PROTEOSE INTOXICATIONS AND INJURY OF BODY PROTEIN.

V. The Increase in Non-Protein Nitrogen of the Blood in Acute Inflammatory Processes and Acute Intoxications.

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In the preceding communication (1) we submitted evidence to show that suppurative processes or acute inflammation due to a chemical irritant gave the same increased output of urinary nitrogen as did the same inflammatory reaction when caused by some specific bacterial agent. This, of course, indicates a similar type of injury done to body protein with elimination of the nitrogenous end-products in the urine. It is rather striking to note the great rise in urinary nitrogen above the base-line level which may be caused by a sterile abscess or pleurisy. We can scarcely imagine that any such increase can be explained entirely by a local destruction of tissue with the elimination of the nitrogen derived from these destroyed cells, but we must assume the formation of toxic split products in the abscess area which are absorbed and cause a general intoxication, cell injury, and resultant nitrogen increase. Proteose-like substances have been isolated from these inflammatory exudates and shown to be toxic. The total amount of nitrogen in the pus of a sterile abscess will rarely exceed 1 gm. but the dog may show an excess urinary nitrogen excretion of 2 to 4 gm. per 24 hours which can scarcely be accounted for by the local injury and tissue destruction alone.

We have pointed out (2) that during the intoxication of intestinal obstruction there develops a great increase in the output of urinary nitrogen; further, (3) that with the progressive intoxication of obstruction the blood non-protein nitrogen usually shows an appreciable rise

and at times a very great rise above normal, even to 100 mg. per 100 cc. of blood or higher. This has considerable clinical significance in this condition and when the non-protein nitrogen of the blood is much above normal one can feel certain that the intoxication is serious no matter what the clinical picture may be, provided the kidneys are normal.

When it was established that inflammatory processes due to a sterile irritant were able to bring about this great increase in the output of urinary nitrogen, it seemed important to follow the blood non-protein nitrogen in certain of these experimental conditions as well as in clinical cases. The data given below show that there is a distinct increase in the blood non-protein nitrogen in a variety of acute inflammatory conditions whether due to chemical or bacterial agents. There is considerable individual variation as in the intoxication of obstruction, but as a rule there is an increase in the non-protein blood nitrogen, at times a very considerable increase above normal (Table III).

Methods.

The dogs used in these experiments were kept in standard metabolism cages as described in previous articles and were fasting. The detailed protocols of most of the animals listed in Table II will be found in the preceding paper of this series. In the human blood examinations the following method was used: With a volumetric pipette 5 cc. of blood which had been drawn into a little solid sodium oxalate and shaken were added to 30 cc. of distilled water in a 50 cc. volumetric flask. To this 5 cc. of a 20 per cent solution of a freshly prepared solution of metaphosphoric acid were added, the flask was shaken, and allowed to stand at least 30 minutes. Distilled water was then added to the 50 cc. mark, the flask again thoroughly shaken, and the mixture filtered. The nitrogen in a 30 cc. sample of the filtrate, representing 3 cc. of blood, was determined by the Kjeldahl method. Duplicate estimations of blood samples were made in each instance. Urea was determined by the method of Marshall as modified by Van Slyke and Cullen (4).

EXPERIMENTAL OBSERVATIONS.

Blood Non-Protein Nitrogen in Sterile Abscess Formation.

Three dogs (Nos. 17–85, 17–86, and 17–87) were allowed to fast 5 days and each animal was given 1.5 cc. of turpentine subcutaneously over the thorax. Blood was collected daily from the jugular vein.

With the formation of the abscess typical clinical symptoms of fever and general intoxication developed with diuresis such as have been noted in the preceding paper (1). On the 3rd day after the subcutaneous injection the abscess in each animal was opened and drained. Two of the animals recovered as usual but the third (Dog 17–86) died the day following the opening of the abscess.

Table I shows in all animals a slight but definite rise in the non-protein nitrogen of the blood accompanying the formation of the abscess. Although the increase is relatively slight when compared with cases of intestinal obstruction and acute proteose intoxication,

TABLE I.

Blood Nitrogen with Experimental Sterile Abscess.

Date.	Dog 17-87.		Dog 17-85.		Dog 17-86.		Remarks.
	Non-protein nitrogen.*	Urea nitrogen.*	Non-protein nitrogen.*	Urea nitrogen.*	Non-protein nitrogen.*	Urea nitrogen.*	
1916	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	
Dec. 7	36.3	13.4	33.1	12.2	36.4	10.8	
" 9	38.8	11.3	37.8	13.8	33.1	7.6	1.5 cc. of turpentine subcutaneously.
" 10	37.3	11.0	44.3	9.0	50.6	24.6	
" 11	48.2	13.4	41.2	14.0	46.7	24.6	
" 12	42.0	12.6	51.3	16.5	53.4	22.4	Abscess opened and drained.
" 13	47.2	10.9	41.1	13.4	Died.	–	

* Non-coagulable and urea nitrogen given in terms of mg. per 100 cc. of blood.

it must be remembered that the severity of the intoxication in simple abscess formation is not to be compared with the marked intoxication in intestinal obstruction (Table II).

The first group of animals in Table II illustrates again the very high non-protein nitrogen that may accompany intestinal obstruction. In the first case noted (Dog 16–138), the renal obstruction was probably the chief factor in the blood nitrogen increase, but the infection may also have augmented it. The second group furnishes examples of the increase which accompanies experimental acute inflammations of various sorts. This increase is well marked, ranging from 15 to 40 mg. per 100 cc.

TABLE II.

Blood Nitrogen in Acute Infections and in Intestinal Obstruction.

Dog No.	Diagnosis.	Nitrogen per 100 cc. of blood.	
		Non-protein nitrogen.	Urea nitrogen.
		mg.	*mg.*
16–138	Urethral calculus; left pyonephrosis; right hydronephrosis; uremia	190.0	151.0
17–29	Isolated closed loop; intestinal obstruction; peritonitis	228.4	100.5
1–53	Intestinal obstruction	146.2	74.4
17–32	" " peritonitis	98.0	60.6
17–26	Empyema; early pericarditis	45.9	16.2
16–168	" acute endocarditis	57.3	20.5
17–24	Healed pneumonia; acute endocarditis	50.3	25.5
17–14	Experimental pneumonia; pulmonary abscess	71.5	18.6
17–22	" "	73.6	14.9
16–172	Distemper	51.7	24.2
17–89	Experimental pneumonia	46.7	28.4

Blood Non-Protein Nitrogen in Infections of Human Beings.

In this series a number of cases from the medical and surgical services of the University of California Hospital was studied. Certain of the cases had chronic nephritis which was recognized clinically or at postmortem examination, while others had no acute inflammatory lesions. In order that the chronic kidney lesions might not be a confusing factor we are omitting entirely any cases in which there was a suspicion of a chronic nephritis. Autopsies were performed on all the fatal cases except two and the clinical pictures in these latter as well as in the cases which recovered were such that the diagnoses were unquestioned.

The careful clinical and pathological observations made on the cases of this series make them comparable with experimental data obtained from animals and we consider it fortunate that the series studied included cases which were so typical and relatively uncomplicated.

In a recent paper of Schwartz and McGill (5) are recorded many blood urea determinations upon clinical material. They report forty-two urea readings in twenty cases of pneumonia of which thirty-

TABLE III.

Blood Nitrogen in Acute Infections and Intoxications of Human Beings.

Case No.	Date.	Clinical diagnosis.	Nitrogen per 100 cc. of blood.	
			Non-protein nitrogen.	Urea nitrogen.
	1916		*mg.*	*mg.*
1	Sept. 27	Postoperative pneumonia; pulmonary abscess.	79.3	40.9
	" 28		62.3	37.2
	" 30		58.4	23.2
	Oct. 25		44.1	20.1
2	Oct. 7	Acute lobar pneumonia.	42.0	20.8
3	Nov. 11	Acute lobar pneumonia.	51.5	33.3
	" 13		84.9	49.8
4	Nov. 10	Postoperative peritonitis.	58.8	24.3
	" 13		88.7	—
	" 16		60.2	24.1
	" 19		109.2	57.8
5	Oct. 6	Acute and chronic endocarditis; acute pleuritis; cardiac decompensation.	38.3	10.9
	" 13		41.6	16.8
	" 25		38.8	10.6
	1917			
	Jan. 31		47.6	14.0
	1916			
6	Oct. 20	Acute and chronic endocarditis; decompensation.	87.4	51.5
	" 24		133.4	63.8
	" 26		107.8	47.6
	" 30		107.3	55.4
	" 31		139.1	67.8
7	Oct. 5	Cancer of gall bladder; duodenal stenosis; acute bronchitis and bronchopneumonia.	234.7	137.2
8	Oct. 26	Cancer of stomach with stenosis and tetany.	129.7	66.1
	" 27		161.0	82.3
9	Oct. 18	Acute yellow atrophy of liver.	56.2	6.7
10	Sept. 28	Mitral and tricuspid insufficiency; decompensation.	35.0	14.8
	" 29		36.4	14.8
	Oct. 6		41.1	19.6
11	Aug. 28	Mitral and tricuspid insufficiency; decompensation.	40.1	18.2
	Oct. 6		43.7	21.3
12	Oct. 27	Emphysema; tricuspid insufficiency; decompensation.	42.9	17.2

six readings are above normal. Some readings were as high as 100 mg. per 100 cc. of blood. Three cases of septicemia showed high readings: 51, 92, and 127 mg. of urea per 100 cc. of blood.

Table III shows as a rule some increase in the blood non-protein nitrogen in pneumonia, endocarditis, and peritonitis.

Case 6 with acute endocarditis and septicemia shows a very high blood non-protein nitrogen (139.1 mg. per 100 cc. of blood) on the day of death, and the week preceding death shows a mounting curve of non-protein nitrogen. The last three cases (Nos. 10, 11, and 12) give control observations on severe cases of broken cardiac compensation and marked passive congestion of the viscera. The blood non-protein nitrogen is normal.

Cases 7 and 8 with duodenal stenosis (cancer) and pyloric stenosis (cancer) show very high blood non-protein nitrogen. The obstruction is undoubtedly in part responsible but we have some observations to suggest that the intoxication associated with cancer may at times show a rise in the blood non-protein nitrogen. It is obvious that the tissue autolysis, either cancer tissue or invaded and destroyed host tissue, may be directly responsible for this change.

Case 9 is of great interest because of the low urea figures. This person was certainly suffering from grave liver insufficiency for several days before death. The blood non-protein nitrogen is above normal, and this is to be expected with this type of liver autolysis and intoxication. Yet in spite of this increased protein catabolism which usually, as we know, breaks down to urea, in this instance the usual amount of urea could not be formed. May not this lack of urea formation be attributed to the extreme liver injury? This speaks against any great activity on the part of other body tissues in the formation of urea. We hope to supplement this observation by animal experiments which will admittedly be difficult because of the remarkable reserve capacity of the liver and its ability to regenerate after injury.

Protocols.

Case 1. Pneumonia; Pulmonary Abscess.—F. L., woman, age 42 years, who developed bilateral pneumonia with pulmonary abscess after a pelvic operation Sept. 25, 1916. Physical signs, sputum, and x-ray examination confirmatory. Probable etiology was dislodgment of infected thrombi in pelvic veins. Larger

abscess (right) drained by thoracotomy Oct. 20. Pus showed streptococcus. Died Oct. 30. No autopsy.

Case 2. Lobar Pneumonia.—C. R., man, age 22 years, with typical consolidation of left lower lobe and dry pleurisy. Blood examination on 5th day of disease. Crisis on 9th day with uneventful recovery.

Case 3. Lobar Pneumonia.—E. B., woman, age 37 years, with typical lobar pneumonia involving left lower lobe. Severe intoxication and delirium. Died Nov. 13, 1916. No autopsy.

Case 4. Postoperative Peritonitis.—J. M., man, age 50 years, who had had a preparatory gastroenterostomy and a later gastrectomy for adenocarcinoma of pyloric region before blood observations were made. Following latter operation gastric fistula developed. Died Nov. 20, 1916.

Autopsy.—Anatomical diagnosis: Recent gastrectomy for adenocarcinoma of stomach and regional lymph nodes with breaking down of gastrectomy wound and gastric fistula; subacute peritonitis; pulmonary edema; scarring of pulmonary apices and calcification of bronchial lymph nodes on right side (obsolete tuberculosis); arteriosclerosis; chronic pleuritis; chronic perihepatitis; chronic splenitis; pulmonary emphysema.

Case 5. Acute Endocarditis; Acute Pleuritis.—J. C., boy, age 18 years, with chronic disease of aortic and mitral valves and badly decompensated heart with general anasarca. Had also chronic pericarditis and an acute pleuritis. Improved only slightly during 4 months' stay in hospital. Acute endocarditis not recognized clinically. Died Feb. 13, 1917.

Autopsy.—Anatomical diagnosis: Chronic endocarditis of mitral valve with mitral insufficiency; acute vegetative endocarditis of mitral and tricuspid valves; acute mural endocarditis of left auricle; relative tricuspid insufficiency; hypertrophy and dilatation of heart; chronic passive congestion of viscera; chronic adhesive pericarditis; acute fibrinous pleuritis; chronic adhesive pleuritis.

Case 6. Acute Endocarditis; Streptococcus Septicemia.—D. W., man, age 25 years, who had had arthritic attacks 5, 10, and 20 years previously, had much enlarged decompensated heart with usual symptoms and signs, slight fever, leukocytosis, and streptococcus in blood culture. Died Oct. 31, 1916.

Autopsy.—Anatomical diagnosis: Streptococcus septicemia; extensive acute vegetative endocarditis of mitral valve; chronic endocarditis of aortic, mitral, and tricuspid valves; aortic insufficiency, mitral stenosis and insufficiency, and relative tricuspid insufficiency; chronic fibrous myocarditis; thrombi in right auricle; hypertrophy and dilatation of heart; chronic passive congestion of viscera with general anasarca; infarction of spleen; thrombosis of veins around prostate; multiple pulmonary infarctions; acute pancreatitis with fat necroses; fatty degeneration of liver.

Case 7. Carcinoma of Gall Bladder; Duodenal Stenosis; Acute Bronchitis and Bronchopneumonia.—M. D., woman, age 62 years, with gastric symptoms of 3 years' duration. Examination showed dilated stomach due to pyloric obstruction. Blood examination on day of death.

Autopsy.—Anatomical diagnosis: Carcinoma of gall bladder with constriction of duodenum from fibrous tissue at liver hilum; metastatic carcinoma of liver; moderate dilatation of stomach; acute bronchitis and bronchopneumonia; acute cystitis; chronic pelvic peritonitis; chronic perihepatitis; arteriosclerosis.

Case 8. Cancer of Stomach with Pyloric Stenosis and Tetany.—J. W., man, age 60 years, with greatly dilated stomach (capacity 3,700 cc.), pyloric stenosis, and classical symptoms of tetany. Died Oct. 27, 1916, after enterostomy was performed for feeding.

Autopsy.—Anatomical diagnosis: Colloid carcinoma of stomach with pyloric stenosis and gastric dilatation; recent enterostomy (jejunum); gastric ulcer.

Case 9. Acute Yellow Atrophy of Liver.—N. B., woman, age 24 years, with jaundice of 3 weeks' duration. Admitted in comatose condition; intensely jaundiced and little history obtained. Leukocytes 74,000. Died the day blood sample was taken.

Autopsy.—Anatomical diagnosis: Subacute and chronic hepatitis with marked diffuse hepatic necrosis and atrophy; subacute perihepatitis; splenic tumor; acute bronchitis and bronchopneumonia; subserous hemorrhages (pleura, pericardium, peritoneum); minute focal necroses in myocardium with acute interstitial myocarditis; jaundice; marked epithelial degeneration of renal tubules; heart's blood and spleen cultures sterile.

Case 10. Decompensated Heart.—F. S., man, age 60 years, with chronic mitral and aortic disease with insufficiency of the valves, including tricuspid, following acute articular rheumatism many years previously; decompensation progressive for past 5 months, characteristic symptoms of cardiac failure with passive congestion and edema; no infection. Died suddenly Oct. 10, 1916.

Autopsy.—Anatomical diagnosis: Chronic endocarditis of mitral and aortic valves; mitral insufficiency, aortic stenosis and insufficiency, relative tricuspid insufficiency, chronic adhesive pericarditis with calcification; hypertrophy and dilatation of heart; generalized chronic passive congestion and anasarca; pulmonary edema; arteriosclerosis; chronic adhesive pleuritis; chronic perisplenitis; pulmonary emphysema.

Case 11. Decompensated Heart.—W. W., man, age 49 years, with chronic valvular disease, mitral stenosis and insufficiency, tricuspid insufficiency, and generalized passive congestion with edema. Tenth admission to hospital for broken compensation. No signs of intercurrent infection.

Case 12. Decompensated Heart.—W. H., man, age 53 years, with emphysema, chronic myocarditis, relative tricuspid insufficiency, and chronic passive congestion. Third admission for decompensated heart. No evidence of infection.

DISCUSSION.

It is of some interest to speculate as to the accumulation of these non-protein substances in the blood in these conditions. The amount of excess nitrogen elimination in the urine does not indicate necessarily

the severity of the intoxication. Given two cases of obstruction or of proteose intoxication, we can assume with safety that the one showing the greater nitrogen elimination was more severely poisoned. But we cannot compare the intoxication of obstruction with the intoxication due to an abscess, according to the excess urinary nitrogen elimination. It is easy to compare two dogs, one with obstruction and one with a sterile abscess, both dogs showing a similar increase in urinary nitrogen, and yet the obstruction dog is much more severely intoxicated and may even be on the verge of death. We know that on the day after the relief of an obstruction or the drainage of an abscess there is a considerable rise in urinary nitrogen and a rapid return to normal clinical condition. This suggests a retention of nitrogenous products in the blood and body cells, as can be demonstrated in the blood.

Why is there this retention of protein split products in the body cells and fluids during these intoxications? There are several possibilities. One may assume that the cell protoplasm is injured and holds fast to these diffusable protein split products just as it may hold fast to fluids in very acute proteose intoxication (6). It may be claimed that the protein breakdown or autolysis is so rapid that the kidneys cannot concentrate and eliminate these nitrogenous substances as fast as they are formed. Or it may be assumed that the kidney cells are in some way injured so that the substances are not allowed to pass, for the normal kidney can take care of enormous amounts of urea injected into the blood (7). We believe it is necessary to determine whether the kidney's eliminative function for nitrogenous substances is in any way impaired in acute proteose intoxication or other intoxications and hope to report on this work in the near future. There is no anatomical evidence of any kidney injury in these conditions: at the most one can only note the appearance of cloudy swelling in the tubular portion of the kidney cortex. In most cases of experimental intestinal obstruction in dogs the kidneys will be found to be normal in gross and under the microscope.

SUMMARY.

Sterile abscess formation in the dog is accompanied by a large increase in output of urinary nitrogen and also by a small but definite increase in the blood non-protein nitrogen. All this nitrogenous material of course is derived from body protein injury and autolysis.

Septic inflammation in the dog (pleurisy, pneumonia, peritonitis, etc.) likewise shows a distinct rise in the blood non-protein nitrogen. This rise is not often so great as that frequently observed in the intoxication of intestinal obstruction.

Many acute infections in man (septicemia, peritonitis, pneumonia, etc.) show a definite rise in the non-protein nitrogen and urea nitrogen of the blood; some cases show a very great rise above normal (over 100 mg. of non-protein nitrogen per 100 cc. of blood). There may be no anatomical change in the kidney beyond the familiar picture of cloudy swelling. This does not exclude the possibility of some transient functional derangement of the kidney epithelium.

Certain obscure intoxications in man may show a considerable rise in the non-protein nitrogen of the blood, indicating a large amount of protein disintegration.

These findings must be taken into account in any clinical analysis and interpretation of high non-protein nitrogen of the blood in pathological conditions.

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