equilibrium is maintained; and in chronic cases, with moderately elevated nonprotein nitrogen persisting for months at the same level, another interpretation seems hardly possible. This type of case deserves a special interest from the dietetic standpoint; if there is no response of the nonprotein nitrogen on a decreased protein intake, the value of a very restricted diet seems questionable.

This brings up the question of the influence of the diet on the level of the nonprotein nitrogen in normal persons. Contrary to a fairly common statement of its independence of the diet, I feel that it is important to point out that a high protein intake—a common finding in wealthy patients—in a person who, clinically, may be considered normal, may give a nonprotein nitrogen content as high as from 40 to 45 mg. in the whole blood and from about 30 to 35 mg. in the plasma; that is, about 75 per cent. higher than the figures from the same individual after a few days of a low protein diet. The point of practical importance to be emphasized is that the change from a high to a low level does not immediately follow the change in the diet. If the lowest possible nonprotein nitrogen figure is wanted in a person on the boundary of the abnormal, it is, therefore, not sufficient merely to have him drop in any morning before breakfast to have his blood tested.

The usefulness of the nonprotein nitrogen determinations, or of the determination of one or another of its constituents for a differential diagnosis between different forms of chronic interstitial nephritis, is a favorite subject of discussion. In general, it has not proved at all possible as yet to apply the physiologic or pharmacologic theories as to kidney function on the functional disturbances of the different anatomic types of kidney lesions. Further, the considerable interest given to a physiologic differentiation between glomerular and tubular activity cannot be further cultivated in the clinic, since we have to admit the fact, especially emphasized by Löhlein, that a disturbance of the glomerular function, due to anatomic lesions, is necessarily followed by a functional disturbance of the tubular activity, as a consequence of the anatomic unity of the blood supply.

Furthermore, there is reason enough to doubt whether a functional disturbance is always accompanied by any appreciable anatomic lesion at all. In the earlier discussion of the character of nonprotein nitrogen retention, attention was called to the difference between the type mainly discussed in this paper, with a fairly uniform retention of the different waste products, and the types of nonprotein nitrogen accumulation in acute yellow atrophy of the liver and in gout. Certainly, the waste product retention cannot be satisfactorily interpreted in any other way than as a result of a deficient kidney activity. The validity of this interpretation is, therefore, independent not only of the simultaneous occurrence of anatomic lesions but even of the occurrence of other clinical signs of kidney disease. Therefore, when reliable observations are reported of a slight elevation of the amount of waste products in the blood in cases of a decompensated heart, or when moderate or even high figures for the blood urea nitrogen are reported in such different types of disease as epidemic (lethargic) encephalitis (Umbert)¹⁴ and acute intestinal obstruction (Louria),¹⁵ this does not diminish the clinical value of the determination of

the nitrogenous waste products of the blood. On the contrary, the knowledge so gained means an objective, reliable information about kidney function, independent of the presence or absence of other clinical symptoms.

PRESENT STATUS OF BLOOD NITROGEN IN SURGICAL LESIONS OF THE KIDNEY*

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Since Folin and Denis,¹ in 1913, initiated methods for the rapid determination of the nonprotein blood nitrogen, a great mass of work has been done, especially in chronic nephritis, and its value has been demonstrated repeatedly. It has been shown that uric acid in the blood is retained in some cases very early, but not constantly so; that urea is retained at a later stage in the course of nephritis, and that creatinin is retained shortly before death in the great majority of cases.

Before entering further into the discussion of nitrogen retentions, it is well to state our findings as to normal levels. Two years ago, we placed four of the hospital staff on high protein diets. These diets were prepared in the diet kitchen on the metabolic unit. The blood nonprotein nitrogen of these young men before they were given a high protein diet was from 28 to 38 mg. per hundred cubic centimeters. After three days of high protein diet (protein from 150 to

TABLE 1.—CASES SHOWING A NONPROTEIN NITROGEN OF 50 MG. OR MORE PER HUNDRED CUBIC CENTIMETERS OF BLOOD

Condition	Nonprotein Nitrogen *		Results While in Hospital †	
	Became Normal; Number of Patients	Unchanged or Increased; Number of Patients	Died; Number of Patients	Improved; Number of Patients
Chronic nephritis, twenty-six cases.....	2 (9%)	20 (88%)	15 (63%)	8 (30%)
Myocarditis, fifteen cases..	4 (50%)	4 (50%)	9 (60%)	6 (40%)
Enlargement of prostate, twenty cases.....	6 (43%)	8 (58%)	7 (44%)	10 (59%)
Pyelonephritis and pyelonephrosis, ten cases.....	5 (50%)	4	5 (50%)	5 (50%)
Total, seventy one cases...	17	36	36	29

* Only cases having more than one determination are included in percentages.

† Only cases treated included.

‡ Three cases were carcinoma of prostate. Two cases showed a rise as result of operation.

§ Three cases were due to obstruction by carcinoma.

175 gm.) the fasting (before breakfast) blood nitrogen rose in all cases about 5 mg., the highest found being 45 and the lowest 33.²

Folin,³ in his last paper, reported a case of high protein feeding whose fasting nitrogen was 43 mg. The normal level on the average diet is from 25 to 38 mg. per hundred cubic centimeters of blood. Certainly, the blood nonprotein nitrogen must be above 40 mg. per hundred cubic centimeters before retention can be said to be present.

There is considerable difference in the interpretation of the retention of blood nitrogen in the different

* Read before the Section on Urology at the Seventy-Third Annual Session of the American Medical Association, St. Louis, May, 1922.

1. Folin and Denis: *J. Biol. Chem.* 14: 29, 1913.

2. This work was done by Dr. A. E. W. Ochsner.

3. Folin, O., and Berglund, H.: *J. Biol. Chem.* 51: 395 (April) 1922.

14. Umbert, F.: *Deutsch. med. Wchnschr.* 47: 261 (March 10) 1921.
15. Louria, H. W.: *Blood Urea Nitrogen in Acute Intestinal Obstruction*, *Arch. Int. Med.* 27: 620 (May) 1921.

classes of kidney disease. In chronic nephritis, such as is seen in the medical wards of any hospital, there has been a gradual destruction of kidney tissue, analogous, from the functional standpoint, to the experimental surgical removal of kidney tissue; while, in the infectious and obstructive processes of the genito-urinary tract seen by urologists, the loss of kidney function may be, in a large measure, of a functional nature. After drainage and removal of the obstruc-

TABLE 2.—CASES IN WHICH NONPROTEIN NITROGEN BECAME NORMAL FROM A LEVEL OF 50 MG. OR MORE OF NITROGEN PER HUNDRED CUBIC CENTIMETERS OF BLOOD

Case and Diagnosis	Highest Nonprotein Nitrogen, Mg.	Time to Become Normal, Days	Outcome
1. Pyelonephritis.....	156	30	Well after two years
2. Congenital kidney disease and hydronephrosis.....	67	7	Nephrectomy
3. Enlargement of prostate.....	58	3	Punch operation
4. Congenital kidney; hydronephrosis.....	74	14	Nephrectomy
5. Pyelonephritis; pyelonephrosis.....	58	3	No operation
6. Enlargement of prostate.....	58	3	Prostatectomy
7. Enlargement of prostate.....	118	7	Not operated on
8. Enlargement of prostate.....	72	30	Prostatectomy
9. Enlargement of prostate.....	92	6	Following prostatectomy
10. Carcinoma of rectum; pyelonephrosis.....	63	12	Operation for carcinoma
11. Enlargement of prostate.....	60	30	Prostatectomy
12. Carcinoma of prostate	59	4	Prostatectomy

tions, the functional loss may be partially regained. If these latter conditions have gone on long enough, permanent loss of kidney function results, just as in the case of chronic nephritis.

The chemical laboratory of Barnes Hospital, in the course of a year, performs more than 800 determinations of the nonprotein nitrogen. Of patients on whom these determinations were made in the past two years, there were 100 who showed values above 50 mg. per hundred cubic centimeters of blood. The value 50 mg. per hundred cubic centimeters was selected because it shows definitely developed retention of urea. Table 1 presents the difference between the course of cases while in the hospital as regards the nonprotein nitrogen, as well as the clinical outcome.

The cases of chronic nephritis were not materially improved, as shown by the failure of the nonprotein nitrogen to go down after having reached this level, and by the high death rate. Cardiac patients show a decided difference from nephritic. With them, recovery from retention of nitrogen depends entirely on how well the heart will respond to treatment. Still better are the results of kidney disease due to obstructive and infectious processes. Table 1 presents the fact already well appreciated by the urologist. To those interested in the functional ability of the kidney, it shows that obstructive and infectious processes do not injure the kidney cell to the extent that it will not regain some of its function. Johnson's⁴ experimental work on this point showed that, with complete obstruction of the ureter and subsequent removal of ligation, function can be regained even after two weeks of complete obstruction. He demonstrated that it required 150 days for complete restoration of function in a kidney whose ureter has been ligated two weeks. These results agree with clinical observations. An important

point to the urologist is the length of time required to reduce retention cases.

Analyses of these cases, reported in Table 2, show that if the blood nitrogen does not reach normal level within a month of hospital treatment, it will never do so.

Not only can infectious processes depress kidney function when these processes involve both kidneys, but also, with only one kidney diseased, systemic intoxication may result, so that the function of the opposite kidney, and not the main site of disease, is seriously affected. That systemic intoxications can severely depress kidney function has been most strikingly demonstrated experimentally by Whipple⁵ and his co-workers. These observers, while investigating intestinal obstruction, found that there was a great increase in nitrogenous catabolism, as shown by the excretion of nitrogen in animals with experimental obstruction. The blood of these animals showed an increase in nonprotein nitrogen and urea and a small increase in amino-acid and polypeptid nitrogen.

They further showed that the accumulation of nitrogenous products in the blood was accompanied by a definite loss of kidney function, as shown by the rate of urea excretion and by the excretion of phenol-sulphonaphthalein; also that the intoxication as observed in the animals paralleled the loss of kidney function. They further found that this loss of function was temporary and that rapid recovery followed the removal of the obstruction. But, most interesting of all, they found that on sectioning these kidneys there was, by all the staining methods at their command, no apparent lesion of the kidney cells.

They found the same results as far as urinary nitrogen was concerned in sterile abscesses and in experimental peritonitis and pleuritis. The same effect on kidney function was also noted when the proteose obtained from obstructed intestinal loops was injected into animals.

Whipple's work suggests the possibility that, in the case of unilateral disease of the kidney causing systemic intoxication, it would be possible so to injure

TABLE 3.—FINDINGS IN CASE 1

Date	Phenol-sulphonaphthalein in Two Hours per Cent.	Nonprotein Nitrogen per 100 C.c., Mg.	Clinical Notes
November 3.....	..	41	Temperature, 100 F.
November 11.....	50	74	Chills; white blood cells, 9,000; temperature, 103 F.
November 25.....	50	36	Temperature, 100 F.
Nephrectomy, left:			
December 5.....	65	35	

temporarily the good kidney that much increased loss of renal function might result. That such cases do occur can be clearly shown by the following case histories.

REPORT OF CASES

CASE 1.—S., a white man, aged 40, complained of pain in the left flank, radiating down the leg, with tenderness and muscle spasm in the left lower quadrant, where a mass was felt. Cystoscopic examination and pyelogram revealed an ectopic kidney lying behind the bladder, with a considerable degree of hydronephrosis, the ureter being kinked on itself. The urine showed blood and pus.

5. Whipple, G. H., and Van Slyke, D. D.: *J. Exper. Med.* **28**: 213 (Aug.) 1918. Cooke, J. V., and Whipple, G. H.: *Ibid.* **28**: 223, 243 (Aug.) 1918. McQuarrie, I., and Whipple, G. H.: *J. Exper. Med.* **29**: 397 (April) 1919.

4. Johnson, R. A.: *J. Exper. Med.* **28**: 193 (Aug.) 1918.

Congenital kidney disease left (ectopic kidney), hydro-nephrosis, left, and pyonephrosis, left, were diagnosed. Experimental findings and clinical notes are presented in Table 3.

CASE 2.—S., a colored boy, age 8 years, who had undergone appendectomy one year previously, was referred, December 13, because of pyelitis. There were resistance and tenderness in the right kidney region, but no mass. Muscle spasm was present, especially on the right side. The third day in hospital, he suffered a chill, following which he ran a septic temperature for nine days. Abdominal rigidity increased. Nephrostomy was performed, December 18, purulent urine being drained off; a congenital kidney condition was found. Nephrectomy was performed, January 5, with uneventful recovery.

Congenital kidney, right, hydronephrosis, right, and pyelonephritis, right, were diagnosed. Findings and clinical notes are presented in Table 4.

TABLE 4.—FINDINGS IN CASE 2

Date	Phenol-sulphone-phthalein in Two Hours per Cent.	Nonprotein Nitrogen per 100 C.c., Mg.	Clinical Notes
December 14.....	40	..	Abdominal spasm
December 16.....	..	67	Chill; temperature, 102 F.; white blood cells, 16,000
December 17.....	55	..	
December 18.....	Nephrostomy, right	32	
December 23.....	..	82	Temperature normal
January 3.....	45	33	
January 5.....	Nephrectomy, right	..	
January 24.....	55	..	

CASE 3.—S., a white woman, aged 23, an American, had chills and fever, with pain in the right side of the abdomen. The right kidney was tender and enlarged, and there was marked abdominal spasm. The left pole was not so tender. Soreness had been felt in right side for many years. Acute onset occurred five days previously. The temperature was 102 F; pulse, 128; white blood cells, 13,000, later, 23,000. There was pus from both kidneys in large amounts. The right ureter was blocked; cystitis was marked. The patient was treated with forced fluids and hexamethylenamin. There was no surgical treatment.

Pyelonephritis, right and left, nephroptosis, right, and pyelonephritis, right, were diagnosed. The findings and clinical notes are presented in Table 5.

TABLE 5.—FINDINGS IN CASE 3

Date	Phenol-sulphone-phthalein in Two Hours per Cent.	Nonprotein Nitrogen per 100 C.c., Mg.	Clinical Notes
February 3	19	100	Abdominal spasm; temperature, 102 F.; white blood cells, 23,000
February 7	25	116	Temperature normal
February 16	..	59	
March 2	13	..	Patient up
May	..	30	

Cases 1 and 2 show that infection in one kidney, with such insufficient drainage as to cause severe systemic manifestations, will depress the function of the opposite kidney to the extent of causing urea retention. These clinical observations are quite analogous to Whipple's experimental work.

Case 3 shows bilateral infection of a much more severe type, but with partial improvement in function following drainage and subsidence of systemic symptoms. It is possible, in infection of one kidney without obstruction, to impair the function of the other; but such situations are not usual. The most important value of the nonprotein nitrogen is the help it gives in estimating the extent of disease. This is especially important to the surgeon.

Pearce,⁶ in 1908, showed that dogs could be kept in nitrogen balance when one half, and in some instances three fourths, of the total kidney substance had been removed. His work, unfortunately, was done before the present tests for kidney function were in use.

Rowntree and Geraghty,⁷ in their report on the use of phenolsulphonephthalein in functional tests, demonstrated that removal of one kidney did not materially affect the excretion of the dye, even as early as twenty-four hours after operation, and, in surgical cases, they demonstrated that, three weeks after nephrectomy, the kidney function as shown by this test was normal. We have found that there is a fairly constant relation between phenolsulphonephthalein in excretion and blood nitrogen. Cases of nitrogen retention which showed a normal phenolsulphonephthalein excretion have not been observed. In fact, it is extremely rare to see nitrogen retention unless the phenolsulphonephthalein excretion is 40 per cent. or less in two hours. This holds good in any type of low kidney function.

Reid,⁸ in 1918, showed that one kidney might be destroyed by experimental hydronephrosis without any increase of nonprotein in nitrogen in the blood.

Addis⁹ and his co-workers have done very extensive work on the excretion of urea and the factors that control it, and have shown that, from the standpoint of urea and of the ability of the kidney to excrete urea, the kidney substance can take care of seven times the amount of urea ordinarily excreted. In other words, they find, by the process of overburdening the kidney with injected urea, that there is sevenfold the capacity for the excretion of this product that is ordinarily needed. Presumably, then, only one seventh of the kidney substance is ordinarily used.

Certainly more than 50 per cent. of kidney function must be lost before the phenolsulphonephthalein elimination is decreased, and probably more than 60 per cent. before nonprotein nitrogen is increased. If this is true, the retention of urea always means bilateral disease, whether anatomic or functional. In 250 surgical cases involving the kidney in the past two years, we have never seen retention of nitrogen without bilateral disease.

SUMMARY

The interpretation of the retention of urea depends on the nature of the disease present, and especially on the presence of systemic intoxication.

With retention of urea, bilateral disease is always present, whether anatomic or functional or both.

Wall Building—University Club Building.

6. Pearce, R. M.: J. Exper. Med. 10: 632, 1908.

7. Rowntree, L. G., and Geraghty, J. T.: The Phthalein Test, Arch. Int. Med. 9: 284 (March) 1912.

8. Reid, M. R.: Bull. Johns Hopkins Hosp. 29: 55 (March) 1918.

9. Addis, T.; Shevky, A. E., and Bevier, J.: Am. J. Physiol. 46: 11 (April) 1918.

Smallpox in 1922.—Reports from twenty-four American states and 190 cities show that the smallpox prevailing during the first six months of 1922 is far more virulent than the type of disease which prevailed during the same period of 1921. The number of cases was 72 per cent. less this years in twenty-four states combined, and 74 per cent. less in 190 American cities. In these cities, however, the number of deaths during the first six months of 1922 was nearly four times the number reported in the same period of 1921. . . . No American city can be assured of safety in view of the record this year in cities which prior to 1922 had not had experience with the virulent type of the disease.—Statistical Bulletin, Metropolitan Life Insurance Co., August, 1922.