Studies of nitrogen partition in the blood and spinal fluid, with especial reference to the possible causation of albuminuric retinitis / Alan C. Woods, M.D. Boston.

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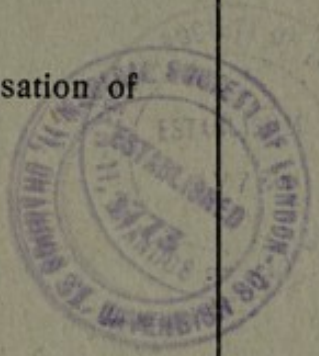

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STUDIES OF NITROGEN PARTITION IN THE BLOOD AND SPINAL FLUID

WITH ESPECIAL REFERENCE TO THE POSSIBLE CAUSATION OF ALBUMINURIC RETINITIS *

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The fact that an albuminuric retinitis, occurring in the course of a chronic nephritis, is a sign of the gravest prognostic import, has long been recognized. Within the last five years, this has been the subject of considerable investigation, especially by the French clinicians, and several very interesting theories have been advanced. Chauffard[1] attempted to explain albuminuric retinitis on the grounds of a hypercholesterinemia, while Onfrey and Balavoine[2] attempted to show that changes in the viscosity of the blood played an important part. The theory that attracted the greatest amount of attention, however, was that advanced by Widal[3] in 1910. He stated that albuminuric retinitis was the result of the retention in the blood of urea, or of some nitrogenous body closely allied to urea. In 1912 Widal[4] reviewed the work of Chauffard and agreed with him that cholesterin, lipoids, and lecithin compounds might often be retained in the blood in nephritis. Widal found, however, that this retention fell as the urea retention rose and stated that retinitis occurred only in those cases which showed a definite nitrogen retention. The prognostic significance of albuminuric retinitis was due, therefore, he believed, to the fact that it stood as a sign of nitrogen retention.

The object of my work has been to determine whether such a relation between nitrogen retention and the occurrence of albuminuric retinitis could be demonstrated, and whether or not albuminuric retinitis could be charged to "urea or to any closely allied nitrogenous body." Using the newer methods, estimations were made of the total non-protein nitrogen, of the ammonia nitrogen, of the urea nitrogen, the

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* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Chauffard: Pathogénie des rétinites albuminuriques, Semaine méd., 1912, xxxii, 193.

2. Onfrey and Balavoine: Viscosité du sang et hémorragies oculaires, Ann. d'ocul., 1911, cxlvi, 433.

3. Widal, Morax and Weill: Rétinite Albuminurique et Azotémie, Ann. d'ocul., 1910, cxliii, 354.

4. Widal, Weill and Landat: La lipémie des brightiques; rapports de la rétinite des brightiques avec l'azotémie et la cholesterinémie, Semaine méd., 1912, xxxii, 529.

uric acid, creatinin, combined creatinin and creatin, and of the amino-acid nitrogen in the blood. Estimations were also made of the total nonprotein nitrogen and urea nitrogen in the spinal fluid, taken at the same time.

In a review of the literature, the first important work on nonprotein nitrogen retention in the blood seems to have been done by von Jaksch[5] in 1893. He gave figures for the nitrogen content of the alcoholic filtrate from blood, and showed there was a marked increase in the nonprotein nitrogen in the blood in chronic nephritis. H. Straus[6] in 1902 gave figures in nitrogen partition, finding 75 per cent. of the total nonprotein nitrogen as urea nitrogen, 2.4 per cent. as uric acid, and 5 per cent. as ammonia. In high nitrogen retention, he found these same figures held. Holweg[7] in 1911, found 60.8 per cent. of the total nonprotein nitrogen as urea nitrogen, 27.4 per cent. as amino-acid nitrogen and 11.7 per cent. as albuminose nitrogen. He found that as the total nonprotein nitrogen retention increases, the urea and amino-acid nitrogen increased proportionally, while the albuminose nitrogen remained stationary. Obermayer and Popper[8] in 1911 reviewed the literature and cited the following results of investigation on the retention of nitrogenous bodies. Jaccoud[9] thought creatin retention the cause of uremia. Coetbeer and Hunden[10] found that in the great nonprotein nitrogen retention following extirpation of the kidney, urea nitrogen was only one-third the total. Oppler and Hoppe-Seyler[11] found creatinin increased in the blood in chronic nephritis, and von Jaksch[12] found an increase in uric acid. Obermayer and Popper themselves found nonprotein nitrogen in the blood in cases of uremia varying from 57 to 658 mg. per hundred c.c. of blood, of which an average of 64 per cent. was urea nitrogen.

Philipp[13] in 1913 reported a series of cases giving the total nonprotein nitrogen and the urea nitrogen content in the blood in cases of uremia. Using phosphotungstic acid to precipitate the proteins in the determination of the total nonprotein nitrogen, he found the urea

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5. Von Jaksch: Ueber die Zusammensetzung des Blutes gesunder und kranker Menschen, Ztschr. f. klin. Med., 1893, xxiii, 187.
6. Straus, H.: Die chronischen Nierenentzündungen in ihrer Einwirkung auf Blutflüssigkeit, Berlin, 1902.
7. Holweg: Ueber das Verhalten des Reststickstoffes des Blutes bie Nephritis und Urämie, Deutsch. Arch. f. klin. Med., 1911, civ, 216.
8. Obermayer and Popper: Ueber Urämie, Ztschr. f. klin. Med., 1911, lxxii, 332.
9. Jaccoud: Quoted by Obermayer and Popper, Note 8.
10. Soetbeer and Hunden: Quoted by Obermayer and Popper, Note 8.
11. Oppler and Hoppe-Seyler: Quoted by Obermayer and Popper, Note 8.
12. Von Jaksch: Quoted by Obermayer and Popper, Note 8.
13. Philipp: Ueber des Verhalten des Harnstoffs und des Reststickstoffs im Blute von Nephritiken, med. Klin., Berlin, 1913, ix, 912.

nitrogen as an average of 91.2 per cent. of the total nonprotein nitrogen. The highest total nonprotein nitrogen he reported was 289 mg. per hundred c.c. of blood in a case of mercury poisoning. Agnew[14] in 1914 reports a series of estimations of total nonprotein nitrogen and urea nitrogen.

The more recent work on the subject of nitrogen partition has been done by Folin and his co-workers. In 1913, Folin and Denis[15] reported on the determination of nitrogenous waste products, and stated that they had found no particular diagnosis to correspond with any particular degree of nitrogen retention. At the same time Seymour[16] reported a series of determinations of total nonprotein nitrogen, urea nitrogen, and uric acid in the blood. In 1914, Folin and Denis[17] reported further on the influence of diet on these same nitrogenous bodies. Again in 1914, Folin and Denis[18] reported a series of twenty-seven estimations of the total nonprotein nitrogen, ammonia nitrogen, uric acid, creatinin, and combined creatinin and creatin, in cases both of health and disease. In four estimations on healthy individuals, the total nonprotein nitrogen varied from 24 to 37 mg. per hundred c.c. of blood, urea nitrogen from 11 to 18 mg.; ammonia nitrogen from 0.1 to 0.14 mg.; uric acid from 2 to 3 mg.; creatinin from 1.1 to 1.3 mg. and combined creatinin and creatin from 6.5 to 9.5 mg. per hundred c.c. of blood. In pathologic conditions, figures were found as high as 326 mg. for the total nonprotein nitrogen in a case of decompensated cardiorenal disease. In uremia the highest figures found for the various nitrogenous bodies were, total nonprotein nitrogen 264 mg., urea nitrogen 228 mg., ammonia nitrogen 0.66 mg., uric acid 6.6 mg., creatinin 26 mg., and combined creatinin and creatin 46 mg., all per hundred c.c. of blood. In 1915 Foster[19] reported he had found substantially the same figures in

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14. Agnew, J. Howard: Comparative Study of Phenolsulphonephthalein Elimination, and the Incoagulable Nitrogen in the Blood in Cardiorenal Diseases, The Archives Int. Med., 1914, xiii, 485.

15. Folin, Otto, and Denis, W.: Nitrogenous Waste Products in the Blood in Nephritis, Their Significance and the Methods of Determination, Medical Communications, Massachusetts Med. Soc., 1913, xxiv, 157.

16. Seymour: Nitrogenous Waste Products in the Blood, Their Effect in Chronic Interstitial Nephritis, Medical Communications, Massachusetts Med. Soc., 1913, xxiv, 163.

17. Folin, Otto, Denis, W., and Seymour, Malcolm: The Nonprotein Nitrogenous Constituents of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism, The Archives Int. Med., 1914, xiii, 224.

18. Folin, Otto, and Denis, W.: On the Creatinin and Creatin Content of Blood, Jour. Biol. Chem., 1914, xvii, 487.

19. Foster, Nellis B.: Uremia. The Nonprotein Nitrogen of Blood, The Archives Int. Med., 1915, xv, 356.

nitrogen partition as had Folin. In addition, four estimations of the amino-acid nitrogen gave values between 4 and 6 mg. per hundred c.c. of blood.

Nitrogen studies in the spinal fluid have been confined largely to estimations of the urea content. The literature was reviewed in 1909 by Mollard and Froment,[20] and brought up to date in 1914 by Soper and Granat.[21] Figures given by various investigators for the normal urea content vary from 0 to 40 mg. per hundred c.c. of spinal fluid, but practically all authors agree that it is greatly increased in uremia. Mestrezat[22] in 1912 gives the normal urea content as 6 mg. and the total nonprotein nitrogen as 16.7 mg. per hundred c.c. of spinal fluid. Galletta[23] in 1908 gave the total nonprotein content as 20.6 mg., and Comba[24] in 1899, as 15 mg. per hundred c.c. of spinal fluid. Both authors cite cases of uremia in which the nonprotein nitrogen retention is vastly increased. Widal[25] and Javal[26] in 1911 showed that the concentration of urea in the various body fluids is substantially the same. Soper and Granat[21] in 1914 reported a series of urea estimations in the spinal fluid, using the hypodermic methods, and emphasized the prognostic significance of these. Moral and Froment[27] in 1913 reported a case of amyloid kidney, in which they found a total nonprotein nitrogen retention of 222 mg., per hundred c.c. of spinal fluid, of which 220 mg. were represented as urea nitrogen.

In my series of cases, about 175 c.c. of blood were received directly from the vein into a cylinder containing 3 c.c. of a 20 per cent. solution of potassium oxalate. The cylinder was rapidly shaken to prevent clotting. Lumbar puncture was done immediately thereafter, and about 10 c.c. of spinal fluid withdrawn.

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20. Mollard and Froment: Urée dans le liquide céphalo-rachidien et urémie nerveuse, Jour. de Physiol. et de Path. Général, 1909, xi, 263.

21. Soper, Willard B., and Granat, Selma: The Urea Content of the Spinal Fluid with Special Reference to Its Diagnostic and Prognostic Significance, The Archives Int. Med., 1914, xiii, 131.

22. Mestrezat: Le Liquide Céphalo-Rachidien, Paris, 1912.

23. Galletta: Quoted by Mestrezat, Note 22.

24. Comba: Quoted by Mestrezat, Note 22.

25. Widal: Le prognostic dans le mal le Bright par le dosage de l'urée du sang. Les rémissions temporaires et trompeuses de l'azotémie, Soc. med. d. hôp. de Paris, 1911, xxxii, 627.

26. Javal: La grande azotémie. Ses formes, son évolution, son prognostic étudiés par le dosage méthodique de l'urée dans le sang et dans les sérosités de l'organisme, Soc. med. d. hôp. de Paris, 1911, xxxii, 485.

27. Moral and Froment: A propos d'un cas de néphrite amyloide; rétention de l'urée dans le liquide céphalo-rachidien, Lyon méd., 1913, cxx, 933.

In all estimations on the blood, whole blood was used. Total nonprotein nitrogen,[28] ammonia nitrogen,[28] creatinin,[29] and combined creatin and creatinin[29] were done by the methods of Folin and Denis. Uric acid was determined by the method of Folin and Denis,[30] using the later modification of Folin and Bell,[31] in which sodium thiocyanate is used in place of hydrogen sulphid. Urea nitrogen was determined by the method of Van Slyke,[32] using the colorimeter. The amino-acid nitrogen was estimated with Van Slyke's micro-apparatus.[33] Chlorids were estimated by the method of McLean.[34] Total nonprotein nitrogen and urea nitrogen determinations in the spinal fluid were done synchronously with the determinations in the blood. All results were controlled and were repeated when the difference between the estimations was appreciable. The systolic and diastolic blood pressures were taken just before bleeding, and phenolsulphonephthalein tests were done in all instances. The creatin was estimated as the difference between the combined creatinin and creatin determination, and the creatinin determination. The uric acid, creatinin, and creatin nitrogen were figured from the structural formula of each, and are reported as mg. per hundred c.c.

The cases are reported in three groups: (1) those cases which presented no retinal changes whatsoever; (2) those cases which presented the retinal picture of arteriosclerosis, with occasional hemorrhages, but without exudates; (3) those cases which showed a marked albuminuric retinitis, with haziness or obliteration of the disk outlines, vascular changes, hemorrhages and exudates, with involvement of the macula region.

While the highest retention observed, 266 and 257 mg. of nonprotein nitrogen per hundred c.c. of blood, happened to occur in cases of albuminuric retinitis, nevertheless marked retinitis occurred at practically any level of nitrogen retention. There appears to be no close relationship whatsoever between either total nonprotein nitrogen retention, or any component part, and the occurrence of albuminuric retinitis. A comparison of the three groups fails to show any appreciable

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28. Folin, O., and Denis, W.: New Methods for the Determination of Total Nonprotein Nitrogen, Urea and Ammonia in the Blood, Jour. Biol. Chem., 1912, xi, 527.

29. Folin, O., and Denis, W.: On the Determination of Creatinin and Creatin in Blood, Milk and Tissues, Jour. Biol. Chem., 1914, xvii, 475.

30. Folin, O., and Denis, W.: A New (Colorimetric) Method for the Determination of Uric Acid in Blood, Jour. Biol. Chem., 1912-1913, xiii, 469.

31. Courtesy of Drs. Folin and Bell. Method as yet unpublished.

32. Van Slyke and Cullen: A Permanent Preparation of Urease and Its Use in the Determination of Urea, Jour. Biol. Chem., 1914, xix, 221.

33. Van Slyke and Meyer: The Amino-Acid Nitrogen of the Blood, Jour. Biol. Chem., 1912, xii, 399.

34. Courtesy of Dr. McLean. As yet unpublished.

difference in the proportions of either urea, ammonia, uric acid, creatinin, creatin, or amino-acid nitrogen. The same proportions prevail in cases in which there is albuminuric retinitis and those in which the fundi are normal. Neither to urea nor to "any closely allied nitrogenous body" can albuminuric retinitis be attributed. This holds true for the cerebrospinal fluid, also, so far as nitrogen retention could be studied. The three groups show essentially the same picture. Case 13 was of especial interest in that the patient presented a fresh albuminuric retinitis together with a normal nitrogen content throughout. He was a man of 52 years, admitted in apoplectic coma, with a systolic blood pressure of 285 mm. Hg, marked retinitis and a phenolsulphonephthalein output of 28 per cent. He made a good recovery and was discharged from the hospital in fair condition.

An analysis of the figures shows that the urea maintains roughly the same concentration as the total nonprotein nitrogen rises, an average throughout of 63.4 per cent. of the total nonprotein nitrogen. While the ammonia nitrogen increased slightly as the total nonprotein nitrogen rose, this rise was not proportional. The relation of ammonia nitrogen to total nonprotein nitrogen accordingly varied from about 0.4 per cent. at the low levels of total nonprotein nitrogen to about 0.1 per cent. at the highest levels. The uric acid figures were the last to show any marked increase as the total nonprotein nitrogen rose. But two cases showed any marked uric acid retention—Nos. 9 and 17B, in which the uric acid content was respectively 5 and 8.35 mg. per hundred c.c. of blood. In these two cases blood was taken 36 and 12 hours before death. The creatinin showed roughly a proportionate increase as the total nonprotein nitrogen rose, averaging in all 3.4 per cent of the total nonprotein nitrogen. The creatin percentage, excluding Case 18, varied from about 2 per cent. to 7 per cent. throughout, averaging 3.9 per cent. In Case 18 it reached the high value of 12 per cent. The amino-acid nitrogen, however, showed no constant increase as the total nonprotein nitrogen rose to higher levels, remaining generally between 4 and 7 mg. per hundred c.c. of blood. In Cases 9, 10, 15B and 16A it reached higher levels, but in each of these cases there was an extraneous factor. Case 9 was one of complete anuria for seven days, the blood being taken on the fifth day, while in Cases 10, 15B and 16A the blood was taken about one hour after the midday meal. In all other cases blood was taken four hours after the midday meal.

In the limited number of cases in which as complete partitions as possible were done, figures are given showing the "residual nitrogen." These figures were obtained by subtracting the sum total of the determined component nitrogen constituents from the total nonprotein

nitrogen. It includes, therefore, the total error of all the various estimations, and such other unknown nitrogenous bodies as may enter the blood stream. These figures are of interest in that they seem in several cases to run roughly parallel with the severity of the case as observed clinically. In Case 9, in which the high figure for "residual nitrogen" of 31.55 mg. per hundred c.c. of blood was reached, after five days of complete anuria, death occurred in thirty-six hours. In Cases 7, 8 and 16, in which the values were all over 10 mg. per hundred c.c. of blood, death occurred in two days, one month and two months respectively. In Cases 11 and 12 with high figures for residual nitrogen, the prognosis from the clinical standpoint seemed extremely poor. In the remaining cases in which residual nitrogen was estimated, the patients were all in reasonably fair condition.

The total nonprotein nitrogen in the spinal fluid was, as a rule, about 25 per cent. lower than that in the blood. In two cases, however, the total nonprotein nitrogen was the same in both. The first of these (No. 8) was one of mercurial poisoning, with practically complete anuria for five days previous to death. Blood and spinal fluid were taken eighteen hours before exitus. The figures here are comparatively low when compared to Philipp's case of mercurial poisoning, which showed a nonprotein nitrogen retention of 289 mg. The second of these two cases was one of seven days' complete anuria and the blood and spinal fluid were taken on the fifth day. It seems possible that certain nitrogenous bodies, normally not present in the spinal fluid, are, in anuria, excreted from the blood into the spinal fluid until an equilibrium is reached. Sufficient spinal fluid was never obtained in any case to determine if these bodies were any of the common nitrogenous constituents of the blood, for example, uric acid, creatinin, creatin or amino-acids. The urea content of the spinal fluid throughout approximately equaled that of the blood, as shown before by Widal, Javal and others. It does not seem probable that nitrogen determinations in the spinal fluid give any greater diagnostic or prognostic significance than those in the blood.

The concentration of urea in the spinal fluid, in relationship to the total nonprotein nitrogen, was fairly constant throughout, averaging approximately the same percentage at high as at low levels, an average of 78 per cent. in the series as a whole.

The chlorids in the blood showed little variation, varying in most cases between 0.42 and 0.53 gm. per hundred c.c. In the case of mercury poisoning the low figure 0.34 gm. per hundred c.c. was reached. Isolated determinations of blood chlorids without taking into consideration the relative intake and excretion, give little or no information about salt retention.

TABLE I.—Chronic Nephritis with Normal Fundi

No.	Hosp. Med. No.	Blood Nitrogen									Spinal Fluid Nitrogen		Blood Pressure	Phthalein Excretion Percentage in 2 Hrs.	Remarks
		Total Non-protein	Urea	Ammonia	Uric Acid	Creatinin	Creatin	Amino-Acid	"Residual"	Chlorids, Gm.	Total Non-protein	Urea			
1	2,358	26.77	14.38	0.09	0.40	0.77	0.99	6.78	3.36	0.4476	17.85	11.09	130- 85	48	Normal control
2	2,319	29.43	15.63	0.15	0.34	0.57	0.65	5.42	6.67	0.4435	24.68	15.45	240-160	47	
3	2,357	35.70	18.49	0.10	0.67	0.67	0.95	8.44	6.48	0.4391	27.35	18.50	210-108	52	Chr. myocarditis
4	2,348	43.48	23.57	0.12	0.40	0.59	1.19	6.52	11.09	0.4707	35.70	21.25	185- 95	52	
5	1,992	55.30	38.98	0.14	0.67	3.07	4.27	....	....	0.5153	.....	.....	260-110	12	
6	1,954	57.60	36.85	0.15	0.64	0.82	5.70	....	....	0.4296	.....	.....	235-115	21	
7A†	2,006	95.27	66.66	0.15	0.64	3.68	2.89	....	....	0.5363	.....	.....	190- 98	Unreadable trace	
7B‡		90.90	62.50	0.19	0.53	5.08	2.32	6.42	13.86	0.5682	66.66	60.24	190-100	Unreadable trace	
8	2,259	128.00	95.10	0.16	0.68	5.29	7.08	5.89	13.80	0.3429	128.00	95.21	130- 80	.....	Mercury poisoning
9	2,174	138.10	79.76	0.24	1.67	4.09	4.37	16.32	31.56	0.4216	142.96	85.88	185-140	Unreadable trace*	

* Phthalein estimation made three weeks previously at Massachusetts General Hospital. † 7A on December 12. ‡ 7B on December 17

TABLE 2.—Chronic Nephritis with Vascular Changes Only in Fundi

No.	Hosp. Med. No.	Blood Nitrogen									Spinal Fluid Nitrogen		Blood Pressure	Phthalein Excretion Percentage in 2 Hrs.	Remarks
		Total Non-protein	Urea	Ammonia	Uric Acid	Creatinin	Creatin	Amino-Acid	"Residual"	Chlorids, Gm.	Total Non-protein	Urea			
10	2,132	47.51	29.58	0.18	0.40	2.02	3.58	10.23	1.52	0.4500	.....	.....	265-140	33	
11	2,202	71.34	43.07	0.11	0.66	1.71	2.10	6.50	17.28	0.5362	47.62	40.32	245-150	18	17 cells in sp. fl.
12	2,316	95.23	60.00	0.16	0.43	3.68	4.34	8.05	18.57	0.4649	80.00	60.16	213-124	Unreadable trace	

TABLE 3.—Chronic Nephritis with Marked Albuminuric Retinitis

No.	Hosp. Med. No.	Blood Nitrogen									Spinal Fluid Nitrogen		Blood Pressure	Phthalein Excretion Percentage in 2 Hrs.	Remarks
		Total Non-protein	Urea	Ammonia	Uric Acid	Creatinin	Creatin	Amino-Acid	"Residual"	Chlorids, Gm.	Total Non-protein	Urea			
13	2,354	23.81	14.60	0.10	0.35	0.61	0.99	4.02	3.14	0.4243	20.00	12.50	285-160	28	Apoplexy
14	2,074	40.98	27.00	0.17	0.39	1.67	2.21	5.22	4.32	0.4400	33.28	26.32	180-130	19	
15A†	2,043	54.05	32.14	0.12	0.46	2.74	2.74	....	....	0.4558	43.46	26.59	250-166	10	
15B‡		60.61	41.54	0.12	1.26	2.30	3.12	10.64	1.63	0.4735	46.58	31.25	250-160	10	
16A‖	2,108	55.55	29.35	0.09	0.60	2.63	1.59	9.44	11.85	0.4407	37.21	27.77	190-150	15	Four cells per cm. in spinal fluid
16B¶		47.54	25.50	0.15	0.98	2.45	3.66	6.56	8.24	0.3997	33.33	26.00	150-130	11	Herpes zoster complicating uremia. Ninety-one cells
17A#	1,882	192.30	113.80	0.20	0.62	8.01	14.39	....	....	0.4788	125.00	111.11	248-128	Unreadable trace	Sixteen cells per cm. spinal fluid
17B§		266.66	166.45	0.21	2.78	7.85	7.66	....	....	0.5141	188.69	166.66	250-130	Unreadable trace	Uremia. Twenty-three cells per cm. in spinal fluid
18	1,975	257.70	181.80	0.33	1.51	6.01	30.93	....	....	0.4752	.....	.....	208-152	Unreadable trace	Uremia

† 15A on December 19. ‡ 15B on December 30. ‖ 16A on January 4. ¶ 16B on January 19. # 17A on November 30. § 17B on December 14.

The relationship between nonprotein nitrogen retention and phenolsulphonephthalein excretion was fairly constant. When the nitrogen retention was high, the phenolsulphonephthalein excretion was generally low, and vice versa, confirming the results of the numerous investigators in this field. No relationship between the nonprotein nitrogen retention and blood pressure was observed.

CONCLUSIONS

1. There is no apparent relationship between the retention of any nitrogenous body and the occurrence of albuminuric retinitis, and there is certainly no evidence that they stand in the relationship of cause and effect.

2. In the limited number of cases in the series, there seemed to be a more than casual relationship between the "residual nitrogen" of the blood, and the severity of the case as observed clinically.

3. As the level of nonprotein nitrogen rises, the component nitrogenous bodies increase, and in the case of the chief constituents, this rise is proportioned.

4. Estimations of total nonprotein nitrogen and of urea in the spinal fluid give no greater diagnostic or prognostic significance than estimations of these substances in the blood.

5. The variations in chlorid concentration in the blood are so small that in themselves they give no idea of salt retention.

I wish to express my thanks to Dr. Henry A. Christian for his advice and for facilities placed at my disposal during the course of this work, and to Dr. Francis W. Peabody for many helpful suggestions.