the neck and face muscles and grinding of the teeth. The eyes were dilated and staring. There was profuse sweating with distension of the cutaneous blood vessels, although the pulse was very weak. The nostrils were expanded and the respirations were labored, with accessory intercostal breathing. The animal died about 1 hour later.

On post mortem a few small hemorrhages were found on the visceral pleura and the surface of the lungs. There were a few petechiae on the pericardium, and in the heart itself multiple hemorrhages occurred under the endocardium, which extended slightly into the myocardium. The liver showed slight diffuse fatty degeneration. A few hemorrhages, as well as severe gastritis, were found in the stomach. There was marked enteritis. A few subcapsular hemorrhages were noted on the spleen. No marked changes were present in the kidneys, but the bladder showed a diffuse cystitis.

Chemical analysis of the tissue of this animal was made for selenium. The results appear in table 2.

TABLE 2.—Selenium content of body parts and fluids of animals that received single doses of selenium

[Results given in parts of selenium per million, based on weight of samples of body parts and fluids taken on post mortem]

Body part or fluid	Selenium content <sup>1</sup> of indicated body part or fluid of—										
	Horse No.			Mule No.		Calf No.	Pig No.				
	764	875	1009	1033	1035	1	4282	4703	4730	4737	4754
	Parts per million	Parts per million	Parts per million	Parts per million	Parts per million	Parts per million	Parts per million	Parts per million	Parts per million	Parts per million	Parts per million
Bile						5.0	2.0				
Blood	2.0	2.5		0.8	2.0						2.5
Blood and lymph						27.0					
Bone (left humerus)							T.				
Bone (rib)							T.				
Bone marrow (right femur)							5.0				
Brain	.2	.4									.3
Colon and contents							50.0				
Feces	8.0				10.0						
Gall bladder											2.0
Heart	.4	.4	0.5	.3	1.0	16.0	.05	0.05	0.1	0.5	.1
Hide and hair							.0				
Hoof	.2	.2									2.0
Intestines (small) and contents						14.0					
Intestines (small), tissue							5.0				
Kidney	10.0	8.0	10.9	2.0	6.0	18.0		.2	.5	.2	.3
Liver	5.0	8.0	2.0	1.5	2.0	25.0	2.5	.1	.2	.2	1.0
Lung	1.5	1.5	.7	.5	1.0	8.0	1.0	.05	.5	.2	.2
Muscle, leg	.3	.5					T.				.2
Muscle, rib							T.				
Spinal cord											.1
Spleen	.4	.5	.5	.4	1.0	20.0	10.0	.05	.05	.1	.2
Stomach tissue	20.0	62.0									.5
Urine			1.4	20.0	4.0						4.0

<sup>1</sup> T. = trace.

## HORSE 875

Horse 875, which was dosed at the same time as horse 764 (about 1:30 p. m.), was found dead at 8 o'clock the following morning.

On post mortem, the carcass was found to be very fat and there were multiple subcutaneous hemorrhages. In the lungs there were small hemorrhages of the visceral pleura. Numerous petechiae were found on the pericardium, and there were subendocardial hemorrhages in the ventricles. In the stomach there was marked hemorrhagic gastritis. The liver was marbled with fatty degeneration. The spleen contained a few subcapsular hemorrhages of varying size. The kidneys appeared more or less normal, but an ulcerative cystitis was present in the bladder.

Chemical analysis of the tissue of this animal also was made for selenium. The results are given in table 2.

## HORSE 1009

Horse 1009 was treated at 11:30 a. m. At 4 p. m. of the same day, its temperature was 100.6° F., and the animal seemed normal. At 9 a. m. the following day, the temperature was 101.0°. The animal was breathing very hard, and the pulse was rapid. An hour and a half later the horse was down, the temperature was 103.6°, and tonic spasms were noted. Death occurred at 1:10 p. m., or about 26 hours after the selenium had been given.

On post mortem, the blood was found to be almost black in color and had not coagulated 1½ hours after death. No lesions were observed in the lungs or in the liver. There were ecchymotic hemorrhages along the coronary groove of the heart and subendocardial hemorrhages in the ventricles. The kidneys were friable, and there were hemorrhages in the cortex.

Chemical analysis of the tissue of this animal was made for selenium. The results are given in table 2.

## MULE 1033

Mule 1033 was treated about 1 p. m. At 4 p. m. of the same day, the temperature was 102.2° F. The next morning, the temperature was 101.0°, at which time the mule was breathing hard, with nostrils distended. The pulse was very weak. Feed and water were refused. A blood sample collected at this time was black but was not hemolyzed. In the afternoon the temperature was 100.2°. The animal was found dead on the morning of the second day.

On post mortem the lungs appeared more or less normal, except for a few small black hemorrhages under the visceral pleura. There were also many black ecchymotic hemorrhages in the mediastinum at the bifurcation of the bronchi and under the parietal pleura in the intercostal spaces. The heart contained numerous small black hemorrhages along all the coronary vessels as well as on the auricles. In the ventricles a few subendocardial hemorrhages were found. The blood was black and did not coagulate readily. There was some fatty degeneration of the liver. In the spleen, a few subcapsular hemorrhages were found. Areas of acute enteritis appeared along the small intestines, and the blood vessels were distended with black blood. There was an acute nephritis as well as an acute catarrhal cystitis. The urine was coffee colored and contained numerous gelatinous clots.

Chemical analysis of the tissue of this animal was made for selenium. The results are given in table 2.

## MULE 1035

Mule 1035 was treated about 11:15 a. m. At 4 p. m. of the same day the animal's temperature was 101.5° F., pulse 76, and the respirations were fast. It had no appetite and appeared sluggish. On the following day, the temperature was 101.6°, the pulse was weak, and the respirations were fast and labored. The animal had not eaten or drunk since the previous day. At 4 p. m. the pulse was 90, temperature was 101.5°, and the respirations were fast and very labored. It was found dead on the morning of the second day.

On post mortem there were large subcutaneous hemorrhages over the ribs. The lungs were congested. Numerous small hemorrhages were present on the fat of the heart, and very large hemorrhages were found along the coronary groove and under the endocardium of the left ventricle. The blood was black but had not coagulated. There was a fibrinous peritonitis on the lower part of the diaphragm and subperitoneal hemorrhages under the processes of the lumbar vertebrae. Numerous fibrinous tags were present on the surface of the liver, which was marbled with large areas of fatty degeneration. Very few petechiae were observed on the spleen. There were hemorrhagic enteritis and large black hemorrhages in the folds of the mesentery. The kidneys were soft and friable.

Chemical analysis of the tissue of this animal was made for selenium. The results are given in table 2.

## MULE 991

Mule 991 was treated at 1 p. m. The next morning the temperature was 99.4° F., and the pulse was weak. The respirations were labored and fast, and the nostrils were distended. It did not eat and drank little water. A blood sample drawn at this time was black but not hemolyzed. In the afternoon the temperature was 102.2°, but the general condition remained unchanged. The animal drank a considerable quantity of water on the second morning but did not eat. The temperature was 100°. The breathing, however, seemed normal although the pulse remained weak. From this time on the mule improved, and 7 days after the selenium was given it was eating and drinking and appeared entirely normal.

Chemical analysis of the blood sample showed a selenium content of 1 p. p. m.

## HORSE 1003

Horse 1003 was treated at 12:45 p. m. The animal was not eating or drinking on the following day, and there was some diarrhea. It was breathing hard. A blood sample collected on the morning of the second day was very black. At this time, the horse was eating hay and drinking water again and the respiration had returned to normal. There was no change in the temperature at any time, and the horse remained normal for the remainder of the period of observation.

Chemical analysis of the blood sample showed a selenium content of 0.5 p. p. m.

## CALF 1

Calf 1 was treated about 9:30 a. m. and died about 3:30 p. m. the same day. At this time there was a discharge from the mouth and a profuse diarrhea. The animal was not autopsied. Chemical analysis of the tissue of this animal was made for selenium. The results are given in table 2.

## COW 1729

Cow 1729 was lactating and not pregnant. It was treated about 9:30 a. m., and in the afternoon of the same day was salivating profusely and appeared very dull. It did not eat or drink. The condition was about the same on the following morning, except that there was no salivation. The animal was down in the afternoon, the breathing was labored, the eyes were dull, and the extremities were cold. The breath had a marked garlic odor, and the feces a peculiar fetid odor. The animal was found dead on the second morning.

On post mortem the lymph glands throughout the body were hemorrhagic. Extensive pleural adhesions were found in the thoracic cavity, but the lungs appeared relatively normal. In the heart there were numerous subepicardial hemorrhages which were particularly marked on the left ventricle. Three to four liters of straw-colored fluid was present in the peritoneal cavity. There were numerous hemorrhages about 1 cm. in diameter throughout the liver, in one lobe of which was a circumscribed abscess, about the size of a baseball, containing white fluid pus. A few subcapsular hemorrhages were found in the spleen. Both kidneys showed an acute nephritis with a few small hemorrhages under the capsules, but the urine appeared normal.

A milk sample taken on the first day after ingestion of the sodium selenite contained 0.02 p. p. m. of selenium. On the second day at the time of death the milk contained 0.04 p. p. m. and the urine 5 p. p. m. of selenium.

## COW 1912

Cow 1912 was dry and carrying an 8-month-old fetus. It was treated in the morning, and death occurred late in the afternoon of the following day. On post mortem few lesions were found.

## COW 1914

Cow 1914 was lactating and was rather thin at the time it was treated. The next day the animal took little feed or water, and milk production was greatly reduced. On the second day the cow was down practically all the time and had stopped giving milk. It did not eat or drink during this time. Two days later, however, it was eating hay and drinking again and also giving a small quantity of milk. From this time until the cow was autopsied 5 days later it ate only hay, drank little water, and seemed to lose slightly in weight. Milk production did not return to the pretreatment level. Post-mortem findings were entirely negative.

## COW 1839

Cow 1839 was lactating and in good condition when treated. The animal was observed for the next 20 days, and no clinical symptoms of selenium poisoning were shown at any time. There was no evident

impairment of the appetite for either grain or hay, the usual quantity of water was taken, and milk production remained the same as before treatment. However, the feces had a peculiar fetid odor on the second day after the selenium was given, and on the following day a somewhat similar odor was noted in the milk at the time it was drawn. On post mortem, 20 days later, the animal appeared entirely normal.

On the fifth and sixth days after ingestion of the selenium the milk was found to contain 2 and 3 p. p. m., respectively. The selenium content of the urine on the sixth day was 3 p. p. m.

## FIG 4282

Fig 4282 was given dry sodium selenite mixed with a little moistened mill feed, and the mixture was eaten readily. Few clinical symptoms of selenium poisoning were noted during the next 2 days, but the animal was found dead on the morning of the third day.

On post mortem the carcass was in good condition, the hair was firm, but the skin was slightly reddened. The cutaneous blood vessels were filled with dark, coagulated blood. The pleural cavity contained about 150 cc. of clear reddish-yellow fluid. The trachea and bronchi were filled with foam, and some pneumonic changes were found in the lungs. The heart contained a large quantity of black blood, and there were a few hemorrhages along the coronary vessels. About 200 cc. of yellowish fluid was present in the stomach, and the mucosa of the fundic portion was slightly reddened. The intestines appeared practically normal, but the mesentery contained numerous large dark hemorrhagic areas and the mesenteric lymph glands were black.

On histological examination there was extensive congestion in the capillary blood vessels and thrombi in a number of the larger vessels of the liver. Most of the liver cells showed extreme cloudiness with fatty changes, together with cell vacuolation, and many of these cells also contained deposits of bile pigment. Few normal liver cells were observed, but there was no perceptible increase in the interstitial structure of the organ.

In the kidney there was marked capillary engorgement with slight hemorrhages and also thrombi in several of the larger vessels. Changes in the tubular epithelium varied from cloudiness and loss of cell nuclei to complete destruction of the cells. Groups of tubules were seen in various areas which exhibited more advanced degenerative changes than in other parts of the section. Fatty changes with cell vacuolation and exfoliation of the epithelium in many tubules were particularly noticeable in these areas. Varying amounts of pigment were observed in this section.

There was blood engorgement, particularly in the larger vessels of the spleen, and a slight edema. The interstitial tissue appeared to be somewhat increased.

The changes in the lungs were typical of catarrhal pneumonia, such as thickening of the alveolar walls, cellular infiltration, and sloughing of the bronchial epithelium.

Practically all the vessels of the heart muscle were engorged with blood. The muscle fibers showed cloudiness with beginning fatty changes. Rather heavy deposits of greenish-yellow pigment (bile) were observed, particularly along the course of the blood vessels.

Chemical analysis of the tissue of this animal was made for selenium. The results are given in table 2.

## FIG 4754

Pig 4754 was treated about 9:25 a. m. Within the next 5 hours, the pig had vomited four times. On the following day the animal was down, shivering, and had a profuse diarrhea. Post mortem was made 18 days later. During that period the pig was unable to move its legs, although it appeared fully conscious and was able to eat when grain was offered.

On post mortem relatively few lesions of any consequence were found. There was some fatty degeneration of the liver and a few hemorrhages in the cortex of the kidneys. Chemical analysis of tissue for selenium is given in table 2.

## FIG 4737

Pig 4737 was treated at the same time as pig 4754. On the following day the animal was extremely sick, although it was not observed to vomit at any time. This pig lay down most of the time, ate little, shivered, squealed, and ground its teeth a great deal. On the fourth day the animal was able to move about and appeared somewhat better, and by the fifth day it seemed to have returned practically to normal and was eating again.

On post mortem 2½ months later no lesions were found. Chemical analysis of the tissue of this animal was made for selenium. The results are given in table 2.

## FIG 4730

Pig 4730 was treated in the morning. Within the next 24 hours it vomited greenish material several times. At the same time there was considerable depression, no appetite, and disinclination to move about. From this time on the animal recovered gradually until 1 week later it appeared to be entirely normal.

On post mortem, 2½ months later, the only lesions noted were subendocardial petechiae in the left ventricle. Chemical analysis of the tissue of this animal was made for selenium. The results are given in table 2.

## FIG 4683

Pig 4683 was treated in the morning. Although this animal did not vomit, on the following day it showed symptoms of selenium poisoning resembling those of the other pigs, but not so pronounced. Two days later it began to eat and within 5 days returned to normal.

## FIG 4703

Pig 4703 was treated in the morning. The animal was slightly sick for the next 24 hours, as evidenced by lack of appetite and general sluggishness. The following day the animal appeared to have recovered fully.

On post mortem, 2½ months later, a slight pericarditis constituted the only gross lesion found. Chemical analysis of the tissue of this animal was made for selenium. The results are given in table 2.

FIG 4746

Fig 4746 never showed any clinical symptoms of selenium poisoning.

### DISCUSSION

From the results shown in table 1, it appears that the minimum lethal dose of selenium, when administered by mouth in the form of sodium selenite, has been established within reasonably close limits for horses, mules, cattle, and swine. In addition, it has been demonstrated that there is a distinct difference in the ability of the several species of animals to tolerate various quantities of selenium when given orally in single doses. Enough animals were not included in this work to determine whether there is any difference in susceptibility among individuals within a species.

The minimum lethal dose of selenium for horses and mules was determined with somewhat more exactness than that for the other two species. The first three horses to be treated received 3.6 mg. or more of selenium per pound of body weight. The animals survived for 24 hours or less. When the dose was reduced to about 1.5 mg., one mule out of three survived. The two mules that died after receiving about 1.5 mg. per pound of body weight were very fat, whereas the one that survived was thin as a result of having had infectious anemia (swamp fever). However, typical symptoms of acute selenium poisoning were induced by this dose, and a period of about a week elapsed before the mule was eating and drinking normally again. The minimum lethal dose of selenium for horses and mules was therefore about 1.5 mg. per pound of body weight.

It seemed evident from the results obtained that animals in good condition might be more susceptible to the action of selenium than comparatively thin animals. Therefore, in calculating a dose of selenium for an animal with excess weight, if a dose which merely produces symptoms of selenium poisoning in a thin animal of the same weight is reduced in proportion to the excess weight of the former animal, the same results should be obtained in this animal as in the latter one. To test this assumption a fifth horse (No. 1003) was treated. The animal was very fat, its weight being estimated as 200 pounds in excess of normal for a horse of its size and conformation. The quantity of selenium administered was, therefore, reduced by 18 percent. Typical symptoms of selenium poisoning were produced, from which the animal apparently recovered in about 3 days.

The symptoms of acute selenium poisoning in horses are not particularly characteristic. There is first a lack of appetite and refusal to drink water, and the animal stands quietly in the stall. The pulse is slightly accelerated and the respirations are fast. The temperature may be normal or slightly higher. A few hours before death, the animal stands as though fixed to the floor, eyes staring, nostrils dilated, and the breathing is convulsive, fast, and very labored. The temperature has a tendency to rise, and the pulse is fast and weak or imperceptible in some animals. A blood sample taken at this time is almost black in color, but there is no hemolysis.

That death is due to asphyxiation has been mentioned previously by Beath and coworkers.<sup>5</sup> This explanation seems entirely probable,

<sup>5</sup> BEATH, O. A., EPPSON, H. F., and GILBERT, C. S. SELENIUM AND OTHER TOXIC MINERALS IN SOILS AND VEGETATION. Wyo. Agr. Expt. Sta. Bul. 206, 56 pp., illus. 1935.

both from the symptoms presented in acute cases of poisoning and from the analysis of fractions of whole horse blood by Dudley.<sup>6</sup> In his work it was shown that a "protein-like selenium complex" was present in the erythrocytes and none in the serum, plasma, and fibrin. As a consequence of the formation of this new compound in the red cells and in the presence of sufficient selenium, it is possible that the respiratory capacity of the blood is reduced to a point where death follows. A possible explanation for the difference in susceptibility of the three mules which received 1.5 mg. of selenium per pound of body weight is as follows: A fat animal that is given the same quantity of selenium per pound of body weight as a thin one receives a larger dose in relation to its total blood volume because of the avascularity of fat tissue and has a correspondingly poorer chance for survival. There is a possibility, then, that if the dose of selenium could be calculated in terms of blood volume rather than of body weight, the variation in susceptibility among individuals of the same species would not be so pronounced. Furthermore, oxygen-capacity determinations of the blood would perhaps give even more information on this point because of the apparent affinity of selenium for hemoglobin.

The analysis of tissue from the horses and mules that died of toxic doses of sodium selenite brings out some noteworthy points. The selenium content of the stomach, kidneys, and liver of the animals was high as compared with that of the other tissues examined. The high selenium content of the urine and feces of these fatal cases and of chronic cases<sup>7</sup> shows that large quantities of selenium are eliminated through the kidneys as well as through the intestines. The concentration of selenium in the blood of these animals at death was not so great as in the chronic cases over a period of several months.

In cattle the minimum lethal dose of selenium was found to be between 4.5 and 5 mg. per pound of body weight. This was about three times the quantity required to kill horses. The symptoms of acute poisoning in cattle are similar to those observed in horses, although not so marked.

The analysis of tissue from the calf, which died 6 hours after the administration of 9.15 mg. per pound of body weight, showed a relatively high selenium content throughout the animal.

Swine proved to be even more resistant to the action of single doses of selenium than cattle. One animal (No. 4282), which received 10.3 mg. per pound of body weight, died in 72 hours, and a second pig (No. 4754) was paralyzed, but did not die, after receiving 7.9 mg. Since it had vomited at least four times within 5 hours after dosing, it probably did not retain all the selenium given. Had it received the full effect of the entire dose, it is probable that it would not have survived. Of the two pigs given 6 mg. per pound of body weight, No. 4730 vomited shortly after it was drenched, but there were no indications that No. 4737 had done so. Judging from these results, the minimum lethal dose of selenium for swine is between 6 and 8 mg. per pound of body weight.

<sup>6</sup> DUDLEY, H. C. TOXICOLOGY OF SELENIUM. I. A STUDY OF THE DISTRIBUTION OF SELENIUM IN ACUTE AND CHRONIC CASES OF SELENIUM POISONING. *Amer. Jour. Hyg.* 23: 169-180. 1936.

<sup>7</sup> Unpublished data.

The symptoms of acute poisoning in pigs consist largely in lack of appetite, sluggishness, and general depression. Diarrhea was observed in one pig, and grinding of the teeth in another.

On post mortem, in cases of acute poisoning, certain common gross changes were found in all four species of animals. Among these were black-colored blood which did not coagulate readily, hemorrhages in the heart (along the coronary vessels and under the endocardium, particularly in the left ventricle), and small subcapsular hemorrhages on the spleen. Less commonly, large hemorrhages were found subcutaneously, in the mediastinum and in the folds of the mesentery. In a few cases there were marked fatty degeneration of the liver and petechiae in the cortex of the kidney.

The analysis of the tissue from pig 4282 shows that the selenium did not get into the muscles, hide, hair, and bones except in very minute quantities during the 3-day interval between ingestion and death. The blood and urine of pig 4754 contained 2.5 and 4 p. p. m., respectively, 18 days after ingestion of sodium selenite equivalent to 7.9 mg. of selenium per pound of body weight. The elimination was well advanced as the selenium content of the body tissues was low. Examination of pigs 2.5 months after ingestion of relatively large doses of sodium selenite showed the nearly complete elimination of selenium.

#### SUMMARY

Selenium in the form of sodium selenite was given in large single doses to horses, mules, cattle, and swine to determine the minimum lethal dose of the element for these species. It was administered orally in the feed, as a drench, or by stomach tube, the dose being calculated as milligrams of selenium per pound of body weight. Large doses were given at the beginning of each test and the quantity was reduced for other animals until the minimum lethal dose was reached. The experiments were carried on in 1934 and 1938 at the Animal Disease Station, Beltsville, Md.

Five horses and three mules were used. Although all but two had been used previously in infectious-disease experiments, they appeared healthy on clinical examination. The minimum lethal dose of selenium was found to be about 1.5 mg. per pound of body weight.

In the experiments with cattle, one calf and four cows were included. The calf was 5 days old. Two of the cows were between 3 and 4 years of age and the other two were several years older. All these animals appeared healthy clinically and were not known to have been exposed to any infectious disease. The minimum lethal dose for this species was found to be between 4.5 and 5 mg. per pound of body weight.

In the experiments with swine, seven apparently healthy pigs, varying in age from 4 to 6 months, were used. For these animals the minimum lethal dose of selenium was found to be between 6 and 8 mg. per pound of body weight.

