PROTEOSE INTOXICATIONS AND INJURY OF BODY PROTEIN.

IV. The Metabolism of Dogs with Sterile Abscess, Pancreatitis, and Pleuritis.

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We wish to present these experiments as a contribution to the study of sterile inflammatory processes—true non-specific inflammation. There can be no question of bacterial toxins, hypothetical endotoxins, or specific reactions. The injury is a chemical injury of tissue and body wandering cells. The reaction on the part of the body must be due to products absorbed from the areas of injury and inflammation. The substances responsible for the general reaction are almost certainly formed from body protein by autolysis and autolytic ferments are conspicuously present. Earlier investigators have been able to isolate proteoses, peptones, and a variety of other protein split products from certain inflammatory exudates. Proteoses have been isolated recently from various normal tissues and organs by Abel, Pincoffs, and Rouiller (1). We have been able to isolate from certain inflammatory exudates proteose-like substances which are toxic and hope to report on this work in the near future. Whatever these substances may be, formed in inflammatory sterile exudates, they are rapidly absorbed into the general circulation causing a variety of reactions, leukocytosis, fever, loss of weight, etc. The rise in nitrogen output is very striking and reaches as high a level in a fasting dog with a sterile abscess as with a staphylococcus abscess. From the clinical signs and from the nitrogen metabolism no difference can be detected between an abscess due to turpentine and an abscess due to a staphylococcus. We must conclude that the greater part of this

reaction due to the staphylococcus is non-specific. We shall emphasize constantly the important non-specific fraction of all intoxications due to specific bacterial agents.

Methods.

The experiments were all carried out on fasting dogs, which were kept in standard metabolism cages and allowed to reach a relatively constant level of nitrogen elimination before any experiment was performed. 24 hour collections of urine were made and nitrogen was determined in duplicate by the Kjeldahl method. Details of the methods for collection of urine and feces and for non-protein nitrogen and urea in the blood have been described elsewhere (2,3). All operative procedures were done under morphine and ether anesthesia. When irritant material was injected, the animal was given morphine.

EXPERIMENTAL OBSERVATIONS.

Dog 16–46 (*Table I*).—Short haired fox-terrier, male; weight 27 pounds. The dog was allowed to fast 6 days and placed in a metabolism cage. 2 days later 1.25 cc. of turpentine were injected subcutaneously. The clinical signs of intoxication which followed during the formation of the abscess disappeared when the abscess was opened. Abscess contents sterile. Recovery was uninterrupted and the wound healed well.

Dog 17–9 (*Table II*).—Large strong black-and-tan, adult male; weight 35.5 pounds. The dog was allowed to fast 9 days and placed in a metabolism cage. 2 days later 1.5 cc. of turpentine were injected subcutaneously over the shoulder. A large abscess of about 10 cm. diameter developed, and was opened 3 days later, 120 cc. of thick creamy pus being removed. This was sterile. 2 days later a slight nasal discharge developed and later a cough. These symptoms continued with varying intensity for 13 days, when the experiment was discontinued. At this time the animal was dull and listless but showed no frank signs of any localized lesion. The dog recovered promptly when fed. The abscess sinus, meanwhile, drained, granulated, and was almost healed when observations were discontinued.

Dog 16–176 (*Table III*).—Strong bulldog, young male; weight 25.5 pounds. The dog was allowed to fast 5 days and placed in a metabolism cage. 3 days later 1 cc. of turpentine with 2 loopfuls of a 24 hour agar culture of *Staphylococcus aureus* was injected subcutaneously over the thorax (morphine $\frac{1}{8}$ grain). A typical abscess developed with fever and moderate intoxication. The abscess ruptured in about 60 hours and the healing was uninterrupted.

The preceding group of experiments (Tables I, II, and III) are illustrative of a considerable number of experimental observations

which need not all be tabulated because the reaction is so uniform. A turpentine abscess causes a remarkable rise in urinary nitrogen, often 100 to 200 per cent daily increase following the development of the abscess. Still more interesting is the great increase of urinary

TABLE I.

Dog 16–46. Sterile Abscess (Turpentine).

Day.	Urine.		Temperature.	Weight.	Remarks.
	Nitrogen.	Amount.			
	gm.	*cc.*	°C.	*lbs.*	
1	2.55	225	—	24.9	Fasting 6 days.
2	2.59	152	—	24.5	
2	Turpentine, 1.25 cc., injected intravenously.				
3	2.69*	—	40.3	24.1	Clinically sick.
4	5.88	458	39.8	24.0	Abscess forming.
5	5.85	509	40.1	23.5	" soft.
6	5.82	825	39.9	23.1	
6	1 p. m. Abscess opened; 150 cc. of pus containing 1.04 gm. of nitrogen.				
7	7.69	740	38.3	22.1	Wound granulating.
8	3.84	251	37.9	21.6	Clinically well. Feces nitrogen 0.97 gm.
9	3.32	340	38.0	21.1	
10	2.86	125	37.7	20.8	Wound clean.
11	3.22	130	37.9	20.4	
12	2.88	180	—	20.0	
13	2.97	115	38.1	19.6	
14	2.74	105	—	19.5	
15	2.72	81	—	19.0	
16	2.52	50	—	18.9	Wound 1.5 cm. in diameter and healing.

* Feces and cage washings included.

nitrogen on the day following the rupture or drainage of the abscess, at a time when the clinical picture is normal. We must assume that this represents an escape of nitrogenous material which has been held somewhere in the body (blood and tissues) during the period of intoxication. The amount found in excess in the blood the day be-

fore the abscess rupture or drainage cannot account for all of this excess output on the day following operation and drainage.

An infected abscess with or without a chemical irritant gives the same increase in urinary nitrogen excretion but has a tendency to

TABLE II.

Dog 17–9. Sterile Abscess (Turpentine) Complicated by Canine Distemper.

Day.	Urine.		Temperature.	Weight.	Remarks.
	Nitrogen.	Amount.			
	gm.	*cc.*	*°C.*	*lbs.*	
1	3.25	100	38.1	31.9	Fasting 9 days.
2	3.14	107	38.0	31.4	
2	Turpentine, 1.5 cc., injected subcutaneously.				
3	6.41*	235	39.0	31.3	Drinks much water.
4	9.44	454	39.2	31.1	
5	11.48	702	38.7	30.2	
5	Abscess opened; pus contained 0.756 gm. of nitrogen.				
6	11.91	720	38.4	28.6	Feces nitrogen 1.37 gm.
7	6.96	260	38.2	27.8	Nasal discharge.
8	5.99	382	38.1	27.4	" "
9	5.68	196	38.1	27.1	" "
10	5.99	188	37.9	26.6	" " coughing, and sneezing.
11	5.56	178	38.0	26.0	" " no cough.
12	6.34	206	37.6	25.5	" " " "
13	6.42	200	38.1	24.8	" " " "
14	6.73	205	37.1	24.6	" " " "
15	7.36	210	37.1	24.2	No nasal discharge.
16	7.54	245	36.8	23.6	" " "
17	8.89	262	36.6	22.9	Definite nasal discharge; no cough.
18	6.45	257	36.8	22.4	" " " sick and dull.
19	10.64	355	36.4	22.0	" " " " " "
					Discontinued.

* Slight amount of feces included.

spontaneous rupture which is not so pronounced in the sterile abscess. Distemper is a troublesome infection of dogs probably due to *Bacillus bronchisepticus*, which usually localizes in the nasal, pharyn

geal, and bronchial mucous membranes. This infection will invariably cause a considerable rise in the urinary nitrogen output of a fasting dog, and this possibility must be kept in mind in all experiments of this nature with dogs. It is practically certain that this dog (Table II) developed the disease during the experiment as the control period of nitrogen elimination is normal. This complication does not obscure the abscess reaction.

TABLE III.

Dog 16–176. Bacterial Abscess (Staphylococcus and Turpentine).

Day.	Urine.		Temperature.	Weight.	Remarks.
	Nitrogen.	Amount.			
	gm.	*cc.*	*°C.*	*lbs.*	
1	3.16	65	38.0	22.6	Fasting previous 5 days.
2	2.72	85	38.0	22.2	
3	2.86	62	38.0	21.6	
3	Injection of 1 cc. of turpentine and 2 loopfuls of *Staphylococcus aureus* subcutaneously.				
4	4.24	139	39.3	21.6	Abscess size of fist.
5	4.96	138	39.6	20.9	" soft.
6	6.29	—	—	20.3	" ruptured.
7	5.15	177	38.4	19.6	
8	3.28	95	38.0	19.1	Feces nitrogen 0.21 gm.
9	2.98	80	38.2	18.6	
10	3.05	65	38.2	18.2	Discontinued. Wound doing well.

Diuresis is a noticeable feature in these experiments. The dogs were allowed to drink water as they wished and not given any fixed amount by stomach tube.

Dog 16–46 (Table IV).—Strong fox-terrier. The dog was allowed to fast 5 days and placed in a metabolism cage. Operation was done under morphine-ether anesthesia. Sterile bile was injected into the pancreatic duct and the duct then tied; abdominal wound closed as usual. 2 months later the pancreas was examined and showed only few adhesions and puckerings on the gland surface.

Dog 16–172 (Table V).—Young black long haired mongrel; weight 15.2 pounds. The dog was allowed to fast 4 days and placed in a metabolism cage. 3 days

later 8 cc. of sterile (autoclaved) dog bile were injected into the pancreatic duct under morphine and ether anesthesia. The animal remained clinically well under observation during the following 9 days, and the abdominal wound healed promptly. 6 weeks later the pancreas was examined and showed slight scarring and puckering.

Dog 16–175 (Table VI).—Young dog, male; weight 23.5 pounds. The dog was allowed to fast 5 days and placed in a metabolism cage. 2 days later, under morphine and ether anesthesia 10 cc. of sterile (autoclaved) dog bile were injected

TABLE IV.

Dog 16–46. Acute Pancreatitis (Sterile Bile in Pancreatic Duct).

Day.	Urine.		Temperature.	Weight.	Remarks.
	Nitrogen.	Amount.			
	gm.	*cc.*	*°C.*	*lbs.*	
1	3.56	110	38.0	25.2	Fasting 5 days.
2	3.47	80	38.2	24.8	
3	3.30	75	37.9	24.3	
3	Sterile bile injected into pancreatic duct. Duct tied.				
4	3.86	132	39.2	23.6	Slight intoxication. Feces and vomitus nitrogen 2.13 gm.
5	5.31	126	38.7	23.1	Clinically normal.
6	4.68	107	—	22.9	Wound clean.
7	4.19	112	38.1	22.6	
8	4.07	96	38.0	21.9	
9	3.95	85	38.1	21.6	Wound firm.
10	4.34	66	38.2	21.4	
11	4.03	124	38.1	21.1	
12	3.78	80	39.7	20.7	
13	3.50	86	—	20.3	Feces discarded.
14	3.84	85	38.2	20.0	

into the pancreatic duct. The animal showed no clinical signs of intoxication and the experiment was discontinued on the 8th day. The skin incision developed two small stitch abscesses with about 1 cc. of pus but did not break down and healed promptly. 1 month later the pancreas was examined and showed a few indefinite scars. There were old calcified fat necroses in the gastrohepatic omentum.

The preceding three experiments (Tables IV, V, and VI) show the remarkable capacity of the normal pancreas to repair a serious injury. There can be no doubt about the actual injury done the gland by in-

TABLE V.

Dog 16–172. Acute Pancreatitis (Sterile Bile in Pancreatic Duct).

Day.	Urine.		Temperature.	Weight.	Remarks.
	Nitrogen.	Amount.			
	gm.	*cc.*	°C.	*lbs.*	
1	1.48	130	38.0	13.4	Fasting previous 4 days.
2	1.59	58	37.9	13.1	
3	1.61	90	37.8	12.4	
3	Sterile bile injected into pancreatic duct.				
4	1.85	92	38.7	12.5	Not sick.
5	2.04	65	38.9	12.4	
6	2.04	86	—	12.1	
7	1.88	63	38.0	12.1	Wound firm.
8	2.02	55	37.9	11.8	
9	1.99	59	38.0	11.6	
10	1.72	40	38.1	11.4	
11	1.82	54	38.3	11.3	
12	1.96	36	—	11.0	Discontinued.

TABLE VI.

Dog 16–175. Acute Pancreatitis (Sterile Bile in Pancreatic Duct).

Day.	Urine.		Temperature.	Weight.	Remarks.
	Nitrogen.	Amount.			
	gm	*cc.*	°C.	*lbs.*	
1	2.76	72	38.4	21.5	Fasting 5 days.
2	2.39	58	38.3	21.1	
2	Sterile bile injected into pancreatic duct.				
3	3.11	452	38.8	20.9	Clinically well.
4	2.98	132	—	20.8	
5	2.44	100	38.3	20.4	
6	2.18	64	—	20.0	
7	2.23	56	38.2	19.8	
8	2.23	56	38.1	—	Wound shows two stitch abscesses.

jecting sterile bile into the pancreatic duct as the gland was in all cases observed for 5 to 10 minutes after the injection when the edema and hemorrhage were very conspicuous. The clinical reaction in these cases is slight and the increase in nitrogen elimination in the urine is inconspicuous in two cases (Tables V and VI) but very distinct in one experiment (Table IV). In the last experiment the pancreatic duct was tied close to the duodenum after the injection of bile had been completed, and this undoubtedly delayed the drainage of the ducts and intensified the reaction. The experiment illustrates the well known capacity of the pancreatic and bile ducts to establish continuity after simple ligature and crushing.

Dog 16–165 (*Table VII*).—Large black mongrel sheep dog, male; weight 43 pounds. The dog was allowed to fast 4 days and placed in a metabolism cage. 2 days later, under morphine and ether anesthesia 10 cc. of dog bile were injected into the pancreatic duct. Animal showed clinical evidence of intoxication on 2nd day following, with vomiting and slight diarrhea which lasted a week. The abdominal incision was obviously infected from the 3rd day following operation and gradually broke down with necrosis of the deeper tissues. The animal became progressively weaker and was killed.

Autopsy.—There was a necrotic sloughing abdominal wound closed off at the bottom by omentum. Peritoneum clean except for adhesions about pancreas. Lymph glands near pancreas enlarged. Pancreas much indurated and scarred with numerous fat necroses in surrounding tissue varying up to 2 mm. in diameter. These were translucent and obviously organizing at the margins. On section the parenchyma was opaque and gray. No hemorrhages or evidence of an acute process noted. Microscopic sections show areas of cell increase and organization scattered throughout the parenchyma of the gland. Mononuclear cells predominate, but many polymorphonuclears are present. There is considerable increase in connective tissue with distortion of gland architecture. Kidney in gross and microscopically shows only cloudy swelling.

Dog 16–173 (*Table VIII*).—Old active dog, adult male; weight 26.5 pounds. The dog was allowed to fast 5 days and placed in a metabolism cage. 2 days later, under morphine and ether anesthesia, 8 cc. of dog bile were injected into the pancreatic duct. The bile was not sterile. 3 days later the dog was dull, vomited slightly, and appeared somewhat toxic. The next day the wound was swollen and tender and on the following morning was opened, allowing bloody creamy pus to escape. There were necrosis and moderate tissue destruction. During the following week the animal became weaker and more lethargic, developed a slight diarrhea, and on the 14th day after the operation had a convulsion and was killed.

Autopsy.—The pericardium shows numerous small subpericardial ecchymoses and a small early patch of organizing pericarditis over the left ventricle. Beneath the endocardium of the left ventricle, in the mitral valve, and through the myocardium are hemorrhages. Sections show scattered focal necroses with polymorphonuclear infiltration around them and an increase of leukocytes in the capil-

TABLE VII.

Dog 16–165. Acute Pancreatitis (Infected Bile in Pancreatic Duct) with Wound Infection.

Day.	Urine.		Temperature.	Weight.	Remarks.
	Nitrogen.	Amount.			
	gm.	*cc.*	°*C.*	*lbs.*	
1	3.64	100	—	39.8	Fasting previous 4 days.
2	3.32	90	—	39.0	
2	10 cc. of bile injected into pancreatic duct.				
3	3.70*	500*	38.7	37.9	Feces nitrogen 0.87 gm.
4	6.00	710	38.9	37.0	Slightly toxic.
5	11.30†	565	38.6	36.8	Wound edematous and swollen.
6	11.09†	435	38.9	35.5	" " " "
7	11.84†	530	38.5	33.6	
8	9.02†	570	38.5	32.8	Wound infected and discharging pus.
9	8.22†	600	38.2	32.0	
10	9.49†	510	38.2	30.8	
11	4.99*	300*	—	29.9	
12	11.79	780	38.2	29.3	
13	8.96	540	38.1	28.4	
14	9.24	660	38.0	27.4	
15	6.72	510	—	26.9	
16	6.76	490	—	26.1	
17	6.33	555	38.0	25.6	Blood non-coagulable nitrogen 247 mg., urea nitrogen 173 mg.

* Part lost.

† Contains vomitus and fluid feces.

laries beside the small myocardial hemorrhages. The lower surface of the diaphragm is the seat of an organizing peritonitis and the liver is adherent to the laparotomy wound. Pancreas is semitranslucent and firm. Lobulation is obscured and chalky fat necroses are numerous. The lymph glands adjacent are all enlarged. Microscopic sections show diffuse periacinal increase in stroma

which contain foci of wandering cells. Fat necroses show some marginal organization.

The preceding experiments (Tables VII and VIII) show the results of injecting infected bile into the pancreatic duct. Under these

TABLE VIII.

Dog 16–173. Acute Hemorrhagic Pancreatitis (Infected Bile in Pancreatic Duct) Complicated by Wound Infection, Peritonitis, Pericarditis, and Myocarditis.

Day.	Urine.		Feces nitrogen.	Temperature.	Weight.	Remarks.
	Nitrogen.	Amount.				
	gm.	*cc.*	*gm.*	°C.	*lbs.*	
1	3.11	85	0	38.5	23.8	Fasting 5 days.
2	2.83	70	0	38.4	23.4	
2	Bile injected into pancreatic duct.					
3	4.93*	935	1.08	39.2	22.3	
4	6.17	818	0.49	39.3	21.7	
5	7.48	902	0	38.9	21.6	
6	7.06	870	0	39.0	21.0	Wound tender and swollen.
7	7.31	577	0.92	39.3	20.7	
7	Badly infected laparotomy wound opened.					
8	7.46	605	0.59	38.9	20.0	
9	6.97	605	±	39.0	19.3	
10	6.36	577	±	38.5	19.0	
11	5.12	575	0.50	38.4	18.8	
12	4.00	505	±	38.5	18.3	
13	3.75	480	±	—	18.1	
14	3.70	460	1.34	38.7	17.6	
15	3.56	356	±	—	17.0	
16	3.78	360	±	—	—	Killed. Blood nitrogen 66.1 mg., urea nitrogen 26.4 mg.

* Vomitus included.

conditions the urinary nitrogen shows a rise of 100 to 300 per cent above normal. From the data at hand we can assume that a considerable part of this rise in urinary nitrogen is due to the suppurative processes in the abdominal wall. Pancreatic injury is more pro-

nounced than in the experiments with sterile bile where the repair was more rapid and perfect. The non-protein nitrogen of the blood is greatly increased in amount and speaks for the great amount of tissue autolysis which must have been present.

Dog 16–109 (*Table IX*).—Strong fox-terrier, adult male; weight 20.5 pounds. The dog was allowed to fast for 6 days. After a short preliminary period the dog

TABLE IX.

Dog 16–109. Acute Pleuritis (Turpentine).

Day.	Urine.		Temperature.	Weight.	Remarks.
	Nitrogen.	Amount.			
	gm.	*cc.*	*°C.*	*lbs.*	
1	2.21	90	—	18.7	Fasting 6 days.
2	2.35	105	—	18.4	
2	Turpentine, 1.25 cc., injected into right pleura. Morphine ⅛ grain.				
3	2.27*	145	38.6	18.5	Vomited.
4	4.31	335	39.1	17.7	
5	5.80	250	39.3	17.2	Clinically sick.
6	4.73	210	39.2	16.9	
7	4.68	164	39.3	16.6	5 p.m. 50 gm. of cane sugar by stomach tube.
8	4.70	538	38.6	16.1	Vomited.
9	4.20	110	38.2	15.7	Feces nitrogen 0.56 gm.
10	3.81*	114	38.0	15.2	Diarrhea.
11	3.47*	—	37.6	14.9	"
12	—	—	—	—	Died. *Autopsy.*—Hemorrhagic pleurisy, pneumonia, tissue necrosis.

* Feces and cage washings included.

was given morphine, and turpentine, 1.25 cc., was injected into the right pleural cavity. The dog was clinically sick during the following week, vomiting at times. During the last 2 days of life there was considerable diarrhea. Dog died during the night and was autopsied the following morning.

Autopsy.—The right pleural cavity contains 250 cc. of bloody fluid and blood clots. The pleural surfaces are smooth. The lungs collapsed. The upper two lobes are firm, dark red, and quite airless. One portion of this lung tissue shows complete necrosis. Microscopic section shows necrosis and hemorrhage. The necrotic areas contain great numbers of polymorphonuclear leukocytes and very

little fibrin. There is no solution of tissue. The rest of the autopsy is not important to this experiment.

Dog 17–22 (Table X).—Small mongrel, male. The dog was allowed to fast for 4 days. After a short preliminary observation the dog was given morphine and a thick emulsion of aleuronat, 10 cc., was given into the right pleural cavity. This emulsion contained large numbers of *B. coli* and a recently isolated streptococcus. Following this injection the dog was clinically sick with occasional vomiting. The dog was killed.

Autopsy.—Performed at once. The right pleural cavity is dry and sticky. It contains little fibrin, and shows considerable injection of its surface. It contains about 2 cc. of thick, slimy, pinkish exudate. The right lower lobe of the lung is solid, pale, and gelatinous. It is quite airless and moist on section. There are no abscess cavities. There is a uniform pneumonia involving the entire lobe. The upper lobes show a few similar areas of consolidation. The left lung is negative. The rest of the autopsy is unimportant for this experiment.

TABLE X.

Dog 17–22. Acute Pleuritis and Pneumonia.

Day.	Urine.		Temperature.	Weight.	Remarks.
	Nitrogen.	Amount.			
	gm.	*cc.*	°C.	*lbs.*	
1	3.35	130	39.2	13.3	Fasting 4 days.
2	—	—	38.4	13.1	
3	2.86	130	38.2	12.9	
3	Streptococcus and *B. coli* with aleuronat injected into right pleura. Morphine $\frac{1}{8}$ grain.				
4	4.31	115	39.8	12.7	Cough. Vomited. Sick and dull. Feces nitrogen 0.84 gm.
5	4.58	317	39.1	12.4	Sick and dull.
6	4.86	400	39.5	12.0	" " "
7	5.68	225	39.8	11.5	" " " Killed.
					Autopsy.—Acute dry pleurisy and pneumonia.

Dog 17–11 (Table XI).—Large mongrel hound, male; weight 41.5 pounds. The dog was allowed to fast for 6 days. After a short preliminary observation the dog was given morphine and a thick aleuronat suspension inoculated with *Staphylococcus aureus*. This was injected into the right pleural cavity. After a slight clinical reaction the dog appeared perfectly normal. After a period of 8 days a suspension of aleuronat with a heavy emulsion of staphylococcus was injected

into the left pleural cavity. This injection likewise caused little inconvenience although a considerable rise in nitrogen elimination. After a period of 5 days the dog was given morphine and a mixture of aleuronat paste with 0.75 cc. of tur-

TABLE XI.

Dog 17–11. Acute Pleuritis (Staphylococcus) and Peritonitis (Turpentine).

Day.	Urine.		Temperature.	Weight.	Remarks.
	Nitrogen.	Amount.			
	gm.	*cc.*	*°C.*	*lbs.*	
1	3.65	100	—	37.4	Fasting 6 days.
2	4.03	96	38.1	36.8	
2	*Staphylococcus aureus* and aleuronat injected into right pleura. Morphine $\frac{1}{8}$ grain.				
3	4.94	105	38.9	36.1	Very slight intoxication.
4	5.19	125	38.6	35.7	Apparently normal.
5	4.40	100	38.2	35.4	
6	3.96	112	38.4	35.0	
7	3.57	106	37.8	34.2	
8	4.18	103	37.4	33.9	
9	4.17	88	37.5	33.7	
10	4.33	116	37.5	33.4	
10	*Staphylococcus aureus* and aleuronat injected into left pleura. Morphine $\frac{1}{8}$ grain.				
11	5.68	170	38.9	33.0	Apparently normal. Feces nitrogen 0.47 gm.
12	5.46	170	37.9	32.3	
13	4.23	145	37.9	31.9	Not clinically sick.
14	4.33	175	37.9	31.2	
15	5.13	215	37.3	30.7	
15	Turpentine, 0.75 cc., and aleuronat injected into peritoneum. Morphine $\frac{1}{8}$ grain.				
16	5.99	245	38.5	31.2	Feces nitrogen 0.48 gm.
17	8.82	345	38.2	30.5	Abdomen rigid.
18	7.06	272	38.3	29.9	Not sick.
19	6.41	243	—	29.2	Killed.
					Autopsy.—Acute pleuritis, endocarditis, and peritonitis.

pentine injected into the peritoneal cavity. The dog did not appear clinically sick, although the abdomen was somewhat rigid. The dog was killed in spite of the absence of clinical symptoms.

Autopsy.—Performed at once. The right pleural cavity is clear. There is a slight organizing pleurisy close to the hilum of the right lung. The left pleural cavity is clear. There is a slight exudate close to the hilum of the left lung. There is some atelectasis at the base of each lung. Heart shows a definite, acute, hemorrhagic endocarditis with small granular vegetation. Myocardium is clear. Peritoneum shows an organizing fibrinous exudate in the left flank. Intestines are glued loosely together. There is some injection of the serous surfaces. There is also a slight exudate close to the spleen and over the dome of the liver. There is no excess of fluid. Both kidneys show small, linear abscesses extending down through the cortex. Microscopic sections show a slight amount of pneumonia just beneath the pleura close to the hilum of the left lung.

The last three experiments (Tables IX, X, and XI) show the effect of a chemical irritant upon the serous surfaces. It is not necessary to record many experiments, as the results are so uniform. Moreover, it may be argued that an irritant like turpentine when placed in a serous cavity may injure not only the serous surfaces but adjacent tissues (lung, muscles, liver, etc.) as well. So the reaction of the abscess might be expected to recur again and again regardless of whether the injury is located in one spot in the subcutaneous tissue (abscess) or in any serous cavity (pleurisy or peritonitis). The same arguments apply even more forcibly to bacterial inflammation. We observe that the curve of urinary nitrogen is very similar if not identical in all these experiments whether the inflammation is localized (abscess, infected wound) or diffuse (pleurisy, peritonitis). The last experiment (Table XI) demonstrates that the normal pleura has the power to recover from a considerable injury and is able to dispose of a great number of pathogenic bacteria. With each injury to any serous cavity we note a rise in urinary nitrogen with a tendency to recover and return to normal if the injury is not too grave. It makes no great difference whether the injury is sterile or not, when we consider the evidence for injury of body protein.

Control of the ether anesthesia has been recorded in another paper (4) and it has been shown that 1 hour ether anesthesia will cause no recognizable rise in urinary nitrogen. Control laparotomy experiments (4) show a slight rise in urinary nitrogen when the abdominal incision heals with a minimum reaction.

DISCUSSION.

The injury done to an animal by means of a sterile abscess may be made up mainly of two factors, (*a*) local injury of tissue by the chemical irritant, (*b*) general injury of body protein by means of toxic split products absorbed from the site of local injury. The sum of these injuries will account for most of the increase of nitrogen in the urine and the non-protein nitrogen of the blood. There is much evidence to show that by far the greater part of the excess nitrogen in the urine results from the general injury of body protein rather than from the local injury (for example, abscess pus).

A sterile abscess causes a great rise in the output of urinary nitrogen during the time of abscess formation but also during the 24 hours following the drainage of the abscess and disappearance of all clinical signs of intoxication. This recalls the familiar reaction recently described (2) following the injection of a toxic proteose. A non-lethal dose will cause an acute clinical reaction (vomiting, diarrhea, temperature fluctuation, and shock) which is over in 4 to 6 hours. The curve of urinary nitrogen excretion will show a slight rise usually during the first 24 hours after this injection but a maximum rise during the second 24 hours after the proteose injection. There is a delay in elimination of the nitrogen which presumably must result from protein injury effected by the toxic proteose. We wish to explain in the same way the delay in elimination of urinary nitrogen after the drainage of an abscess—the injury done to the body protein is not immediately followed by a rise in urinary nitrogen. We are not prepared to explain this peculiar lag in the escape of nitrogen following a toxic injury. The following paper shows that there may be a considerable piling up of nitrogenous substances in the blood during periods of acute intoxication. This suggests a rapid breakdown of protein substances but as well a slowing of the elimination by the kidney. We have no evidence of anatomical renal changes but the functional capacity of the kidney has not been sufficiently studied under similar experimental conditions.

Diuresis is noted in the experiments tabulated above and comes out very clearly when the dogs are allowed access to water at all times. Diuresis is not a noticeable factor when the dogs are on a uniform fluid intake given by stomach tube, so it may be that the diuresis noted

above is due to increased thirst or a craving of the body tissues for fluid. This may be a part of the peculiar reaction on the part of the body cells toward these various toxic split products.

Many of the experiments show clearly a summation effect following a combination of injuries or intoxications. A given injury will cause a certain increase in urinary nitrogen and when combined with some similar injury the nitrogen elimination will roughly correspond to the sum of the two separate injuries. One factor must be considered in any such grouping of injuries and that is the tolerance which may be established toward one injury by some related injury. It has been established (2) that preceding proteose injections render a dog more tolerant to subsequent injections. Also that the presence of a chronic intestinal intoxication will render a dog tolerant to subsequent proteose injections.

Peritonitis will cause a considerable rise in the output of urinary nitrogen and often a rise in the non-protein nitrogen of the blood. It is known that a general peritonitis is usually associated with a paralytic ileus, so there was some doubt whether or not the increase in protein disintegration was due to the intoxication of the ileus or of the peritonitis alone. Probably both factors are concerned but we have been able to isolate toxic proteose-like substances from the exudate of certain cases of general peritonitis. Further, the reaction of an acute pleurisy shows that a simple inflammation of a serous cavity can be associated with considerable injury of body protein and increase in nitrogen elimination.

The term "endotoxin" is still used today in many instances where it is impossible to isolate a toxin from a given bacterium. It is becoming increasingly evident that the word "endotoxin" is used to cloak the non-specific intoxication which may follow invasion by a given microorganism. The "endotoxin" in reality is a poison derived from autolysis of the host protein.

Some of the experiments given above (Tables IV, V, and VI) show the remarkable capacity of the normal pancreas to resist injury and to repair tissue destruction, as has been pointed out elsewhere (5). The surgeon often has a mistaken idea about the various inflammatory reactions of the pancreas, and assumes that drainage is necessary. Granting that drainage of this region can remove exudate, which is at least debatable, it is quite clear from experimental data given here

and elsewhere (5) that the gland can repair itself in a remarkable manner if left alone in a closed peritoneal cavity. There can be no question of the injury done to a pancreas by an injection of bile into the pancreatic duct. The reaction is rapid and at the end of 5 to 10 minutes the edema and hemorrhage are much in evidence. At the end of 24 hours the fat necroses, edema, and hemorrhages with peritoneal exudate are conspicuous, and yet these dogs will almost invariably recover unless the injury is extreme.

When a lethal amount of bile is injected into the pancreatic duct, there is a profound intoxication with death in 24 to 36 hours, too short a time to show any distinct modification of the urinary nitrogen curve. We are convinced that there is a very narrow margin between the non-fatal dose which permits recovery with but little reaction and the fatal dose which shows a profound intoxication and rapidly fatal outcome. A condition of delicate equilibrium may be assumed to exist in the normal pancreas—a small injury is promptly controlled but a large injury has a tendency to become intensified by the ferment activity of the injured gland. To state our belief in another way, we may assume that the pancreas has a large amount of ferment substance or proferments in its acini and a large amount of antiferment to maintain a normal balance. When an injury is produced which comes within the limits of control of the antiferment factor, the reaction is promptly limited and there is little intoxication. But if the injury is sufficient to overcome these limits of control, then the large amount of ferment material in the pancreas is set free to act on all proteins available and this reaction of the gland by its own cell autolysis forms sufficient toxic split products to cause fatal intoxication. Acute pancreatitis produced by a sterile irritant (bile) is a good example of an acute non-specific intoxication due to protein split products which must be derived from the proteins of the host.

When infected bile is injected into the pancreatic duct, the picture is complicated by a progressive and continuous inflammatory reaction. But in these experiments too the pancreas shows great ability to recover and return toward normal with a prompt control of the acute initial intoxication produced by the initial injury. When this initial injury is too grave, the intoxication is very acute, and if the autolytic processes get beyond body control, the dog will die in 24 to 36 hours in a characteristic condition of surgical shock.

SUMMARY.

Sterile abscess, pleuritis, and pancreatitis give a clinical reaction in the experimental animal very like the same acute inflammatory processes due to bacterial activity, provided the bacterial agents are limited to the initial location.

The curve of urinary nitrogen excretion in the fasting dog shows the same precipitous and sustained rise in sterile and bacterial inflammatory reactions. This indicates that the same type of protein injury and autolysis in the body is produced by the sterile inflammatory reaction as by the bacterial reaction.

It is assumed that the primary effect of the chemical agent or of the bacterial growth in the tissues is local cell injury or necrosis. This injured cell protoplasm undergoes prompt autolysis with escape of toxic protein split products. These toxic protein split products may be, in part at least, of the proteose group and are absorbed into the circulation, producing the familiar general reaction.

The injury of body protein is obvious from the great increase in elimination of nitrogen in the urine and appears to be the same in sterile and in bacterial inflammation. The injurious agent in the sterile inflammation must be derived from the host protein, and we may assume with safety that much of the injurious material emanating from a septic inflammation must come from the host protein rather than from the bacteria.

Acute sterile pancreatitis is one of the purest examples of an acute non-specific reaction where the intensity of the host's intoxication may reach a maximum in 12 to 24 hours. We believe that fundamentally this reaction is very similar to that observed after the production of a sterile abscess or pleurisy.

Non-specific intoxication must account for the sterile reactions described above. Septic inflammations show the same acute reaction and injury of body protein. The deduction is obvious—that a great part, at least, of the reaction in septic inflammation is truly non-specific and results from the primary injury of the host's protein and cell autolysis.

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