STUDIES IN RENAL FUNCTION WITH SPECIAL REFERENCE TO NON-PROTEIN NITROGEN AND SUGAR CONCENTRATION IN THE BLOOD, PHENOLSULPHONEPHTHALEIN ELIMINATION AND BLOOD PRESSURE *

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Until the theories of nephritis are reduced to one and until that one has been conclusively proved to be correct, continued investigations, both clinical and experimental, seem to be demanded.

These studies in nephritis deal on the one hand, with the accumulation or retention in the blood of the end-products of protein metabolism and glucose concentration in the blood, and on the other hand, with the functional capacity of the kidneys in so far as the latter may be determined by the elimination of phenolsulphonephthalein. In short, the purpose of this paper is to study:

1. The relation of protein feeding to nitrogen retention in the blood.
2. The relation of nitrogen retention to renal function.
3. The relation of blood-sugar, blood-pressure, phenolsulphonephthalein elimination and nitrogen retention.

So far as we can ascertain, there have been no studies covering all of these phases simultaneously and the possible relationship existing between them; though quite recently Folin¹ and Frothingham and Smillie² have reported on somewhat similar studies, the latter presentation having been published shortly before the completion of this work.

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1. Folin, Otto, Denis, W., and Seymour, Malcolm: The Non-Protein Nitrogen Content of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism, *THE ARCHIVES INT. MED.*, 1914, xiii, 224.

2. Frothingham, Channing, and Smillie, Wilson, G.: The Relation Between the Phenolsulphonephthalein Excretion in the Urine and the Non-Protein Nitrogen of the Blood in Human Cases, *THE ARCHIVES INT. MED.*, 1914, xiv, 541.

I. THE RELATION OF PROTEIN FEEDING TO NITROGEN RETENTION IN THE BLOOD

With but two exceptions, these observations were made on ward patients in the University Hospital on the service of Dr. Alfred Stengel.

To study the effect of the level of protein diets on the retention of nitrogen in the blood, we first placed the patient on a diet of about 2,300 calories, which represented approximately 5 gm. of nitrogen; then on a diet of 2,150 calories, corresponding to 12 gm. of nitrogen, and finally, on a diet of 2,300 calories or about 18 gm. of nitrogen.

TABLE 1.—INFLUENCE OF PROTEIN FEEDING ON RETENTION OF NITROGEN IN BLOOD IN CARDIORENAL DISEASE

Case	Diagnosis	Age	Sex*	Date	Nitrogen per hundred c.c. of blood, mg.		
					Low Protein Diet	Ward Diet	High Protein Diet
1. J. H. B.	Chronic nephritis; chronic endocarditis	39	♂	4/1	23	18	30.8
2. J. McW.	Chronic nephritis; chronic myocarditis	48	♂	4/1	28	28	35.5
3. J. H.	Chronic interstitial nephritis; chronic myocarditis	34	♂	4/1		28	33.6
4. J. W.	Chronic nephritis; chronic myocarditis	45	♂	4/2	26	28	
5. H. L.	Chronic interstitial nephritis; myocardial weakness; arteriosclerosis	75	♂	5/9	26	32	39
6. A. P.	Chronic nephritis; chronic myocarditis	49	♂	5/9	30	36	39
7. L. S.	Chronic interstitial nephritis; myocardial weakness	55	♀	7/21	23	30	37
8. S. C.	Arteriosclerosis.....	70	♀	7/21	18	29	35
9. F. G.	Chronic nephritis; chronic myocarditis; asthma	49	♀	10/19	29	28	

* In this and the following tables, ♂ denotes male, and ♀ female.

The duration of each period was three days, and in the afternoon of the third day the blood was withdrawn from a vein in the arm and analyzed according to the recent method of Folin and Farmer³ with the modification that the ammonia liberated was collected in standardized fiftieth normal sulphuric acid and titrated with fiftieth normal sodium hydroxid. It is generally conceded that by this method normal values are those with a total nitrogen of less than 30 mg. per hundred c.c. of blood. We found that all but two cases revealed higher figures at the end of the high protein diet, as will be seen in Tables 1 and 2,

3. Folin, O., and Farmer: Jour. Biol. Chem., 1912, xi, 527.

which are good illustrations of the influence of protein feeding on the retention of nitrogen in nephritics.

In several cases of pure nephritis of the chronic interstitial type and in which there was an increase in non-coagulable nitrogen on a low protein diet, there was a striking reduction in tolerance for an increasing amount of proteid, as was shown by the marked rise in retention products as well as by nausea and vomiting in a few cases (Table 2). Clinically, these results indicate not only the importance of a low proteid diet in certain types of nephritis, but they also illustrate the advantages of this test for a more accurate diagnosis of these types.

TABLE 2.—RISE IN RETENTION PRODUCTS FOLLOWING INCREASE IN PROTEIN INGESTION IN CASES OF CHRONIC INTERSTITIAL NEPHRITIS

Case	Diagnosis	Age	Sex*	Date	Nitrogen per hundred c.c. of blood, mg.		
					Low Protein Diet	Ward Diet	High Protein Diet
1. W. P.	Chronic interstitial nephritis	65	♂	4/1	26	33	40
2. L. L.	Chronic interstitial nephritis	55	♀	4/1	29	30	32
3. D.	Chronic interstitial nephritis	55	♀	4/9	43	54	60
4. G. C. B.	Chronic interstitial nephritis	40	♂	2/26	28	25	43
5. M. W.	Chronic interstitial nephritis	28	♀	5/4	43	35	
6. Mr. R.	Chronic interstitial nephritis	27	♂	6/15	67	88	92
7. S. R.	Chronic interstitial nephritis	26	♂	6/28	56		
8. E. B.	Chronic interstitial nephritis	43	♂	7/6	30	46	56
9. E. H.	Chronic interstitial nephritis	21	♀	7/7	22	29	37
10. P. F.	Chronic interstitial nephritis	61	♂	6/13	39	33	42
11. M. L.	Chronic interstitial nephritis	53	♀	10/1	36	37	
12. S. B. J.	Chronic interstitial nephritis	43	♂	11/27	50		

In fact, observations on nitrogen retention are becoming more and more frequent in the literature. Macwitz, Rosenberg and Tscherkoff,⁴ in an exhaustive study of the pathology of nephritis and its functional diagnosis by various tests, conclude that nitrogen retention is indicative of vascular disease and that, in chronic cases, it is a good index of the degree of insufficiency and gives a valuable clue for both prognosis and therapy.

With regard to the influence of chronic passive congestion on nitrogen retention in the "cardiorenal" symptom-complex, our results

4. Macwitz, Rosenberg and Tscherkoff: München. Med. Wchnschr., 1914, No. 23, p. 1268.

TABLE 3.—RESULT OF EXAMINATION OF A SERIES OF CARDIORENAL CASES

Case	Diagnosis	Age	Sex	Blood Nitrogen Mg. per 100 c.c. of Blood	Blood Sugar Gm. 100 c.c. of Blood	Phtha- lein Elimi- nation % in 2 Hrs.	Blood Pressure	Eye-Grounds	Edema	Liver*	Albu- min	Casts	Sp. Gr.
1. J. H. B.	Chronic nephritis; chronic endocarditis	39	♂	23	0.07	10	110/80		++	10	+	+	1.007
2. J. McW.	Chronic nephritis; chronic myocarditis	48	♂	28	0.076	40	135/98		++	4	++	++	1.025
3. J. H.	Chronic interstitial nephritis; chronic myocarditis	34	♂	28	0.085	40	190/130	Early sclerosis	++	10	+	+	1.015
4. J. W.	Chronic nephritis; chronic myocarditis	45	♂	26	0.09	45	133/70		++	4	++	++	1.021
5. H. L.	Chronic interstitial nephritis; myocardial weakness; arteriosclerosis	75	♂	26	0.131	30	155/90	Indentation of veins. Arteries thickened	—	5	+	+	1.015
6. A. P.	Chronic nephritis; chronic myocarditis	49	♂	30	0.159	15	150/99		+	4.5	++	++	1.025
7. L. S.	Chronic interstitial nephritis; myocardial weakness	55	♀	23		25	155/80	Moderate sclerosis	+	1.5	+	—	1.017
8. M. C.	Chronic interstitial nephritis; chronic myocarditis	41	♀	28	0.09	8	153/105	Incipient sclero- tic changes	+	6	++	+	1.013
9. F. G.	Chronic nephritis; myocar- ditis; asthma	49	♀	28	0.153	33	200/130	Normal.....	+	?	++	++	1.021
10. B. J. B.	Chronic nephritis; myocar- dial weakness	65	♂	67		30	160/70		++	10	++	++	1.019

* Centimeters below costal border in midclavicular line.

TABLE 4.—RESULT OF TESTS IN CASES OF CHRONIC INTERSTITIAL NEPHRITIS WITH HYPERTENSION

Case	Diagnosis	Age	Sex	Blood Nitrogen Mg. per 100 c.c. of Blood	Blood Sugar Gm. per 100 c.c. of Blood	Phtha- lein Elimi- nation % in 2 hrs.	Blood Pressure	Eye-Grounds	Albumin	Casts	Sp. Gr.
1. W. P.	Chronic interstitial nephritis	65	♂	26	0.120	35	180/130		+	+	1.025
2. L. L.	Chronic interstitial nephritis	55	♀	29	0.082	43	225/110		+	+	1.021
3. D.	Chronic interstitial nephritis	55	♂	43	0.106	..	210/150		+	+	
4. G. C. B.	Chronic interstitial nephritis	40	♂	43	0.075	48	185/136		+	+	1.015
5. M. W.	Chronic interstitial nephritis	28	♀	43	0.123	10	256/163		++	+	1.013
6. Mr. R.	Chronic interstitial nephritis	27	♂	67	0.117	18	210/130		++	++	1.009
7. S. R.	Chronic interstitial nephritis	26	♂	56	0.123	22	205/150	Disk edematous. Hemorrhages	++	++	1.013
8. E. B.	Chronic interstitial nephritis	43	♂	46		16	155/110		+	+	1.014
9. E. H.	Chronic interstitial nephritis	21	♀	35	0.07	40	210/115	Edema. Veins full and dark. Patches of exudate	+	+	1.008
10. P. F.	Chronic interstitial nephritis	61	♂	39	0.074	24	190/110	Neuritis, hemor- rhages, sclerosis	++	++	1.019
11. M. L.	Chronic interstitial nephritis	53	♀	36	0.082	37	170/135	Vessels sclerotic. Sen- ile choroidal changes	+	+	1.013
12. C. B.	Chronic interstitial nephritis	40	♀		0.146	10	250/150	Retinitis. Hemor- rhages	++	++	1.015
13. B. W.	Chronic interstitial nephritis	22	♀	33	0.085	60	205/170	Sclerotic changes....	+	—	1.009
14. S. B. J.	Chronic interstitial nephritis	43	♂	50	0.083	37	242/152	Marked sclerosis....	+	+	1.017
15. McC.	Chronic interstitial nephritis	66	♂	58	0.08	75	178/95	Veins full. Hemor- rhagic exudation	+	++	1.021

confirm those of Rowntree and Fitz,⁵ in that there is practically no increase in waste nitrogenous products provoked by such congestion per se; although Strauss and Hohlweg⁶ state that this factor is responsible for a moderate increase in these products. See Tables 1 and 3.

In our series of cardiorenal cases, in many of which chronic passive congestion was very evident, only one presented a rise in blood nitrogen. To be of real value in therapy and prognosis, we believe that the test should be repeated at intervals, that due consideration should be given the time and the amount of protein intake, and finally, that each test should be accompanied by a determination of the phenolsulphone-phthalein elimination. When both the clinical picture and these details are observed, the value of the test cannot be disputed.

In Table 3, it will be noted that of the cardiorenal group investigated, the absence of retained nitrogen is striking when contrasted with Table 4, in which cases of pure chronic interstitial nephritis with hypertension are considered. In the latter group, eleven out of fourteen cases show evidence of retention, and it is this same group in Table 2 which illustrates a marked reduction in tolerance for proteins as noted above. Certain it is that excessive amounts of nitrogen in the blood afford an index of renal functional capacity. The significance of these results in the pure nephritic cases, however, both from the prognostic and therapeutic point of view, will be dealt with later.

II. THE RELATION OF NITROGEN RETENTION TO RENAL FUNCTION AS DETERMINED BY THE PHENOLSULPHONE-PHTHALEIN ELIMINATION

The technic of the phenolsulphonephthalein test used was that originated by Rowntree and Geraghty.⁷ Before discussing the results in our three groups of cases, it may be advisable to note certain conditions under which marked variations in the phthalein output occur. These are:

1. Chronic passive congestion.
2. Various stages of nephritis.
3. Hyperpermeability.

1. *Chronic Passive Congestion*.—Several workers have shown that marked chronic passive congestion greatly decreases the phenolsulphonephthalein output and that as the circulation improves, the output

5. Rowntree, L. G., and Fitz, R.: Studies of Renal Function in Renal, Cardiorenal and Cardiac Diseases, *THE ARCHIVES INT. MED.*, 1913, xi, 258.

6. Strauss and Hohlweg: Quoted by Rowntree and Fitz, *THE ARCHIVES INT. MED.*, 1913, xi, 278.

7. Rowntree and Geraghty: *Jour. Pharm. and Exper. Therap.*, 1910, i, 579.

rises if there is no coexisting renal involvement.^{8, 9} This fact may well be utilized in determining the relative responsibility of heart or kidney in the troublesome symptom complex, cardiorenal disease, as successful therapy in this condition rests largely on our knowledge of the underlying causative factor.

2. *Various Stages of Nephritis.*—Phenolsulphonephthalein elimination varies during the course of the illness (nephritis), a fact well established and one which we have frequently observed. Our most striking example of this is Case 4 in Table 5, in which the phenolsulphonephthalein rose from 17 per cent. to 70 per cent. in five weeks, and in which there was no marked evidence of cardiac disease. The patient's improvement paralleled this rise. We freely concede that a rise as marked as this in so short a time cannot be an index of the actual degree of change in renal tissue, but that it is rather an illustration of the fluctuation in functional capacity during the course of the illness. Thus again, if the phenolsulphonephthalein test is repeated at intervals, its value from the point of view of prognosis is evident. We believe that too much emphasis should not be laid on one phenolsulphonephthalein elimination, and in the differentiation of nephritis from chronic passive congestion, it would seem that a series of both phenolsulphonephthalein and nitrogen tests should be carried out in order to reach any definite conclusions.

3. *Hyperpermeability.*—In the past year, Pepper and Austin¹⁰ have called attention to the existence of cases of nephritis in which the functional capacity of the kidney is normal or even above normal. Baetjer¹¹ has described such cases and considers that there may be a stage in nephritis when hyperpermeability exists at least to phenolsulphonephthalein and some other substances. We have also noted a few cases, but so far the opportunity for serial studies of them has not been presented. It may be that this so-called hyperpermeability is merely an illustration of the possible existence of damaged kidneys with normal functional capacity, at least for some substances. Cases of this type are usually accompanied by chlorid retention.

In our series of pure nephritis of the chronic interstitial type, several interesting facts may be noted (see Table 4). Nearly every case showed retention of nitrogen, decreased phenolsulphonephthalein elimination and high blood-pressure, while the blood-sugar was slightly

8. Farr, C. B., and Austin, J. H.: Jour. Exper. Med., 1913, xviii, 228.

9. Rowntree, L. G., Fitz, R., and Geraghty, J. T.: The Effects of Experimental Chronic Passive Congestion on Renal Function, THE ARCHIVES INT. MED., 1913, xi, 121.

10. Pepper and Austin: Am. Jour. Med. Sc., 1913, cxlv, 254.

11. Baetjer, Walter A.: Superpermeability in Nephritis, THE ARCHIVES INT. MED., 1913, xi, 593.

TABLE 5.—RESULT OF THE STUDY OF A SERIES OF CASES OF CHRONIC PARENCHYMATOUS NEPHRITIS

Case	Diagnosis	Age	Sex	Blood Nitrogen Mg. per 100 c.c. of Blood	Blood Sugar Gm. 100 c.c. of Blood	Phtha- lein Elimi- nation % in 2 Hrs.	Blood Pressure	Eye-Grounds	Edema	Liver	Albu- min	Casts	Sp. Gr.
1. A. S.	Chronic parenchymatous nephritis	22	♀		0.065	27	146/90		++	—	++	++	1.013
2. W. M.	Chronic parenchymatous nephritis; weakness myocardial	24	♂	33	0.072	20	98/65	Related retinal veins	++	—	++	++	1.028
3. A. K.	Chronic parenchymatous nephritis	25	♀	74		7	170/130	Normal.....	++	—	++	++	1.019
4. F. A.	Chronic nephritis.....	24	♀	36		17	115/70	Normal.....	+	—	+	+	1.031
5. S. G.*	Chronic parenchymatous nephritis	20	♀	81		5	145/110		++	—	++	++	1.020
6. J. McV.	Chronic parenchymatous nephritis	47	♂	145	0.087	0	140/80		+	4 cm.	++	++	1.012

* At necropsy the kidneys were found to be secondarily contracted.

above normal in six of the fourteen cases studied. It should be noted that nine of these fifteen patients ranged from 26 to 43 years of age, and that the prognosis was grave in most instances.

Less striking results were obtained in a series of cardiorenal cases as will be seen in Table 3. One case gave evidence of nitrogen retention while the phenolsulphonephthalein varied from 8 per cent. to 45 per cent. The blood pressure was high in three cases, as was the blood sugar.

The series of cases of chronic parenchymatous nephritis shown in Table 5 is too short to permit of definite conclusions.

III. THE RELATION OF BLOOD-SUGAR, NITROGEN RETENTION, PHENOL-SULPHONEPHTHALEIN ELIMINATION AND HIGH BLOOD PRESSURE

The question of hyperglycemia in high-pressure nephritis is of considerable theoretical interest. Since Neubauer¹² first called attention to this, several workers have confirmed his findings while a few have failed to do so. Thus the present status of blood-sugar concentration in nephritis may be regarded as one of the many points at issue and for that reason is included in these studies. The blood-sugar was determined by the micro method of Bang¹³ in which a small amount of blood is required for each test. The blood is obtained by finger puncture, which insures simplicity and the elimination of unnecessary discomfort to the patient. All food was withheld from the patient for at least six hours before the blood was withdrawn. Normal figures by this method lie between 0.06 and 0.1 per cent.

In a former publication, one of us (Hopkins¹⁴) reported on a study of the blood-sugar in twenty-eight cases of nephritis. Briefly stated, the conclusions to be drawn from that work and the cases here presented are as follows:

A slight hyperglycemia occurs in many high-pressure nephritics and frequently in those with low phenolsulphonephthalein elimination (Table 4). There is no relation between the height of the blood pressure and the degree of hyperglycemia. In most nephritics without high pressure, the blood-sugar is normal. Edema and hepatic congestion do not seem to influence the concentration of blood-sugar (Tables 3 and 4).

Of the eight cases in this series which showed a retention of over 40 mg. of nitrogen, four gave an elevation in blood-sugar. This con-

12. Neubauer: *Biochem. Ztschr.*, 1910, xxv, 284.

13. Bang, I.: *Der Blutzucker*, Wiesbaden, 1913.

14. Hopkins, A. H.: *Am. Jour. Med. Sc.*, 1915, cxlix, 254.

firms the recent work of Borchardt and Bennigson,¹⁵ who also found nitrogen retention a frequent accompaniment of hyperglycemia.

Of the eight cases in which two or three estimations of blood-sugar were made after the various periods of protein feeding, no constant changes were noted.

Alimentary hyperglycemia was pronounced in three out of four cases in which 100 gm. of glucose were fed by mouth and serial tests of blood-sugar made each half hour for several hours.

CONCLUSIONS

1. Protein feeding in nephritis has a direct influence on the retention of nitrogen in the blood. This is most pronounced in the pure chronic interstitial type with hypertension.

2. The estimation of retention by blood analysis is of definite clinical value from the point of view of therapy, and though this series is too limited to permit of definite conclusions with regard to its prognostic value, our findings so far confirm those of other workers who advocate its usefulness in this field.

3. Chronic passive congestion does not cause an increase of waste nitrogenous products in the blood.

4. In the presence of nitrogen retention, the phenolsulphonephthalein output is usually low and the blood pressure frequently high.

5. Chronic passive congestion may greatly impair the phenolsulphonephthalein output. Variation in the elimination of this dye may also be noted in different stages of nephritis, and in cases with "hyperpermeability."

6. To be of value, the nitrogen retention and phenolsulphonephthalein tests should be repeated at intervals, the value of the former being increased when combined with clinical observations of the patient, diet, etc.

7. A slight hyperglycemia occurs in many high-pressure nephritics and frequently in those with retention of nitrogen and impaired phenolsulphonephthalein elimination.

15. Borchardt, L., and Bennigson, W.: *München. Med. Wchnschr.*, October, 1913, p. 2275.