

## THE TOTAL NONPROTEIN NITROGEN CONSTITUENTS OF THE BLOOD IN ARTERIAL HYPERTENSION \*

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Arterial hypertension is regarded frequently as a manifestation of chronic nephritis. In recent years, however, there is a growing belief that hypertension alone is not necessarily evidence of nephritis. Allbutt<sup>1</sup> was among the first to recognize from clinical observations that hypertension may be present without nephritis; this condition he termed "hyperpiesis." Under the title "primary hypertensive cardiovascular disease," Janeway<sup>2</sup> described the same disorder, while more recently Mosenthal<sup>3</sup> and others have suggested the term "benign or essential hypertension." Krehl<sup>4</sup> observed hypertension in a number of patients with other clinical symptoms not supporting the diagnosis of chronic nephritis. Gross and microscopic examination of the kidneys of one of these patients failed to reveal abnormal changes.

Until renal function was estimated by the phenolsulphonephthalein test and by the quantitative determination of the nonprotein nitrogen constituents of the blood, the evidence of the kidney disease obtained was chiefly anatomical or clinical. Mosenthal observed essential hypertension in two patients with normal blood urea and phenolsulphonephthalein excretion; the postmortem examinations revealed practically normal kidneys. Rappleye<sup>5</sup> studied the kidney function in 100 patients with hypertension. Almost 70 per cent. of these had normal phenolsulphonephthalein excretion or blood urea nitrogen values. In the remainder, the renal function so determined was impaired only slightly. Thirteen of these 100 patients died, and in ten of the eleven postmortem examinations made death was found to have been due to cardiovascular disease or to an intercurrent infection.

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1. Allbutt, C.: *Diseases of the Arteries, Including Angina Pectoris*, London. Macmillan & Co. 1915; *Arteriosclerosis and the Kidneys*, Brit. M. J. **1**:854, 922, 1911.

2. Janeway, T. C.: *A Clinical Study of Hypertensive Cardiovascular Disease*, Arch. Int. Med. **12**:755 (Dec. 1913).

3. Mosenthal, H. O.: *Essential Hypertension*, Med. Clin. N. America **1**:101 (July) 1917.

4. Krehl, L.: *Deutsch. med. Wchnschr.* **3**:1872, 1905.

5. Rappleye, W. C.: *The Kidney Function in 100 Cases of Hypertension*, Boston M. & S. J. **179**:441, 1918.

The patients studied by Stengel<sup>6</sup> and designated by him as "arterio-lar fibrosis" were without functional evidence of renal disease. Many of them lived for several years and finally died from cardiovascular disease. In Meara's group<sup>7</sup> of patients with symptoms corresponding to the hyperpiesia of Allbutt, a few patients had a slight impairment of renal function, but uremia was rarely a cause of death.

Folin and Denis,<sup>8</sup> Myers, Fine and Lough,<sup>9</sup> Baumann and others<sup>10</sup> regard the estimation of the uric acid of the blood as the most delicate test for kidney efficiency. They observed many patients with "early interstitial nephritis" in whom the uric acid was the only nonprotein nitrogen substance of the blood increased. Hopkins<sup>11</sup> found that in climacteric hypertension kidney function is not materially affected.

That pure hypertension may be due to sodium chlorid retention in the blood is a conclusion reached by Allen<sup>12</sup> from observation of hypertension with clinical symptoms improved by water and salt restriction; the kidney function of these patients, except for the salt retention, was normal.

This report is primarily that of a chemical study of the nonprotein nitrogen constituents of the blood of patients with arterial hypertension but with no clinical evidence of nephritis. The results of such determinations on the blood of fifty-five patients from the medical services of Drs. J. L. Miller, J. A. Capps, A. R. Elliott and R. B. Preble at St. Luke's Hospital, Chicago, furnish the basis of this report, and the patients themselves are divided into two groups, depending on the amount of the various nonprotein nitrogen substances in the blood and the alterations of the urine. Some of these patients were examined repeatedly over a period of from one month to two years.

The blood urea nitrogen was determined by the Van Slyke and Cullen<sup>13</sup> modification of the Marshall urease method. The other non-protein nitrogen constituents of the blood were determined according

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6. Stengel, A.: The Classification of Chronic Nephritis and the Relation of Infection to Kidney Disease, *Med. Clin. N. America* **1**:217 (Sept.) 1917.

7. Meara, F. S.: Hyperpiesia of Clifford Allbutt, *Med. Clin. N. America* **2**:1 (July) 1918.

8. Folin, O., and Denis, W.: The Diagnostic Value of Uric Acid Determination in the Blood, *Arch. Int. Med.* **16**:33 (July) 1915.

9. Myers, V. C.; Fine, M. S., and Lough, W. G.: The Significance of Uric Acid, Urea and Creatinin of the Blood in Nephritis, *Arch. Int. Med.* **17**:570 (April) 1916.

10. Baumann, L.; Hansmann, G. H.; Davis, A. C., and Stevens, F. A.: The Uric Acid of the Blood as Compared with the Renal Dietary Test, *Arch. Int. Med.* **24**:70 (July) 1919.

12. Allen, F. M.: Arterial Hypertension, *J. A. M. A.* **74**:652 (March 6) 1920.

11. Hopkins, A. H.: Climacteric Hypertension, *Am. J. Med. Sc.* **157**:826, 1919.

13. Van Slyke, D. D., and Cullen, G. E.: *J. A. M. A.* **62**:1558 (May 16) 1914.

to the recent methods of Folin and Wu.<sup>14</sup> The nonprotein nitrogen substances of the blood of many patients were estimated at repeated intervals.

#### GROUP I

In this group there are included thirty-six patients with arterial hypertension and with only slight clinical evidence of nephritis. The illness in five of these was diagnosed chronic nephritis by the attending physicians, in spite of very little change in the urine. In this group there are eleven men and twenty-five women; the age average was 54.3 years. The clinical diagnosis for five patients was hypertension alone; for five others it was chronic nephritis or cardiorenal disease; for five each it was colitis and arteriosclerosis; for four, tertiary syphilis or syphilitic myocarditis; for three each, chronic cholecystitis, cardiac decompensation and angina pectoris; for two each, cystitis, gout, diabetes, chronic arthritis and chronic myocarditis; for 1 each, cirrhosis of the liver, fibromyoma uteri and abdominal adhesions. Neither albumin nor casts were found in the urine of twenty-one patients, a trace of albumin was found in three cases, a few casts only in one case, and albumin and casts in eleven cases. Repeated examinations of the urine demonstrated the presence of albumin and casts in minimal amounts for most of the patients.

The blood urea nitrogen varied from 10.1 to 29.9 and averaged 18.9 mg. per 100 c.c.; the total nonprotein nitrogen varied from 22.4 to 59.0 and averaged 37.6 mg.; the uric acid varied from 1.8 to 6.95 and averaged 3.06 mg.; and the creatinin varied from 1.29 to 2.3 and averaged 1.7 mg. Only thirteen of these patients had a blood urea nitrogen of more than 20 mg., twenty-three had a total nonprotein nitrogen of more than 35 mg. per 100 c.c. The blood uric acid of seven of twenty-three patients was more than 3 mg. per 100 c.c.; and of three of twenty-two patients the creatinin was more than 2 mg. per 100 c.c. of blood.

The blood pressure was determined frequently and with many patients it varied markedly. The maximum systolic pressure ranged from 170 to 248 mm. of mercury, the diastolic from 70 to 160 mm. The phenolsulphonephthalein test of the kidney function of twenty-nine patients (thirty determinations) ranged from 21 to 90 per cent. for the two hour period, and averaged 53.3 per cent. For twenty-one patients the excretion was less than 60 per cent.; the urea and total nonprotein nitrogen of the blood of six of these patients were moderately increased, in fifteen cases they were normal or slightly increased. Both tests gave evidence of renal impairment in six patients. For two the blood urea

14. Folin, O., and Wu, H.: A System of Blood Analysis, *J. Biol. Chem.* **38**:81, 1919.

and total nonprotein nitrogen were normal and the 'phthalein excretion was normal or increased (90 per cent. in one patient). Excluding patients with cardiac decompensation, the two tests agreed in 75 per cent. of the cases. The blood Wassermann test for syphilis was positive in two of twenty-three patients.

Dyspnea on exertion was the most common symptom, and was present in sixteen patients. In thirteen patients the symptoms were headache; in eleven dizziness and swelling of the feet and legs; in eight each, nocturia and abdominal distress; in seven each, precordial pain and cardiac palpitation; in six each, weakness and nervousness; in five each visual disturbances or spots before the eyes, flatulence and nausea; in four each, cramps in the legs, loss of weight, anorexia, and cough; in three each, hoarseness, tinnitus aurium, constipation, and polykinuria; in two each, polyuria, dysuria, incontinence, backache, vomiting and diarrhea.

Four patients had scarlet fever in childhood; four had syphilis. In one case the hypertension was ascribed to a pregnancy seven years before. One patient had had erysipelas several years previously; another had had rheumatism, and a third had had typhoid fever. Two patients were alcohol and tobacco habitués, and one patient was intemperate in eating. The average duration of the arterial hypertension as far as could be determined was 3.2 years.

Hypertrophy of the heart, the most common alteration found in the physical examination, was observed in twenty-seven patients. The liver was enlarged in thirteen. There was a secondary mitral murmur in twelve. Sclerosis of the peripheral arteries was pronounced in nine; a dilated aorta in six; edema of the feet and legs was present in seven. Five patients had hypostasis of the lungs; four a gallop rhythm; three an alternating pulse; three a palpable kidney or kidneys, and three some degree of cyanosis. Obesity and enlarged joints each were present in four cases. In three patients the teeth were badly decayed. Two patients each had generalized edema, marked emaciation, hydrothorax and a palpable colon. Ophthalmoscopic examination of the eye grounds of eight patients was negative in four, but revealed sclerosis of the retinal vessels in two, arteriovenous compression in one case, and a low grade retinitis in another.

There was no relation between the height of the blood pressure and the amount of any of the nitrogenous waste substances found in the blood. Two patients—one with the highest, the other with the lowest blood pressure—had nitrogen values that differed only slightly. The patients having dyspnea with cardiac decompensation had the highest values for nonprotein nitrogen of the blood of the group. In these patients the slight nitrogen retention could be accounted for by the

passive hyperemia of the kidneys. No relationship could be established between any of the other symptoms or physical findings and the amount of nitrogen in the blood.

Of the thirty-six patients, thirty-one are known to be living for as long as from two months to two years, and of these eighteen are improved, twelve are as before, and two are worse. The condition of three patients is unknown, and two are dead. Both died of cardiac failure, this diagnosis for one being confirmed by a postmortem examination. Among the changes observed during this examination were hypertrophy and dilatation of the heart, passive hyperemia of the liver and kidneys, and moderate sclerosis of the aorta and larger arteries. In the kidneys a few scattered hyalinized glomeruli were found, such as are present in the kidneys of any person at that age dying of a disease unrelated with arterial hypertension.

#### GROUP II

The symptoms of the disease in the patients of this group differed very little from those in Group I, but in the urine there were larger quantities of albumin and more casts, whereas the blood contained more of the nitrogenous waste products, particularly uric acid. There are nineteen patients in this group, thirteen men and six women, varying in age from 40 to 69 and averaging 58.2 years of age. The clinical diagnosis in six cases was chronic nephritis or cardiorenal disease; in two each, tertiary syphilis, angina pectoris, arteriosclerosis, diabetes and hypertension alone; and in one each, abdominal adhesions, cardiac decompensation, chronic cholecystitis and cerebral hemorrhage. The urine of four patients contained neither albumin nor casts, of three, only albumin, of one, hyalin casts, and of ten both albumin and casts. The blood urea nitrogen varied from 11.4 to 32.7 mg. and averaged 21.5 mg. per 100 c.c., the total nonprotein nitrogen from 28.1 to 56.4 and averaged 42.9 mg.; the uric acid from 2.48 to 9.02 and averaged 5.39 gm., and the creatinin from 1.49 to 2.24 and averaged 1.80 mg. The urea nitrogen of the blood of ten patients was more than 20 mg. per 100 c.c. and of thirteen the total nonprotein nitrogen was more than 35 mg. The uric acid of the blood of twelve patients in this group was more than 3 mg. per 100 c.c., and the creatinin content for four of ten patients was more than 2 mg. per 100 c.c. As has been stated in Group I, the higher values for nitrogen retention are associated with the symptoms of cardiac insufficiency, dyspnea, edema of the feet and legs, nocturia and precordial pain.

The systolic blood pressure ranged from 160 to 268 mm.; the diastolic from 72 to 160. The phenolsulphonephthalein excretion in two hours for fifteen patients varied from 30 to 74.3 per cent. and

averaged 47.2 per cent. Nocturia was the most common symptom observed in nine cases, headache and dyspnea each in six; cough, dizziness, and abdominal distress each in four; blurred vision, polyuria, weakness, nervousness, nausea and vomiting each in three; tinnitus, cardiac palpitation, polykinuria, backache, insomnia, precordial pain, and loss of weight each in two. One patient (Wassermann negative) reported a previous syphilitic infection, another reported an attack of scarlet fever in his youth, and a third excessive alcoholism.

Hypertrophy of the heart as in the patients of the first group was common (fifteen of the nineteen patients); in eight cases the liver was enlarged; in five there was a regurgitant mitral systolic murmur; in four, pulmonary hypostasis and sclerosis of the peripheral arteries; in three each, a gallop rhythm, cyanosis and marked edema of the extremities; in two each, an alternating pulse, hydrothorax, a dilated aorta and a regurgitant aortic murmur; and in one each, marked ascites and hypertrophy of the prostate gland.

Twelve of the nineteen patients in Group 2 are living for from two to twenty months; five are dead, and the condition of two is unknown. Five of the living are improved, and the clinical symptoms of seven are unchanged. The cause of death of two patients was cerebral hemorrhage. One patient died of angina pectoris, one of diabetic coma, and one of cardiac decompensation. The last mentioned clinical diagnosis was confirmed by postmortem examination, and the chief anatomic changes noted were hypertrophy and dilation of the heart, senile sclerosis and fatty changes of the lining of the aorta and larger arteries, and marked passive hyperemia and healed infarcts of the kidneys. Microscopic examination of the kidney tissue disclosed no striking changes.

#### DISCUSSION

On comparing the averages of the various nonprotein nitrogen constituents of the blood in the two groups, the urea and nonprotein nitrogen are each a few milligrams higher in Group 2 than in Group 1. The uric acid averages of Group 2 are almost double those of Group 1, 5.39 mg. as compared with 3.03. The creatinin is almost the same in both groups.

The uric acid of the blood was increased in 54 per cent. of the patients of both groups; the total nonprotein nitrogen was slightly increased in 65 per cent.; and the urea was slightly increased in 42 per cent.

The phenolsulphonephthalein excretion for two hours was slightly more for the patients in Group 1 than for those in Group 2. The average phenolsulphonephthalein excretion of both groups is a trifle lower than the minimum normal value for two hours, but included in

the averages are some patients with cardiac decompensation and it is well known that this materially diminishes the amount of dye excreted. The extreme passive hyperemia of the kidneys in such patients may explain the slight increase of the non-protein nitrogen substances in the blood where anatomically there is no nephritis.

Of the prominent symptoms of the two groups, dyspnea is most common in Group 1, while nocturnal polyuria occurred twice as frequently in Group 2 as in Group 1. Edema of the feet and legs was present in 31 per cent. of the patients of Group 1, and in 16 per cent. of those in Group 2. Polyuria troubled 16 per cent. of the patients in Group 2, but only 6 per cent. in Group 1. Precordial pain and palpitation occurred almost twice as frequently in Group 1 as in Group 2. The other common symptoms, headache, dizziness, abdominal distress, nervousness, visual disturbances, nausea and vomiting were of almost the same frequency in both groups.

The changes in the urine differ slightly in that the patients of Group 2 had more evidence of renal impairment as shown by the presence of albumin and casts in the urine. Four patients of this group, however, had no albuminuria or cylindruria.

In Group 1, there is a large majority of women while in Group 2 the men largely predominate. The ages in Group 2 average slightly more than those in Group 1. In Group 2 a higher percentage of patients was diagnosed clinically as chronic nephritis, but other than this there is no striking disparity in the diagnoses.

#### CONCLUSIONS

1. There is a disease, arterial hypertension, which when uncomplicated by nephritis or cardiac decompensation gives no functional evidence of kidney insufficiency.
2. Cardiac decompensation with marked passive hyperemia of the kidneys is associated with a moderate retention of nonprotein nitrogen in the blood.
3. The height of the blood pressure bears no relationship to the amount of the nonprotein nitrogen substances in the blood.
4. Arterial hypertension with normal nonprotein nitrogen values in the blood and normal kidney excretion, determined by functional tests and urine examinations, does not justify the clinical diagnosis of chronic nephritis.

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