STUDIES ON THE PATHOLOGY OF ARSANILIC ACID TOXICITY IN CALVES

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INTRODUCTION

Since time immemorial, arsenic derivatives have been employed in the treatment of disease and for a variety of other uses. Utilization for medicinal purposes declined greatly after the introduction of the sulfonamides and antibiotics. The latter agents have therapeutic action and possess relatively no toxicity compared to the poisonous action of arsenic. In 1949 (22), it was reported that organic arsenicals promote growth when added to the feeding rations of animals. Since that time, arsanilic acid (para-Aminophenylarsonic acid) has been widely used as an additive in poultry and swine feeds at various recommended levels. Though the quantity used for this purpose is minute, consumption of greater amounts in the daily diet leads to poisoning with symptomatology and lesions similar to those observed in poisoning with other arsenic derivatives.

The object of this study was to determine the effect of arsanilic acid on calves and to observe the symptoms, gross and histopathological lesions produced by toxic doses of this chemical.

LITERATURE

In 1921 Hooper, *et al.* (13), working experimentally on the toxicological effects of subletnal doses of arsenic derivatives on mice and dogs, found kidney injury in both species. Lethal amounts of these derivatives administered intravenously to dogs were followed by jaundice and liver necrosis, in some instances comparable with so-called acute yellow atrophy.

In recent years, as a result of the widespread use of arsenic compounds in pest control, the number of cases of arsenical poisoning has increased substantially in the large domestic animals. During the drought year of 1936 in Iowa, grasshopper bait (bran treated with arsenic) was often scattered around fields, and the arsenic, being virtually indestructible, caused poisoning in cattle in various manners and places. The symptoms were dyspnea, paralysis of the larynx, watery diarrhea and hypothermia. Necropsy revealed congestion and swelling of the abomasum and intestine, watery intestinal content, petechial hemorrhages, subendocardial hemorrhages and pulmonary emphysema.

In Poland, Niec and Zadura (21) reported that some cows died, while others exhibited only symptoms of gastro-intestinal upset after eating bran contaminated with arsenic.

In Ireland (7), necropsy of yearling cattle revealed acute yellow atrophy of the liver and enteritis typical of arsenic poisoning.

Seibold (28), described arsenic poisoning in a calf six months old with signs of nervousness, nasal discharge, generalized weakness and diarrhea. Necropsy disclosed large ulcers in the larynx, pharynx and ileum, fluid content of the intestinal tract and yellow liver. Microscopically, focal necrosis in the liver and degenerative changes in the renal tubular epithelium were demonstrated.

Chronic arsenic poisoning of horses was described by Darraspen, et al. (9). Early symptoms were wasting and emaciation. Gastro-intestinal and nervous symptoms appeared suddenly three to five days before death. On post mortem examination there was dehydration of the tissues, but in the alimentary canal abundant liquid was found.

Arsenic when fed to pigs at 15 times the recommended dosage produces incoordination and blindness. It can, however, be used safely if incorporated in feeds at low dosage levels.

Growth promotion is a property of arsanilic acid independent of its ability to supress intestinal organisms (22). Wahlstrom, et al. (33), used arsanilic acid for counteracting the effects of chronic selenium poisoning in pigs.

Originally arsanilic acid was thought to be virtually non-toxic, but it was found to be capable of producing acute and chronic poisoning in animals when fed in excessive quantities. The lesions in animals vary with the species. Bucy, *et al.* (5), found that arsanilic acid administered to growing-fatting lambs produced convulsions and damage to the liver and kidney. Renal hemorrhages were seen in dogs, and lesions in the brain and spinal cord were found in poisoned cats (22).

In animals and man, arsanilic acid can produce blindness by degeneration of the optic nerve and degenerative changes in brain tissue. Oliver and Roe (22) reported toxic effects produced within one week after feeding a ration containing approximately 15 times the level of arsanilic acid recommended for growth promotion in swine. The symptoms were progressive central nervous disturbances, incoordination and some blindness. Conciousness, temperature and appetite were normal.

Malherbe (16) found characteristic lesions in the gizzard of six birds dead from malicious arsenic poisoning.

No reports on the symptomatology and pathological lesions produced in cattle by arsanilic acid were encountered in the available literature.

MATERIALS AND METHODS

Eight clinically normal calves of different breeds were used in this study. All the animals were treated for parasites before the experiment was started and then maintained in isolation units.

Clinical, hematological and urinary examinations were performed before the experiment in order to determine the state of health and to obtain a physiological standard of values. The animals were given daily doses of arsanilic acid (Pro-Gen Abbott) varying from 1.4 to 6 mgs/lb. of live body weight with subsequent individual increases up to 20 mgs/lb. Daily physical examinations were carried out on each animal. Samples of blood and urine were taken two or three times a week. Counting of erythrocytes and leukocytes was made in a Neubauer chamber using Thoma pipettes. Blood smears, for differentiation of leukocytes, were processed with Wright's stain. The volume of packed erythrocytes was carried out in Wintrobe hematocrit tubes (15). For determination of hemoglobin, a Cenco Photelometer was used (6). Determination of prothrombin time was made on four animals according to the method of Quick (15). Analysis of glucose, creatinine, bilirubin and urea nitrogen were performed in a Spectronic 20 colorimeter. A Micro-Kjeldahl apparatus was used for determination of serum proteins and non-protein nitrogen (12).

Carbon dioxide was determined on four animals using a Van Slyke apparatus (11). Percentage of serum albumin and serum globulins were determined with a Durrum-type paper electrophoresis apparatus (30).

Urine was analyzed by physical examination, determination of reaction, specific gravity, microscopic examination of the sediment and analysis for albumin, acetone, sugar, blood, indican, bile and bilirubin (8).

Necropsies were performed immediately after killing the animals or as soon as possible after death. Tissues were fixed in 10% formalin and sectioned by both the freezing and paraffin embedding techniques. Most of the sections were stained with Harris hematoxylin and counterstained with eosin. Special stains were made for fat, calcium and myelin fibers (1).

CASUISTIC

CASE No. 1. ANGUS. MALE. No. 835. THREE MONTHS OLD.
BODY WEIGHT: 276 LBS.

DOSAGE

11/18/57	STARTED	DAILY	DOSAGE	OF	1.4 MGS/LB.
12/ 4/57	"	"	"	"	2.9 "
12/20/57	"	"	"	"	4.5 "
1/28/58	KILLED.				

DURING THE ADMINISTRATION OF THE ABOVE DOSAGE SCHEDULE, THE GAIN IN WEIGHT APPEARED NORMAL. NO ABNORMAL CLINICAL SYMPTOMATOLOGY OR APPRECIABLE CHANGES IN BLOOD AND URINE WERE OBSERVED; THE ONLY EXCEPTION WAS A SLIGHT INCREASE IN THE QUANTITY OF ALBUMIN AND DECREASE IN GAMMA-GLOBULIN AFTER STARTING THE LAST DAILY LEVEL OF 4.5 MGS/LB.

GROSS EXAMINATION. AT NECROPSY THE GENERAL CONDITION OF THE ANIMAL WAS GOOD. IN THE PLEURAL CAVITY A SMALL AMOUNT OF SEROUS FLUID WAS FOUND. SLIGHT SCARRING SEEMED TO BE PRESENT IN THE LIVER. ONE OR TWO OLD, WHITE INFARCT-LIKE AREAS WERE NOTED IN THE KIDNEYS.

HISTOLOGICAL EXAMINATION. ALL THE TISSUES SHOWED NO SIGNIFICANT LESIONS.

Case No. 2. Guernsey. Male. No. 196. Four months old.
Body weight: 318 lbs.

DOSAGE

11/18/57	started	daily	dosage	of	1.8	mgs/lb.
12/ 4/57	"	"	"	"	3.8	"
12/20/57	"	"	"	"	9.3	"
1/ 8/58	Killed.					

After beginning the last dose level a slight increase in erythrocytes, hematocrit, hemoglobin and urea nitrogen was observed; there was a decrease at first in glucose with a slight increase before death. The leukocytes, creatinine and serum proteins were within normal ranges. Serum albumin underwent a gradual decrease. The electrophoretic patterns showed a decrease in albumin and an increase in globulins at the 9.3 mgs/lb. dosage level. On 12/27/57, acetone (xx), albumin and traces of blood were found in the urine. A few hyaline casts were present in the urinary sediment. On later examinations an increased number of leukocytes were found, fine granular casts, increased quantity of albumin (xxx) and sugar (xxx) and deviation of the pH to the acid side. During the experiment the animal lost 60 pounds in 45 days but was clinically normal until 12/25/57, at which time slight diarrhea was noted. In the following days anorexia,

DEHYDRATION AND DEPRESSION WITH SLIGHT SALIVATION ALSO OCCURRED. ON 1/6/58, THE ANIMAL WAS INJECTED WITH 400 ML. OF GLUCOSE AND 10 ML. OF BALANCED SALT SOLUTION. THE ANIMAL WAS KILLED IN EXTREMIS ON 1/8/58.

GROSS EXAMINATION. BODY THIN. RIGOR MORTIS. MARKED ICTERUS. EDEMA AND ICTERUS OF THE LYMPH NODES. SMALL AMOUNT (15-20 ML.) OF MUCOID, YELLOWISH MATERIAL IN PLEURAL CAVITY. 30-40 ML. OF ICTERIC FLUID IN THE PERITONEAL CAVITY. ICTERIC AORTA. LIVER: ENLARGED, BROWNISH COLOR WITH MULTIPLE YELLOW-WHITE FOCI OF NECROSIS. MARKED GALLBLADDER DILATATION AND PIGMENT STONES. EDEMA ON FUNDUS OF ABOMASUM; HEALING EROSIONS. EDEMA OF COLON MESENTERY. EDEMATOUS KIDNEYS. BLOODY URINE (PORT WINE). JOINTS: ICTERIC, INCREASED SYNOVIA.

HISTOLOGICAL EXAMINATION. LIVER: MARKED FOCAL PERIPORTAL AND/OR MIDZONAL NECROSIS. THERE WAS COAGULATION NECROSIS AND FINE DROPLET FATTY DEGENERATION WITH ACCUMULATION OF MASSES OF BILE PIGMENT AND NEUTROPHILES IN NECROTIC AREAS. PERIPHERY OF NECROTIC AREAS SHOW CELLS UNDERGOING FINE DROPLET FATTY DEGENERATION AND COAGULATION NECROSIS. MARKED BILIARY STASIS WAS PRESENT IN BILE CAPILLARIES AND INTERLOBULAR (PORTAL) BILE DUCTS. GENERAL FATTY DEGENERATION WAS NOT PRESENT, ONLY FOCAL PRENECROTIC AREAS. MINIMAL PORTAL FIBROPLASIA WAS OBSERVED. KIDNEY: SCATTERED, BUT NUMEROUS COLLECTING TUBULES IN THE MEDULLA WERE PLUGGED WITH BILE

CASTS. TUBULAR EPITHELIUM WAS PYCNOTIC OR RARELY HYPERTROPHIC. FINE FATTY DROPLETS WERE PRESENT IN BILE CASTS AND/OR IN TUBULAR EPITHELIAL CYTOPLASM. HYALINE CASTS WERE NOTED IN THE CONVOLUTED TUBULES. ADRENAL: HEAVY FINE DROPS OF LIPID THROUGHOUT CORTEX, PARTICULARLY TOWARD THE RETICULARIS. FAT IN THE FASCICULATA IS UNEVENLY DISTRIBUTED FROM FIELD TO FIELD.

CASE No. 3. HOLSTEIN. MALE. No. 421. FOUR MONTHS OLD. BODY WEIGHT: 334 LBS.

DOSAGE

11/18/57	STARTED	DAILY	DOSAGE	OF	2.3	MGS/LB.
12/ 4/57	"	"	"	"	4.8	"
12/20/57	"	"	"	"	8.1	"
1/ 3/58	DEATH.					

AT THE TIME OF BEGINNING THE LAST DOSAGE THE GAIN IN WEIGHT SEEMED TO BE NORMAL. THE HEMATOLOGICAL PICTURE WAS NORMAL WITH ONLY A SLIGHT DECREASE IN THE QUANTITY OF HEMOGLOBIN AFTER THE FIRST DOSE, SUBSEQUENTLY RETURNING TO NORMAL INDIVIDUAL LEVEL. AFTER STARTING THE DOSAGE WITH 8.1 MGS/LB., THERE WAS AN INCREASE IN ERYTHROCYTES, HEMATOCRIT, HEMOGLOBIN, GLUCOSE AND UREA NITROGEN. THE LEUKOCYTES FIRST UNDERWENT A DECREASE AND LATER SHOWED AN INCREASE BUT WITHIN THE NORMAL LEVELS FOR CATTLE. THE CREATININE AND SERUM PROTEINS

REMAINED WITHIN THE NORMAL LEVELS. THE BILIRUBIN, NORMAL UNTIL THIS DATE, UNDERWENT A GRADUAL INCREASE UNTIL A READING WAS OBTAINED TWO DAYS BEFORE DEATH THAT WAS BEYOND THE CAPACITY OF THE RECORDING INSTRUMENT. ELECTROPHORETIC DETERMINATION OF PROTEINS SHOWED AN INCREASE OF ALBUMIN AFTER THE 8.1 MGS/LB. DOSAGE WITH A SUBSEQUENT DECREASE BELOW THE NORMAL INDIVIDUAL LEVEL. THE ALPHA AND BETA GLOBULINS SHOWED AN INCREASE AND THE GAMMA-GLOBULIN ALSO SHOWED SOME VARIATIONS, BUT WITHIN NORMAL LEVELS. ON 12/23/57, SOFT DIARRHEIC FECES WAS NOTED. THIS DIARRHEA BECAME MORE LIQUID IN THE FOLLOWING DAYS ACCOMPANIED WITH ANOREXIA, DEPRESSION AND RECUMBENT POSITION. ON 12/27/57, THE ANIMAL SHOWED MARKED DEHYDRATION, WEAKNESS, SALIVATION, FAST PULSE AND A TEMPERATURE OF 103.6° F. EXAMINATION OF THE URINE SHOWED PRESENCE OF ALBUMIN (x), BILIRUBIN (xx), BLOOD (x) AND PRESENCE OF A FEW ERYTHROCYTES AND CELL DETRITUS IN THE SEDIMENT. THREE DAYS LATER THERE WAS AN INCREASE IN THE QUANTITY OF BILIRUBIN (xxx), ALBUMIN (xxx) AND BLOOD (xxxx); THE URINARY SEDIMENT SHOWED ERYTHROCYTES AND HYALINE OR CELL CASTS. THIS CLINICAL SYMPTOMATOLOGY PERSISTED UNTIL THE ANIMAL DIED ON 1/2/58.

GROSS EXAMINATION. CACHEXIA; EMACIATION; RIGOR MORTIS. ICTERUS OF SUBCUTANEOUS TISSUE. LYMPH NODES: SOME EDEMA; HYPEREMIA AND ICTERUS OF HYLAR TISSUE. PULMONARY EDEMA WITH LARGE QUANTITY OF FOAM IN BRONCHI AND TRACHEA. AORTA: ICTERIC.

SEROUS ICTERIC ATROPHY OF CORONARY FAT. LIVER: ENLARGED, ROUND EDGE, YELLOW-ORANGE WITH MULTIPLE 3-5 MM. GREENISH CASEOUS FOCI. FOCAL HEMORRHAGE PICTURE IN CAUDATE LOBE. COMMON BILE DUCT, HEPATIC DUCTS AND CYSTIC DUCT ENLARGED, THICKENED AND CONTAINED MULTIPLE DARK ULCER-LIKE NECROSIS. BILE: THICK, MUCOID. ENDOCRINE GLANDS: NO LESIONS. SCATTERED HEALING, SMOOTH EDGED ULCERS IN ABOMASAL FUNDUS AND PYLORUS. REST OF TRACT EMPTY. KIDNEYS: NO LESIONS. URINARY BLADDER DILATED WITH PORT WINE HEMOGLOBINURIA. JOINTS: MARKEDLY ICTERIC.

HISTOLOGICAL EXAMINATION. KIDNEYS: HIGH GRADE HYPEREMIA; SOME CELLULAR AND PIGMENT CASTS. LIVER: LARGE FOCUS OF COAGULATION NECROSIS, WITH STRUCTURAL RETENTION, INVOLVING PORTAL AND LOBULAR TISSUE. FATTY DEGENERATION IN ADJACENT LIVER CELLS. MARKED BILE RETENTION IN ALL CAPILLARIES AND LIVER CELLS.

CASE NO. 4. HOLSTEIN. MALE. NO. 205. FOUR MONTHS OLD. BODY WEIGHT: 334 LBS.

DOSAGE

11/18/57	STARTED	DAILY	DOSAGE	OF	3.0 MGS/LB.
12/ 4/57	"	"	"	"	6.0 "
12/20/57	"	"	"	"	10.0 "
12/31/57	DEATH.				

UNTIL BEGINNING THE LAST DOSAGE THE GAIN IN WEIGHT SEEMED NORMAL. EXAMINATION OF BLOOD AND URINE SHOWED VARIATIONS, BUT WITHIN NORMAL RANGES. AN EXCEPTION WAS FOUND IN THE ELECTROPHORETIC PATTERN WHICH SHOWED A DECREASE IN ALBUMIN AND AN INCREASE IN GAMMA-GLOBULIN; THESE REACHED NORMAL LEVELS, HOWEVER, AFTER STARTING THE 6 MGS/LB. DOSAGE. THE 10 MGS/LB. DOSAGE RESULTED IN AN INCREASE OF THE HEMOGLOBIN, HEMATOCRIT, ERYTHROCYTES, GLUCOSE AND UREA NITROGEN. THERE WAS AN INCREASE OF LEUKOCYTES BUT WITHIN NORMAL LEVELS. NO VARIATION IN CREATININE AND SERUM PROTEINS WAS FOUND. THE BILIRUBIN LEVELS, NORMAL UP TO THIS TIME, UNDERWENT A VERY GREAT INCREASE (26.04) ON THE DAY OF DEATH. URINARY EXAMINATIONS, ALTHOUGH PREVIOUSLY NORMAL, SHOWED PRESENCE OF ALBUMIN (++), TRACES OF ACETONE AND A FEW HYALINE AND EPITHELIAL CASTS. THE CLINICAL SYMPTOMATOLOGY WAS THE SAME AS FOUND IN FORMER CASES: DIARRHEA, ANOREXIA, DEPRESSION, DEHYDRATION, SALIVATION AND WEAKNESS. THESE SYMPTOMS WERE MORE MARKED IN THE COURSE OF THE FOLLOWING DAYS UNTIL DEATH OCCURRED ON 12/31/57.

GROSS EXAMINATION. BODY WARM; VERY THIN BUT NOT HIDEBOUND. SUBCUTANEOUS FAT GONE. SEROUS ATROPHY. MARKED ICTERUS OF ALL SUBCUTANEOUS TISSUES. LYMPH NODES: PALE, MODERATELY JUICY WITH OCCASIONAL HEMORRHAGIC POINTS IN CORTEX. ICTERUS OF TRACHEA. CHRONIC OR VIRUS-LIKE PLUM COLORED CONSOLIDATION AND FIRMNESS OF VENTRAL PORTIONS OF APICAL AND CARDIAC LOBES

OF RIGHT LUNG. LYMPHATICS DILATED WITH YELLOWISH LYMPH. HEART: CORONARY FAT; SEROUS ATROPHY AND ICTERUS. AORTA AND BLOOD VESSELS: ICTERUS OF ALL INTIMA EXAMINED. LIVER: DILATED GALLBLADDER WITH PATCHY HYPEREMIA. APPARENT NECROTIC ULCERS THROUGHOUT BILIARY TREE. CONSPICUOUS DUODENAL OPENING. MUCUS AND NECROTIC MATERIAL IN DUCTULAR LUMINA. ENTIRE LIVER ORANGE-YELLOW, ENLARGED AND DEFORMED. APPEARED TO BE CENTRAL NECROSIS IN MOST LOBULES. THYMUS: ATROPHY. ADRENALS: NO GROSS FAT. GASTRO-INTESTINAL TRACT: MULTIPLE SMOOTH-EDGED ULCERS IN FUNDUS AND PYLORUS OF ABOMASUM WITH HEMORRHAGES IN BOTTOMS. NO GROSS INFLAMATION EXCEPT FOR SCATTERED HEALING ULCERS IN INTESTINE. SOME PETECHIAE. URINARY SYSTEM: SCATTERED WHITE SMOOTH INFARCTS IN BOTH KIDNEYS, NOT NUMEROUS. EARLY SEROUS ATROPHY OF PERIRENAL FAT. BRAIN: MODERATE INCREASE IN CEREBRO-SPINAL FLUID. JOINTS: MARKED INCREASE IN THE AMOUNT OF VISCID AND ELASTIC SYNOVIA; MARKEDLY ICTERIC. HISTOLOGICAL EXAMINATION. HEART: NORMAL. LIVER: FATTY DEGENERATION-DROPLETS OF ALL SIZES PLUS FOCAL NECROSIS, INVOLVING MAINLY PERIPORTAL AREAS AND AFFECTING ONE QUADRANT OF LOBULE. NEUTROPHILES AND BILE PIGMENT IN NECROTIC AREAS. FAT DISTRIBUTION UNIFORM THROUGHOUT. PORTAL BILE DUCTS CONTAIN BILE PLUGS. LINKING UP OF PORTAL AREAS BY FIBROUS TISSUE HAD BEGUN.

Case No. 5. Jersey. Male. No. 323. Four months old.
Body weight: 170 lbs.

DOSAGE

4/29/58	started	daily	dosage	of	3.0	mgs/lb.
5/12/58	"	"	"	"	6.0	"
5/23/58	"	"	"	"	20.0	"
6/ 4/58	Death.					

Until the beginning of the last dose level the animal was in good condition. The gain in weight seemed to be normal and the examination of blood and urine showed no variations beyond normal levels. Three days after starting the 20 mgs/lb. dosage, the animal showed anorexia and slight diarrhea. During the following days, these symptoms persisted with loss of weight, recumbent position, slight ataxia, absence of rumen movements, weakness and moaning. The diarrhea became profuse. The head was turned to one side of the body and in a raised position. On the day of death there was opisthotonus with continuous running movements. After the 20 mgs/lb. dose there was an increase in erythrocytes, hematocrit, hemoglobin, prothrombin time, non-protein nitrogen and bilirubin. The leukocytes, creatinine, glucose, serum proteins and carbon dioxide were maintained within normal levels. The urine showed a slight decrease in its specific gravity. There was a marked quantity of albumin (xxx) and presence of acetone (x). The electrophoretic pattern

SHOWED AN INCREASE OF ALPHA-GLOBULIN AND DECREASE OF GAMMA-GLOBULIN.

GROSS EXAMINATION. BODY THIN BUT NOT HIDEBOUND. SUBCUTANEOUS FAT GONE. ICTERUS. LYMPH NODES: HYPERTROPHY, EDEMA AND OCCASIONAL ZONES OF CONGESTION. SLIGHT HEPATIC ADHERENCE TO THE ABDOMINAL WALL. JOINTS: INCREASE OF THE AMOUNT OF SYNOVIA; ICTERUS. LUNGS: SLIGHT INTERSTITIAL EDEMA; FOAM IN THE TRACHEA. HEART: SUBENDOCARDIAL HEMORRHAGES OF THE LEFT VENTRICLE. LIVER: SHOWED NECROTIC ZONES OF DIFFERENT SIZE,THE LARGEST BEING 3 CM. IN DIAMETER. GALLBLADDER PRESENTED HEMORRHAGIC AREAS. SCLEROTIC BILIARY DUCT, PARTIALLY OBSTRUCTED. GASTRO-INTESTINAL TRACT: EDEMA OF ABOMASAL MUCOSA. EMPTY INTESTINES. KIDNEYS: HEMORRHAGIC ZONES IN THE PELVIS. CENTRAL NERVOUS SYSTEM: HEMORRHAGIC SUBDURAL FLUID. EDEMA OF THE BRAIN; ICTERUS IN THE WHITE MATTER.

HISTOLOGICAL EXAMINATION. LYMPH NODES: MILD LYMPHADENITIS; HYPEREMIA. LUNGS: MODERATE INTERSTITIAL EDEMA. HEART: SUBENDOCARDIAL HEMORRHAGES; FOCAL FATTY DEGENERATION IN MYOCARDIAL FIBERS. LIVER: PERIPORTAL NECROSIS; BILE PLUGS IN BILE DUCTS; BILE PLUGS IN INTRALOBULAR BILE CAPILLARIES; CENTRAL LOBULAR NECROSIS; FATTY INFILTRATION; PORTAL CIRRHOSIS; FIBROSIS. ABOMASUM: SUBMUCOSAL EDEMA. INTESTINE: NECROSIS; NECROTIZING INFLAMATION OF THE BILE DUCT; HYPEREMIA; SMALL HEMORRHAGES. KIDNEYS: ACUTE SEGMENTAL NEPHROSIS; SLIGHT

DYSTROPHIC CALCIFICATION. BRAIN: PERIVASCULAR EDEMA. ADRENALS: VACUOLATION OF THE FASCICULATA ZONE; MORE FAT THAN NORMAL. SPLEEN: MODERATE SPLENIC CONGESTION. BONE: HYPOPLASIA OF THE BONE MARROW.

Case No. 6. JERSEY. MALE. No. 315. FOUR MONTHS OLD. BODY WEIGHT: 192 LBS.

DOSAGE

4/29/58	STARTED	DAILY	DOSAGE	OF	4.0	MGS/LB.
5/12/58	"	"	"	"	6.0	"
5/23/58	"	"	"	"	20.0	"
6/ 4/58	DEATH.					

UNTIL THE BEGINNING OF THE LAST DOSAGE, THE HEMATOLOGICAL AND URINARY EXAMINATIONS AS WELL AS CLINICAL INSPECTION WERE NORMAL. THE WEIGHT GAIN SEEMED TO BE NORMAL. AFTER THE FIRST DOSAGE OF 4.0 MGS/LB. THERE WAS A SLIGHT INCREASE IN THE ERYTHROCYTE COUNT AND PERCENTAGE OF GAMMA-GLOBULIN. THIS INCREASE WAS CONSIDERED TO BE A RESULT OF THE STIMULATION BY THE DRUG; AFTER FOUR DAYS THESE FIGURES WERE AGAIN WITHIN NORMAL LEVELS.

THE FIRST SYMPTOMS OF POISONING STARTED TO APPEAR THREE DAYS AFTER RECEIVING THE 20 MGS/LB. DOSAGE. THERE WAS SLIGHT DIARRHEA AND ANOREXIA. IN THE FOLLOWING DAYS THE

ANOREXIA PERSISTED AND THE DIARRHEA BECAME PROFUSE AND WATERY. THERE WAS AN ABSENCE OF RUMEN MOVEMENTS, WEAKNESS, ATAXIA AND MOANING. THE ANIMAL LAY DOWN AND PREFERRED TO REMAIN IN THIS POSITION; THE HEAD WAS TURNED TO ONE SIDE AND RAISED. CONCOMITANT WITH THIS SYMPTOMATOLOGYTHERE WAS AN INCREASE IN ERYTHROCYTES, HEMATOCRIT, HEMOGLOBIN, LEUKOCYTES AND PROTHROMBIN TIME. THE BILIRUBIN WAS EXTREMELY HIGH. THE LEUKOCITIC DIFFERENTIAL, CREATININE, SERUM PROTEINS, NON-PROTEIN NITROGEN AND CARBON DIOXIDE REMAINED AT NORMAL LEVELS. THERE WAS A REDUCTION OF GLUCOSE IN THE BLOOD AND DECREASE OF SPECIFIC GRAVITY OF THE URINE WITH SOME ALBUMIN AND TRACES OF ACETONE ALSO PRESENT. THE ANIMAL DIED ON JUNE 4, 1958 AND IT WAS NOT POSSIBLE TO PERFORM THE NECROPSY UNTIL MANY HOURS AFTER DEATH.

GROSS EXAMINATION. BODY THIN BUT NOT HIDEBOUND. LYMPH NODES: HYPERTROPHY, CONGESTION. HEPATIC ADHERENCE TO THE ABDOMINAL WALL. JOINTS: ICTERUS. LUNGS: INTERSTITIAL EDEMA. HEART: SUBENDOCARDIAL HEMORRHAGES. LIVER: ICTERUS; MICROABCESSATION AND SCLEROSIS OF THE BILIARY TREE. GALLBLADDER: HEMORRHAGES: SCLEROSIS OF THE BILIARY DUCT. INTESTINES: ULCERS AND HEMORRHAGES. KIDNEYS: ABSCESSES IN THE CALYCES.

MICROSCOPICAL EXAMINATION. LYMPH NODES: LYMPHADENITIS; DEPLETION OF LYMPHOCYTES. TONSYL: ACUTE HYPEREMIA. LUNGS: INTERSTITIAL EDEMA, HYPEREMIA. HEART: SUBENDOCARDIAL HEMORRHAGES. LIVER: SEVERE GENERALIZED NECROSIS. BILE DUCT

AND GALLBLADDER: SEVERE HEMORRHAGE AND NECROSIS. INTESTINE: CATARRHAL DUODENITIS; INFLAMATION OF VATER'S AMPULLA; ULCERS AND HEMORRHAGES; SEVERE EDEMA OF THE SUBMUCOSA. KIDNEYS: ACUTE SEGMENTAL NEPHROSIS; INFARCTION; ACUTE GLOMERULITIS; SLIGHT DYSTROPHIC CALCIFICATION. BLADDER: HYPEREMIA. BRAIN: MICROFOCUS OF LYMPHOCYTES. ADRENALS: HYPEREMIA; MORE FAT THAN NORMAL IN FASCICULATA ZONE; HEMORRHAGES. TESTICLE: HYPERPLASIA OF INTERSTITIAL CELLS. SPLEEN: ACUTE SPLENIC CONGESTION. BONE: HYPOPLASIA OF THE BONE MARROW.

Case No. 7. HOLSTEIN. MALE. No. 320. FOUR MONTHS OLD. BODY WEIGHT: 220 LBS.

DOSAGE

4/29/58	STARTED DAILY DOSAGE OF			5.0	MGS/LB.
5/12/58	"	"	"	8.0	"
5/23/58	"	"	"	20.0	"
6/ 4/58	DEATH.				

UNTIL THE BEGINNING OF THE LAST DOSE LEVEL, CLINICAL, URINARY AND HEMATOLOGICAL EXAMINATIONS WERE NORMAL WITH THE EXCEPTION OF THE PROTHROMBIN TIME WHICH INCREASED GRADUALLY. PERCEPTIBLE SYMPTOMATOLOGY OCCURRED THREE DAYS FOLLOWING THE 20 MGS/LB. DOSAGE. THERE WAS ANOREXIA WITH SLIGHT DIARRHEA WHICH BECAME WATERY IN SUBSEQUENT DAYS. MARKED EMACIATION, WEAKNESS,

ATAXIA, MOANING AND ATONY OF THE RUMEN WERE NOTED. THE HEAD WAS TURNED TO ONE SIDE AND RAISED; THE ANIMAL APPEARED TO BE IN ACUTE PAIN. CONCOMITANT WITH THIS SYMPTOMATOLOGY THERE WAS A SLIGHT INCREASE OF ERYTHROCYTES, HEMATOCRIT, HEMOGLOBIN, NON-PROTEIN NITROGEN AND BILIRUBIN. A MARKED INCREASE IN LEUKOCYTES OCCURRED ALTHOUGH THE DIFFERENTIAL WAS NORMAL. THE CREATININE, GLUCOSE, SERUM PROTEINS AND CARBON DIOXIDE WERE AT NORMAL LEVELS. IN THE URINE THERE WAS A SLIGHT INCREASE IN THE AMOUNT OF ALBUMIN (XX) AND A DARK AMBER COLOR SUGGESTING THE PRESENCE OF BLOOD THOUGH THE TEST WAS NEGATIVE. THE ANIMAL DIED ON JUNE 4, 1958.

GROSS EXAMINATION. BODY EMACIATED; ICTERUS. LYMPH NODES: EDEMA; SOME PETECHIAE. FLUID IN THE THORACIC CAVITY (2 LITERS). MUSCLES: ICTERUS. THYROIDS: EDEMA AND PETECHIAE. LUNGS: INTERSTITIAL EDEMA; PNEUMONIC ZONES. HEART: SUB-ENDOCARDIAL HEMORRHAGES. LIVER: SLIGHT CIRRHOSIS; ICTERUS; NUMEROUS FOCI OF NECROSIS OF DIFFERENT SIZE UP TO 3 CM. IN DIAMETER. KIDNEYS: ICTERIC ZONES OF NECROSIS IN THE CALYCES. BLADDER FILLED WITH DARK AMBER URINE; ABCESS IN THE URETERAL ORIFICE. RIGHT TURBINATE BONE: HEMORRHAGE AND CONGESTION.

HISTOLOGICAL EXAMINATION. LYMPH NODES: EDEMA; HYPEREMIA; DEPLETION OF LYMPHOCYTES; ACUTE LYMPHADENITIS. MUSCLE: MUSCULAR ATROPHY. LUNGS: ALVEOLAR AND INTERSTITIAL EDEMA; MARKED PROLIFERATION OF LYMPHOCYTES BOTH SUBPLEURAL AND IN INTERSTITIAL TISSUES; THROMBI IN VESSELS; FIBRIN THROMBI IN

LYMPHATICS; BRONCHONEUMONIA; DILATATION OF SUBPLEURAL LYMPHATICS. HEART: SUBENDOCARDIAL HEMORRHAGES. LIVER: PERIPORTAL NECROSIS; BILE PLUGS IN BILE DUCTS; BILE PLUGS IN INTRALOBULAR BILE CAPILLARIES;NORMAL QUANTITY OF FAT; CIRRHOSIS. GALLBLADDER: HYPEREMIA; NECROSIS IN MUCOSA AND SUBMUCOSA; PRESENCE OF MACROPHAGUS AND NEUTROPHILES; NECROTIZING INFLAMATION OF THE GALLBLADDER; EDEMA; SLIGHT HEMORRHAGE IN SUBMUCOSAL GLANDS. INTESTINE: HYPEREMIA. KIDNEYS: DEGENERATION; INFARCTION; EDEMA SURROUNDING THE BLOOD VESSELS; LYMPHOCYTIC INFILTRATION; SLIGHT DYSTROPHIC CALCIFICATION. THYROIDS: FAT NECROSIS SURROUNDING THYROIDS. ADRENALS: MORE FAT THAN NORMAL IN FASCICULATA. THYMUS: EDEMA; HYPEREMIA. SPLEEN: ACUTE CONGESTION. BONE: HYPOPLASTIC BONE MARROW.

<u>CASE No. 8</u>. GUERNSEY. MALE. No. 836. EIGHT MONTHS OLD. BODY WEIGHT: 300 LBS.

DOSAGE

4/29/58	STARTED DAILY DOSAGE OF			5.0	MGS/LB.
5/12/58	"	"	"	8.0	"
5/23/58	"	"	"	20.0	"
6/ 4/58	DEATH.				

UNTIL THE BEGINNING OF THE LAST DOSE LEVEL, CLINICAL EXAMINATION REVEALED NO ABNORMAL SYMPTOMATOLOGY. THREE DAYS AFTER STARTING THE 20 MGS/LB. DOSAGE THERE WAS A SLIGHT DIARRHEA

AND ANOREXIA. ON THE FOLLOWING DAYS THE DIARRHEA BECAME WATERY; ATONY WAS NOTED IN THE RUMEN. THE HEAD WAS TURNED TO ONE SIDE AND RAISED ACCOMPANIED BY MOANING, ATAXIA AND WEAKNESS. THE ANIMAL PREFERRED TO LIE DOWN WITH THE LIMBS EXTENDED FORWARD AND THE HEAD IN OPISTHOTONUS POSITION. EPISTAXIS OF THE RIGHT NOSTRIL. EXAMINATION OF THE PROTHROMBIN TIME SHOWED A GRADUAL INCREASE FROM THE BEGINNING OF THE FIRST DOSE REACHING A HIGH FIGURE BEFORE DEATH. OTHER HEMATOLOGICAL AND URINARY EXAMINATIONS WERE NORMAL UNTIL THE BEGINNING OF 20 MGS/LB. DOSAGE. THE ANIMAL SHOWED AT THIS TIME A MARKED INCREASE IN ERYTHROCYTES, HEMATOCRIT, HEMOGLOBIN, NON-PROTEIN NITROGEN AND NEUTROPHILES. THE COUNT OF LEUKOCYTES, CREATININE, SERUM PROTEINS AND CARBON DIOXIDE WERE WITHIN NORMAL LEVELS. BLOOD GLUCOSE UNDERWENT A SLIGHT DECREASE AS DID THE QUANTITY OF LYMPHOCYTES. IN THE URINE THERE WERE NO APPRECIABLE CHANGES WITH THE EXCEPTION OF THE COLOR THAT WAS YELLOW AMBER. NO BLOOD WAS FOUND UPON TESTING. THE ANIMAL DIED ON JUNE 4, 1958.

GROSS EXAMINATION. BODY THIN BUT NOT HIDEBOUND. LYMPH NODES: HYPERTROPHY AND EDEMA. HEPATIC ADHERENCE TO THE ABDOMINAL WALL. JOINTS: ICTERIC SYNOVIA. LUNGS: INTERSTITIAL EDEMA; TRACHEA WITH FOAM. HEART: SUBENDOCARDIAL HEMORRHAGES. LIVER: MILIARY ABSCESSES;SLIGHT CIRRHOSIS; ICTERUS. GALLBLADDER: ABSCESS AND HEMORRHAGES. ABOMASUM: ULCERS AND HEMORRHAGES. SMALL INTESTINE: HEMORRHAGES. KIDNEYS: EDEMA; HEMORRHAGES IN THE CALYCES.

HISTOLOGICAL EXAMINATION. Lymph nodes: slight edema; hyperemia; lymphadenitis. Lungs: interstitial edema; lymphatic dilatation. Heart: subendocardial hemorrhages. Liver: periportal necrosis; bile plugs in intralobular bile capillaries; bile plugs in bile ducts; cirrhosis; fat in Kupffer cells in relation to necrosis. Abomasum: hyperemia; hemorrhages; submucosal hemorrhages, vascular thrombi; fibrosis; neutrophiles. Intestine: congestion; necrosis; focal necrotizing enteritis; catarrhal and hemorrhagic enteritis; hemorrhages. Kidneys: acute glomerulitis; nephrosis; hyaline droplet degeneration; slight dystrophic calcification. Gladder: hyperemia. Adrenals: single cell necrosis; hemorrhages; more fat than normal in fasciculata zone. Thyroids: fat necrosis surrounding thyroids. Testicle: immature. Spleen: moderate splenic congestion. Bone: hypoplastic bone marrow.

RESULTS AND DISCUSSION

Although arsenic derivatives are not as effective as the antibiotics in stimulating growth, arsanilic acid is reported to have growth promoting properties in poultry and swine. These properties are independent of its ability to supress intestinal organisms. It may, however, be poisonous when fed in excessive quantities.

The toxicity of arsenic compounds depends mainly upon their solubility. Arsanilic acid is insoluble in water but is soluble in gastro-intestinal juices. Practically all arsenic compounds which are toxic may be assorbed from the alimentary tract. Little information is available on the rate of absorption of arsanilic acid, but the mode of action is probably similar to other arsenicals which modify the intestinal bacteria and increase capillary permeability.

Although the purpose of this study was to investigate the anatomical lesions produced by toxic levels of arsanilic acid, observations were also made on the effects of this drug as a growth stimulant. No increase over the normal expected weights was found. On the contrary, none of the treated calves reached the expected weights for their breed, age and sex though they were clinically normal. One of them lost as much as 60 pounds in 45 days. This may be due to the action of arsanilic acid upon the rumen bacteria.

THE POISONOUS EFFECT OF ARSANILIC ACID IN CALVES SEEMS TO BECOME MANIFEST WHEN MORE THAN 8.0 MGS/LB. OF BODY WEIGHT ARE GIVEN DAILY. LOWER LEVELS DID NOT CAUSE ANY CLINICAL ALTERATION IN THIS STUDY.

ABNORMAL SYMPTOMS APPEAR A FEW DAYS AFTER THE INGESTION OF TOXIC DOSES, DEPENDING ON THE QUANTITY OF ARSANILIC ACID INGESTED. THESE SYMPTOMS ARE PRIMARILY ANOREXIA, DIARRHEA, DEPRESSION, WEAKNESS, EMACIATION AND DEHYDRATION WHICH BECAME MORE ACCENTUATED IN SUCCEEDING DAYS. SOME ANIMALS SHOWED ATAXIA AND SALIVATION OF VARYING DEGREES, ATONY OF THE RUMEN AND RECUMBENT POSITION. WHEN THE DOSAGE WAS 20 MGS/LB. THE HEAD WAS TURNED TO ONE SIDE AND RAISED. THERE WAS MOANING, OPISTHOTONUS AND RUNNING MOVEMENTS. THE TEMPERATURE WAS NORMAL, REACHING PYREXIC LEVELS ONLY IN CASES WITH PULMONARY COMPLICATIONS. HYPOTHERMIA ALWAYS SUPERVENED IN THE TERMINAL STAGES.

BLOOD ANALYSES SHOWED THAT THE ERYTHROCYTES, HEMOGLOBIN AND HEMATOCRIT WERE MAINTAINED WITHIN NORMAL LEVELS FOR THE BOVINE SPECIES DURING THE EXPERIMENT. ALL ANIMALS, BUT ONE, UNDERWENT AN INCREASE ONE OR TWO DAYS BEFORE DEATH; THIS WAS PROBABLY DUE TO HEMOCONCENTRATION. THE LEUKOCYTES WERE MAINTAINED WITHIN NORMAL LEVELS WITH SLIGHT INDIVIDUAL VARIATIONS.

THE PROTHROMBIN TIME, CHECKED IN FOUR ANIMALS, SHOWED A CONSTANT AND GRADUAL INCREASE FROM THE BEGINNING OF EACH DOSAGE (AV.:24"9/10) UNTIL ONE OR TWO DAYS BEFORE DEATH

(av.:1'93"8/10). This is the only outstanding change found in the blood and was probably caused by an impercertible effect from the small quantities of the drug upon the liver and bone marrow. Further studies are required along these lines with animals of different species in order to compare prothrombin times in animals receiving regular food and those fed with growth promoting arsenicals, or sick animals treated with arsenical drugs.

The bilirubin was normal during this study, only reaching extreme values two or three days before death.

In all animals the values for creatinine were normal with slight increase in the last analyses before the calves died. There was no marked change in the quantity of glucose and protein in the blood. The urea nitrogen, checked in four animals, underwent a slight decrease with the administration of the first low dose in each animal and showed gradual recuperation until reaching concentrations a little higher than normal before death.

Non-protein nitrogen and carbon dioxide were checked in four animals. The values were normal during the course of the experiment with exception of an increase in non-protein nitrogen in the last two days preceding death.

Electrophoretic patterns showed no significant changes during the investigation.

THE URINE SHOWED AN INCREASE OF ALBUMIN, IN MOST CASES, FOLLOWING THE ADMINISTRATION OF TOXIC LEVELS OF ARSANILIC ACID. IN SOME CASES THERE WAS INCREASE IN BILIRUBIN AND TRACES OF ACETONE AND BLOOD. THE URINARY SEDIMENT CONTAINED HYALIN, CELLULAR AND GRANULAR CASTS, SOMETIMES ACCOMPANIED BY ERYTHROCYTES AND LEUKOCYTES.

THE GROSS LESIONS IN POISONING BY ARSANILIC ACID HAVE CERTAIN SIMILARITY WITH THOSE DESCRIBED FOR OTHER ARSENIC DERIVATIVES. AT NECROPSY MOST OF THE ANIMALS SHOWED EMACIATION, CACHEXIA AND ICTERUS WITH HYPERTROPHIC, EDEMATOUS AND HEMORRHAGIC LYMPH NODES. THERE WAS ALSO VISCOUS FLUID IN THE PERITONEAL AND THORACIC CAVITIES. THE AORTA AND OTHER BLOOD VESSELS WERE ICTERIC. THERE WERE SUBENDOCARDIAL HEMORRHAGES. EDEMA, ULCERS OR HEMORRHAGES IN THE ABOMASUM AND SMALL INTESTINE CAN ALSO BE FOUND. THE BLADDER IN SOME CASES WAS FULL OF DARK-AMBER COLORED URINE. THE LUNGS, WHERE COMPLICATIONS OCCURRED, SHOWED ZONES OF PNEUMONIA, PULMONARY EDEMA OR CONSOLIDATION. IN MOST OF THE CALVES THERE WAS AN INCREASE OF ICTERIC SYNOVIA. THE BRAIN ALSO SHOWED EDEMA AND APPARENT ICTERUS IN SEVERAL OF THE ANIMALS.

THE PRINCIPAL LESIONS CAUSED BY ARSANILIC ACID WERE FOUND IN THE LIVER AND KIDNEY BECAUSE THESE ORGANS FUNCTION IN THE DETOXICATION AND EXCRETION OF THE POISON. THE LIVERS WERE ENLARGED, NECROTIC AND SLIGHTLY CIRRHOTIC. IN MOST OF THE CASES, THERE WAS ALSO FOCI OF NECROSIS OF DIFFERENT SHAPES

AND SIZES TOGETHER WITH ULCERATION IN THE BILIARY TREE. THE GALLBLADDER IN SOME CASES WAS DILATED AND HYPEREMIC AND IN OTHERS WAS CONTRACTED WITH VISCID, MUCOID BILE AND PIGMENT STONES. IN THE MAJORITY OF THE CALVES STUDIED, THERE WERE HEMORRHAGES AND NECROSIS OF GALLBLADDER AND BILE DUCT MUCOSAE. THE KIDNEYS SHOWED EDEMA, SEROUS ATROPHY OF PERIRENAL FAT, WHITE-SMOOTH CORTICAL INFARCTS AND HEMORRHAGES AND FOCAL NECROSIS IN THE RENAL PAPILLAE.

HISTOLOGICAL EXAMINATION OF THE LIVERS SHOWED PREDOMINANTLY FOCAL PERIPORTAL AND MIDZONAL NECROSIS (FIGS. 1 AND 2). THERE WAS SOME CENTROLOBULAR NECROSIS. THE PERIPHERY OF THE NECROTIC AREAS SHOWED HEPATIC CELLS UNDERGOING FINE DROPLET FATTY AND COAGULATION NECROSIS. LEUKOCYTES WERE ALSO FOUND IN NECROTIC AREAS. IN SOME CASES, FATTY INFILTRATION AND DEGENERATION TOGETHER WITH FAT IN KUPFFER CELLS INDICATED INCIPIENT FRANK NECROSIS. BILE PLUGS WERE ALSO PRESENT IN THE INTRALOBULAR BILE CAPILLARIES AND PORTAL BILE DUCTS. PORTAL FIBROSIS WAS FOUND IN SOME CALVES, VARYING IN DEGREE FROM ANIMAL TO ANIMAL. IN THE BILE DUCT AND GALLBLADDER EDEMA, HYPEREMIA, SEVERE HEMORRHAGE AND NECROSIS OF THE MUCOSA AND SUBMUCOSA WERE FOUND (FIG. 4).

THE KIDNEYS SHOWED HYPEREMIA, GLOMERULITIS, NEPHROSIS, DEGENERATION AND FRANK NECROSIS OF THE PAPILLAE (FIG. 3). THERE WAS PYCNOSIS OF EPITHELIUM IN SOME CASES AND HYPERTROPHY IN OTHERS (FIG. 5). BILE CASTS IN THE COLLECTING TUBULES AND

HYALIN CASTS IN THE CONVOLUTED TUBULES ALSO WERE FOUND. SLIGHT DYSTROPHIC CALCIFICATION WAS OBSERVED. THE RENAL LESIONS WERE CLASSIFIED AS A COMBINATION OF 1) ACUTE SEGMENTAL NEPHROSIS, 2) BILE NEPHROSIS, 3) NECROTIZING PAPILLITIS. IN SOME CASES THE URINARY BLADDER SHOWED HYPEREMIA.

THE LYMPH NODES SHOWED DEPLETION OF LYMPHOCYTES, EDEMA AND HYPEREMIA; IN CASES WITH HEAVY DOSES OF ARSANILIC ACID THERE WAS ACUTE LYMPHADENITIS. THERE WERE SUBENDOCARDIAL HEMORRHAGES IN ANIMALS WITH GREATER AMOUNTS OF DRUG. FOCAL FATTY DEGENERATION OF THE MYOCARDIUM WAS PRESENT IN ONLY ONE CASE. IN THE ABOMASUM THERE WAS HYPEREMIA, HEMORRHAGE, SUBMUCOSAL EDEMA, VASCULAR THROMBI AND NECROSIS (FIG. 6). IN SOME CASES THERE WAS HYPEREMIA AND HEMORRHAGE IN THE SMALL INTESTINE; IN OTHER CASES THERE WAS NECROSIS, NECROTIZING ENTERITIS (FIG. 7), ULCERATION, SEVERE EDEMA, CATARRHAL DUODENITIS AND NECROTIZING INFLAMATION OF THE INTRADUODENAL PORTION OF THE BILE DUCT.

IN SOME CASES THE LUNGS SHOWED HYPEREMIA, THROMBI IN VESSELS, LYMPHATIC DILATATION WITH FIBRIN THROMBI AND MODERATE BRONCHONEUMONIA. ALL OF THE CASES RECEIVING GREATER AMOUNTS OF ARSANILIC ACID SHOWED INTERSTITIAL EDEMA.

THE ADRENAL GLANDS, ALTHOUGH WITHOUT APPARENT GROSS LESIONS, SHOWED HYPEREMIA, SMALL HEMORRHAGES, SINGLE CELL NECROSIS AND VACUOLATION IN THE FASCICULATA ZONE. THERE WAS

INFILTRATION OF LYMPHOCYTES IN THE RETICULARIS, FASCICULATA AND SINUSOIDS AND MORE FAT THAN NORMAL IN CALVES RECEIVING HEAVY DOSES OF ARSANILIC ACID. IN THE SPLEEN IT WAS POSSIBLE TO FIND MODERATE TO ACUTE SPLENIC CONGESTION.

DESPITE CLINICAL EVIDENCE OF NERVOUS SYMPTOMATOLOGY, IT WAS NOT POSSIBLE TO FIND SIGNIFICANT LESIONS IN DIFFERENT SECTIONS OF THE BRAIN. SPECIAL STAINS SHOWED ONLY PERI-VASCULAR EDEMA IN ONE CASE AND A MINUTE MICROFOCUS OF LYMPOCYTES IN ANOTHER.

HISTOLOGICAL EXAMINATION OF BONES, CARRIED OUT IN CASES RECEIVING HIGHER DOSES OF THE DRUG, SHOWED HYPOPLASIA OF THE BONE MARROW.

SUMMARY

1 - ARSANILIC ACID, IN THIS STUDY, DID NOT SHOW THE GROWTH PROMOTING PROPERTIES FOR CALVES REPORTED FOR POULTRY AND SWINE.

2 - THE TOXIC LEVEL OF ARSANILIC ACID FOR CALVES IS 8 MGS/LB. OF BODY WEIGHT.

3 - BILIRUBINEMIA, BILIRUBINURIA AND ALBUMINURIA OCCURS ON THE LAST TWO OR THREE DAYS PRECEDING DEATH.

4 - PROTHROMBIN TIME IS GRADUALLY INCREASED FROM THE FIRST INGESTION OF ARSANILIC ACID, REACHING THE HIGHEST VALUES TWO DAYS BEFORE DEATH. INCREASES IN PROTHROMBIN TIME OCCURRED EVEN ON LOW LEVELS OF ARSANILIC ACID WHICH PRODUCED NO OTHER CLINICAL OR CLINICAL PATHOLOGICAL CHANGES.

5 - SYMPTOMS AND PATHOLOGICO-ANATOMICAL LESIONS ARE SIMILAR TO THOSE REPORTED FOR OTHER ARSENIC DERIVATIVES.

6 - PRINCIPAL ORGANS INJURED ARE THE LIVER AND KIDNEY.

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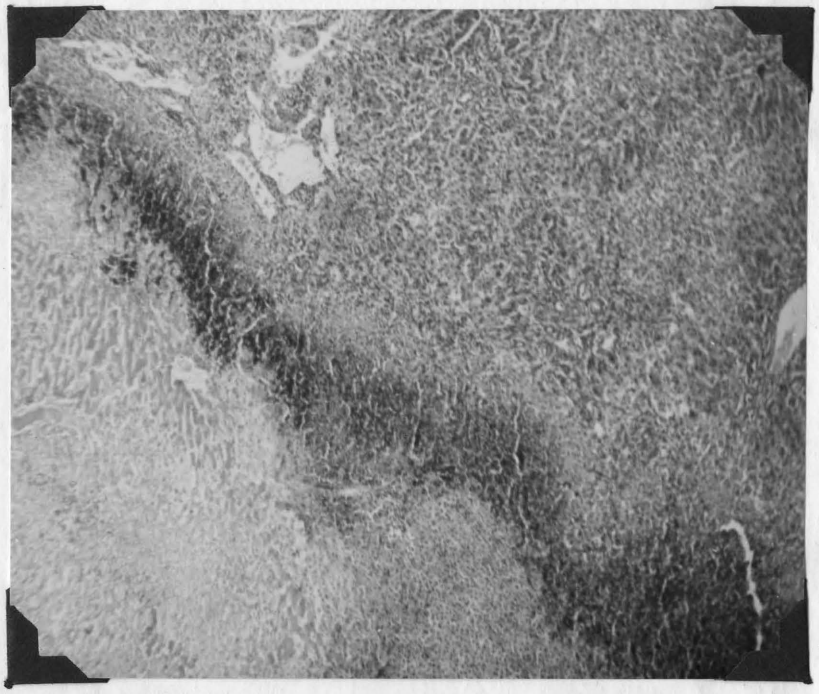

FIG. 1 - LIVER. EXTENSE FOCUS OF NECROSIS.

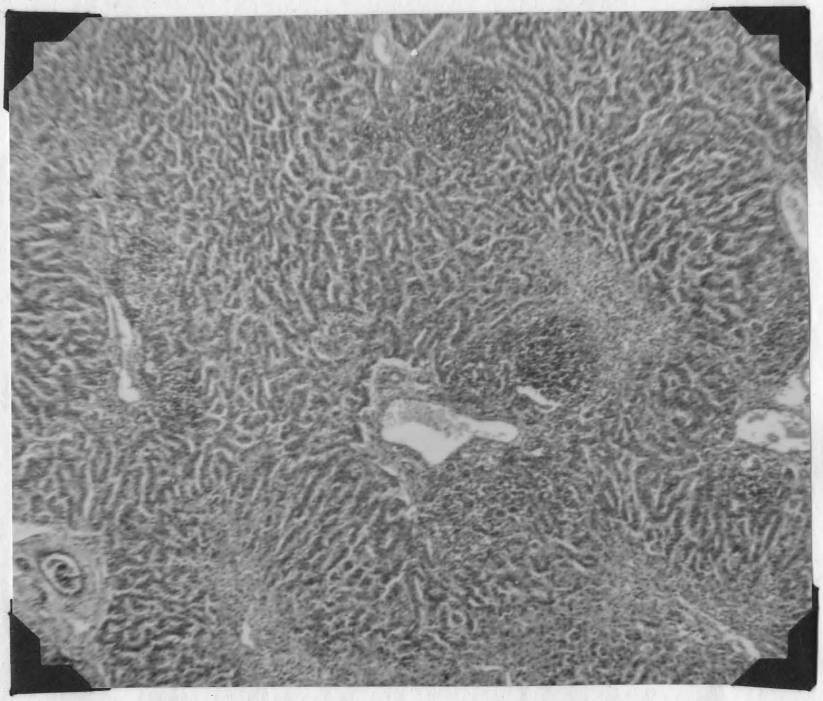

FIG. 2 - LIVER. FOCAL PERIPORTAL AND MIDZONAL NECROSIS.

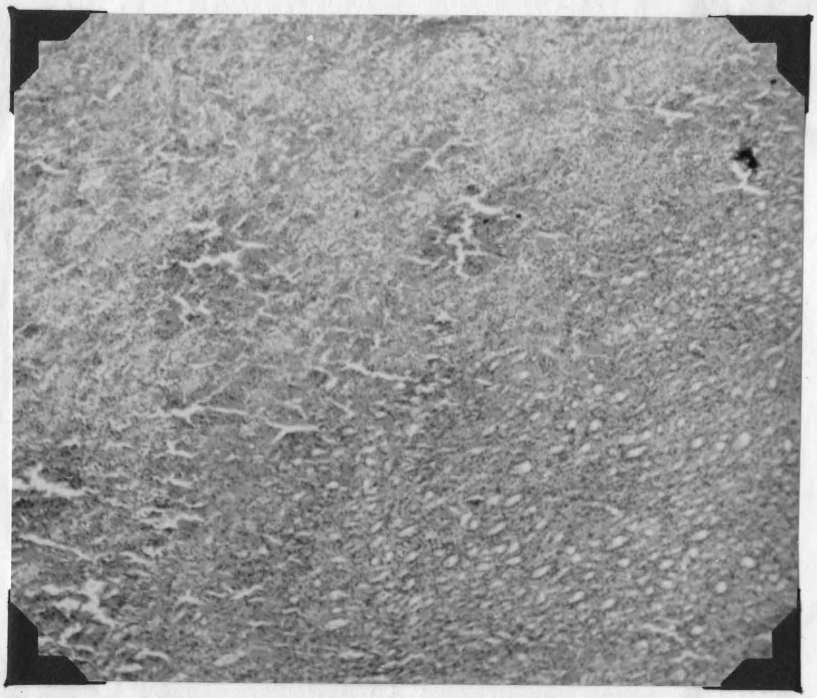

FIG. 3 - KIDNEY. FOCI OF NECROSIS. NECROTIZING PAPILLITIS.

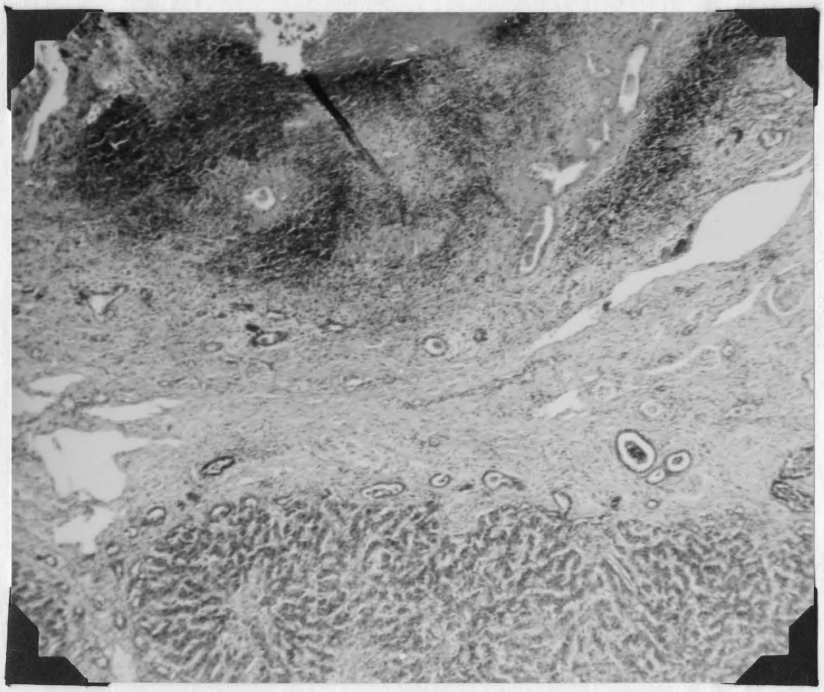

FIG. 4 - LIVER AND BILE DUCT. SEVERE NECROSIS OF MUCOSA AND SUBMUCOSA.

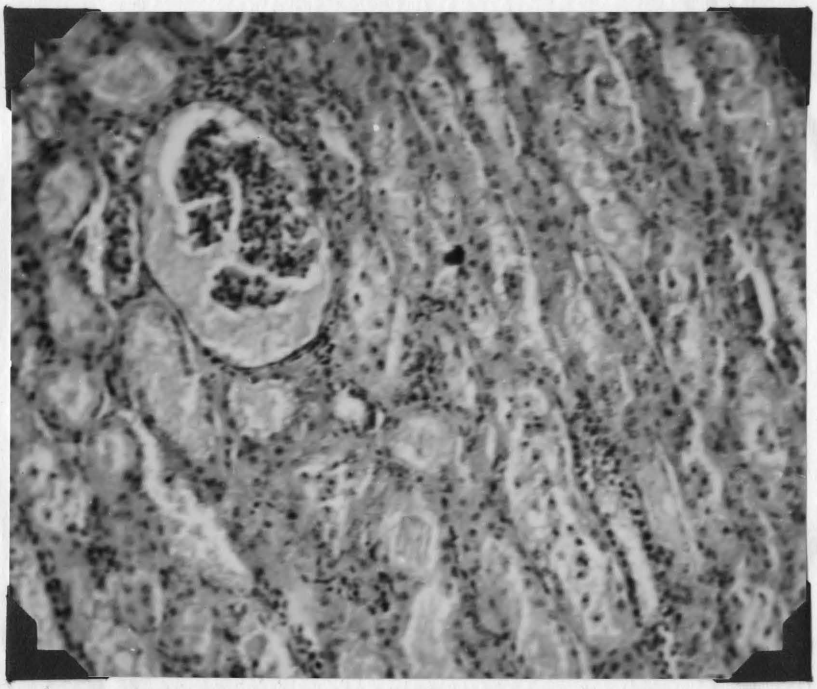

FIG. 5 - KIDNEY. GLOMERULITIS AND EPITHELIAL PYCNOSIS.

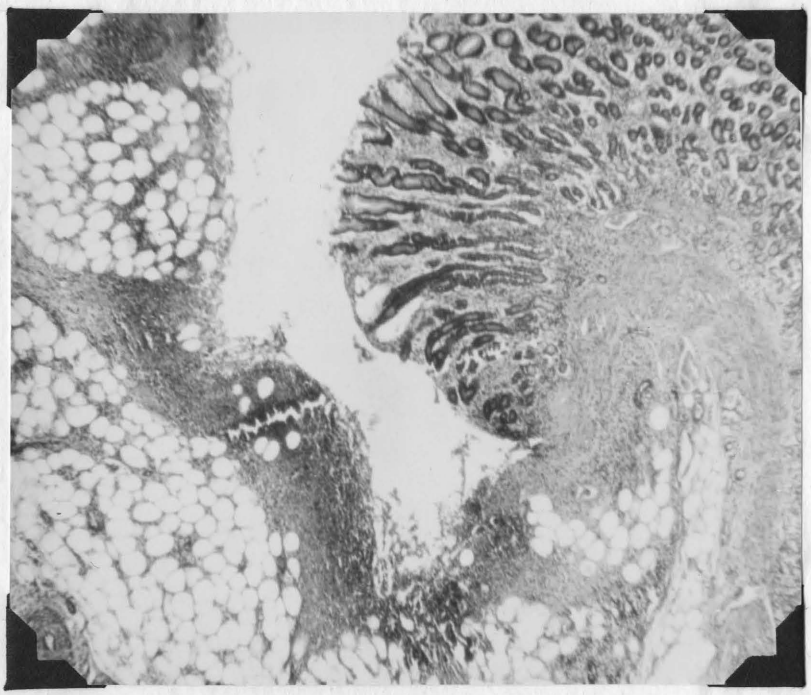

FIG. 6 - ABOMASUM. MUCOSAL NECROSIS AND ULCERATION.

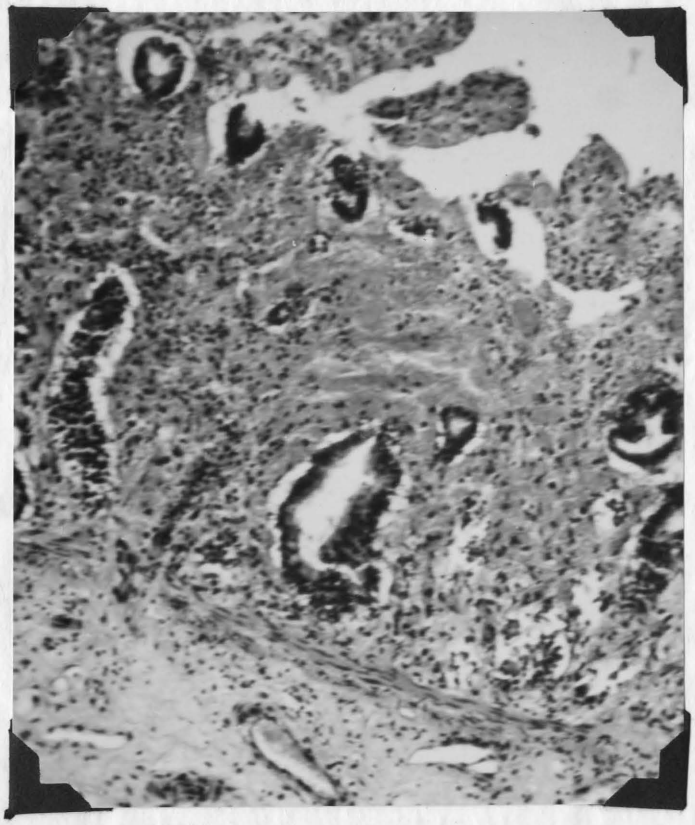

FIG. 7 - NECROTIZING ENTERITIS.
SUBMUCOSAL EDEMA.

ABSTRACT

Studies on the Pathology of Arsanilic Acid Toxicity in Calves

Walter Mestanza

Eight clinically normal calves of different breeds were used in this study. The animals were given daily doses of arsanilic acid (Pro-Gen Abbott) varying from 1.4 to 6 mgs/lb. of live body weight with subsequent individual increase up to 20 mg/lb. Daily physical examination were carried out on each animal. Samples of blood and urine were taken two or three times a week for analysis. After death, tissues were collected for histopathological examination.

Following is a description of the most important findings:

1) Arsanilic acid, in this study, did not show the growth promoting properties for calves reported for poultry and swine.

2) The toxic level of arsanilic acid for calves is 8 mgs/lb. of body weight.

3) Bilirubinemia, bilirubinuria and albuminuria occurs on the last two or three days preceding death.

4) Prothrombin time is gradually increased from the first ingestion of arsanilic acid reaching the highest values two days before death. Increases in prothrombin time occurred even on low levels of arsanilic acid which produced no other clinical or clinical pathological changes.

5) Symptoms and pathologics-anatomical lesions are similar to those reported for other arsenic derivatives.

6) Principal organs injured are the liver and kidney.