

THE ANEMIA OF CHRONIC NEPHRITIS *

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Anemia is commonly observed in nephritis. It may be so severe that the question arises as to whether the anemia is the primary disease.

Various causes of the anemia of nephritis have been suggested, but comprehensive or conclusive studies have not been made. Grawitz ¹ maintains that decrease in the blood elements does not take place if cardiac efficiency is maintained. He recognizes two groups of cases of chronic nephritis: (1) those with efficient cardiac function and adequate peripheral circulation, and (2) those with deficient cardiac function and circulatory stasis. In this latter group, either dilution or concentration of the blood plasma takes place. If the plasma is diluted a relative or dilution anemia occurs. Hamelin ² has noted the association of anemia and uremia. He emphasizes the importance of hydremia and of hemotoxic substances in the blood as possible etiologic factors. Ceconi ³ did not find decrease in resistance of the erythrocytes in nephritis. He concludes that the anemia of chronic nephritis is due to the inhibiting effects of urinary poisons on hematopoiesis. He also observed that the fragility of the erythrocytes bears no specific relationship to the toxicity of the blood serum in nephritis. Da Costa ⁴ recorded the occurrence of a moderate decrease of hemoglobin and erythrocytes in chronic parenchymatous nephritis, and says, that, exceptionally, this may become extreme. He believes that the anemia, loss of albumin through the kidneys, and diseases in other organs are related. Grignani ⁵ believes that some substance which is toxic to the bone marrow is produced and that defective diet and hydremia play some part in the condition.

The material used in this study consists of 187 cases diagnosed chronic glomerular nephritis ⁶ at the Mayo Clinic from July 1, 1919, to Aug. 1, 1921, and other pathologic cases selected at random. Cases of chronic nephritis complicated by diseases in the kidney or other

* From the Section on Clinical Investigation, Division of Medicine, Mayo Clinic.

1. Grawitz, E.: *Klinische Pathologie des Blutes*, Leipzig, Thieme, **4**:1011, 1911.

2. Hamelin, A.: *Contribution à l'étude de l'anémie urémique*. Paris, 1904.

3. Ceconi, A.: *Le Resistenze Globulari Nella Nefrite*, *Clin. Med. ital.* **44**:15, 1905.

4. DaCosta, J. C.: *Clinical Hematology*, Philadelphia, Blakiston's, 1920, p. 474.

5. Grignani, R.: *Il Ricambio Emoglobinico Nei Nefritici. Contributo Allo Studio della Pathogenesi dell 'Anemia dei Nefritici*, *Arch. di path. e clin. med.* **1**:48, 1921.

6. Volhard and Fahr classification.

organs, such as pyelonephritis, hydronephrosis, tuberculosis, malignancy, and so forth, and all cases of hemorrhage were excluded. One hundred and five cases of the 187 showed anemia, which might correctly be designated as the anemia of chronic nephritis; and eighty-two were without anemia.⁷

ETIOLOGY

Etiologically three types of anemia are recognized: (1) anemia secondary to acute or chronic loss of blood, (2) anemia secondary to excessive hemolysis, and (3) anemia secondary to faulty or deficient hematopoiesis.

Hemorrhage.—Probably hemorrhage may play some part in the cause of the anemia of acute nephritis, but in the group of cases herein designated as anemia of chronic nephritis all cases exhibiting macroscopic loss of blood were excluded. Long continued microscopic loss of blood in the urine and stools was investigated in order to ascertain its importance. The blood in the urine is indicated on a basis of 1, 2, 3 and 4. If the amount of blood in the urine is designated as Grade 4, blood is present macroscopically and the case is, therefore, excluded from this study.

Experiments to show the approximate amount of blood present in the urine daily in cases of chronic blood loss indicate that approximately from 0.5 to 1.5 c.c. of blood for each liter of urine is lost, an amount probably insufficient to produce anemia. Examinations of stools were made daily for occult blood and all cases showing macroscopic blood were excluded. The incidence of positive tests for occult blood was so small as to be negligible. Table 1 shows the average amount of blood in the urine in eighty-nine cases of anemia of nephritis, selected at random from the 105.⁸ In thirty-four cases (38 per cent.) the urine did not contain blood cells. It will be seen that no relationship exists between the microscopic amounts of blood in the urine and the anemia.

Excessive Hemolysis.—A hemolytic basis of the anemia deserves special consideration. The common occurrence of vascular injury, and the hemorrhagic tendency in many cases of chronic nephritis suggests that hemolysis may play some part in this connection as may changes

7. In this classification patients were designated anemic whose hemoglobin values were below 70 per cent. on the Dare instrument and with erythrocyte counts less than 4,000,000. The values with the Dare instrument approximate those obtained with the Haldane-Palmer Method when the values are 70 per cent. or lower (Fig. 1); the curves for each are practically parallel to this point. Because the earlier estimations of hemoglobin were made with a Dare instrument, the subsequent estimations were made on this instrument for purposes of comparison.

8. These calculations do not take into consideration the red blood cells destroyed by hemolysis.

in the coagulative substances of the blood. Leopold,⁹ McKee,¹⁰ and Ponder¹¹ have investigated the presence of hemolytic substances in the urine of human beings and have proved their existence in health and in various diseases. This hemolytic action is not due to osmosis but probably to bile acids, as Ponder has pointed out. (Leopold induced uranium nephritis in animals and found hemolytic substances in the urine. Our results correspond closely to those of Leopold).

In order to ascertain the presence of hemolytic substances in the urine, eighty-two patients, selected at random, coming for examination during 1921, were divided into three groups: Group 1, fifty-two normal and nonnephritic patients. Group 2, eighteen patients with chronic nephritis without anemia, and Group 3, twelve patients with chronic nephritis and anemia. The following method was employed:

The erythrocytes washed with physiologic solution of sodium chlorid three times were suspended in this solution (1:100). Six tubes were set up containing erythrocyte suspension and freshly voided urine

TABLE 1.—BLOOD IN THE URINE IN EIGHTY-NINE CASES OF ANEMIA OF NEPHRITIS

Cases	Blood in Urine, Grade	Hemoglobin, Average per Cent.	Erythrocytes, Average Count, Millions
34.....	0	59.0	3.01
39.....	1	54.7	3.31
12.....	2	58.0	3.65
4.....	3	57.0	2.95

in the following proportion: Tube 1, 1:100 erythrocyte suspension, 1 c.c., and urine, 0; Tube 2, suspension, 1 c.c., and urine, 1 c.c.; Tube 3, suspension, 1 c.c. and urine, 0.75 c.c.; Tube 4, suspension, 1 c.c., and urine, 0.5 c.c.; Tube 5, suspension, 1 c.c. and urine, 0.25 c.c.; Tube 6, suspension, 1 c.c. and urine, 0.1 c.c.

After incubation for three hours at 37 C, the tube showing complete hemolysis indicated roughly the amount of hemolytic substance in the urine.

The results in Group 1 were positive 25.5 per cent. and negative 74.5 per cent; in Group 2, positive 65 per cent. and negative 35 per cent; in Group 3, positive 34 per cent, and negative 66 per cent. Specimens of urine of patients with chronic nephritis (Group 3) were examined from day to day, during the development of the anemia. Hemolysins did not increase in the urine. These experiments indicate that hemolytic

9. Leopold, E. J.: Ueber die Hämolyse bei Nephritis, *Ztschr. f. klin. Med.* **60**:480, 1906.

10. McKee, C. S.: On the Hemolytic Action of the Urine in Certain Conditions, *Brit. M. J.* **2**:596, 1915.

11. Ponder, E.: The Presence of Hemolytic Substances in Human Urine, *Brit. J. Exper. Path.* **2**:34, 1921.

substances are present in the urine in normal and in pathologic conditions, and that in the cases of chronic nephritis without anemia they are present in greater amounts than in chronic nephritis with anemia. The findings in anemia of nephritis and in normal conditions lead to the conclusion that these substances in the urine do not have a bearing on the production or maintenance of the anemia of chronic nephritis.

Hemolytic substances are rarely present in the blood serum of chronic nephritis. Grafe and Graham,¹² reported a case of chronic nephritis in which the blood serum intermittently showed hemolytic substances. Many attempts have been made to demonstrate the presence of hemolytic substances in the blood serum in hemolytic anemia, but without success. Noguchi¹³ showed that normal serum has anti-hemolytic properties toward sodium oleate. Much and Holzmann,¹⁴ studying the action of the fresh serum of human beings on the hemolysin of cobra venom, proved that the serum of patients with certain mental diseases had a marked antihemolytic action. Clark and Evans,¹⁵ using sodium oleate as a hemolytic agent and guinea-pig corpuscles, have demonstrated a definite decrease in the protective property of serums of patients with pernicious anemia. In other cases, both normal and pathologic, there was a remarkable constancy in the protective power of the serum. In order to ascertain the status of serum of patients with nephritis and anemia with regard to hemolysis, the following technic was used:

Distilled water (from Pyrex glass flasks) was the hemolytic agent. Racks with a double row of sixteen small Wassermann tubes were set up similar to the technic of Giffin and Sanford.¹⁶ In the first tube in each row at the left was put 0.92 c.c. of 5 per cent. salt solution, in the second tube, 0.88 c.c., and so on, each tube containing 0.4 c.c. less of the salt solution than the tube to the left. In the first tube was placed 0.08 c.c. of redistilled water; in the second tube 0.12 c.c., and so on, each tube containing 0.04 c.c. more of redistilled water than the tube to the left. The final dilutions were: Tube 1, 0.46 per cent. of salt. Tube 2, 0.44 per cent.; Tube 3, 0.42 per cent., and Tube 16, 0.16 per cent. The total volume in each tube was 1 c.c. Volumetric pipets were used in all measurements. The salt solution was made up with extreme care every

12. Grafe, E., and Graham, A. L.: Untersuchungen über Isolyse, München. med. Wchnschr. **58**:2257, 1911.

13. Noguchi, H.: Ueber gewisse chemische Komplementsubstanzen, Biochem. Ztschr. **6**:327, 1917.

14. Much, H., and Holzmann, W.: Eine Reaktion im Blute von Geisteskranken, München. med. Wchnschr. **56**:1001, 1909.

15. Clark, H. M., and Evans, F. A.: One Factor in the Mechanism of Hemolysis in Hemolytic Anemia, Bull. Johns Hopkins Hosp. **31**:354, 1920.

16. Giffin, H. Z., and Sanford, A. H.: Clinical Observations Concerning the Fragility of Erythrocytes, J. Lab. & Clin. M. **4**:465, 1919.

six days and checked against the discarded solution. Pipets did not come in contact with the stock salt solution; enough for the day's needs was taken out of the bottle each day.

Blood was obtained by venipuncture; 2 c.c. was placed in a test tube containing 2 mg. potassium oxalate and 4 c.c. in a centrifuge tube was allowed to clot and then centrifuged for fifteen minutes. One-tenth of a cubic centimeter of the fresh serum thus obtained was placed in each tube of the second row and the tubes were shaken gently; 0.02 c.c. of oxalated blood¹⁷ was added to each tube; the tubes were again shaken gently and allowed to stand two hours at room temperature.

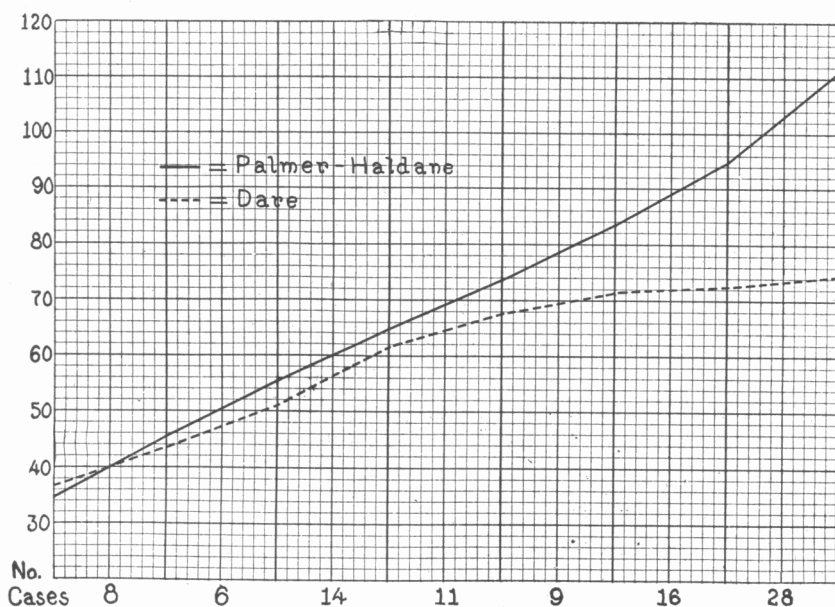


Fig. 1.—Comparative hemoglobin values obtained with the Haldane-Palmer method and the Dare hemoglobinometer.

The readings of beginning and complete hemolysis in the tubes of the first row indicate the fragility range of the red blood cells to hypotonic salt solution. In the tubes showing beginning hemolysis, the supernatant fluid shows a faint trace of the dissolved hemoglobin. Complete hemolysis is indicated by the absence of red blood cells in the bottom of the tube and the clear red transparent solution. The tubes showing beginning and complete hemolysis are compared in first and second rows. The difference in the per cent. of hypotonic salt solution

17. If the erythrocyte count was 4,000,000 or more, the amount of oxalated blood used was 0.02 c.c.; if from 2,000,000 to 4,000,000, 0.03 c.c., and if under 2,000,000, 0.04 c.c.

necessary to cause beginning and complete hemolysis indicates the degree of antihemolytic property of the serum examined. In Table 2 and in Figure 2 will be seen the average protection afforded by the blood serum in five types of cases: normal, pathologic condition other than nephritis without anemia, secondary anemia, anemia of chronic nephritis, and chronic nephritis without anemia.

A comparison of the five groups demonstrates that the serum exerts definite protection against hemolysis by hypotonic salt solution for red

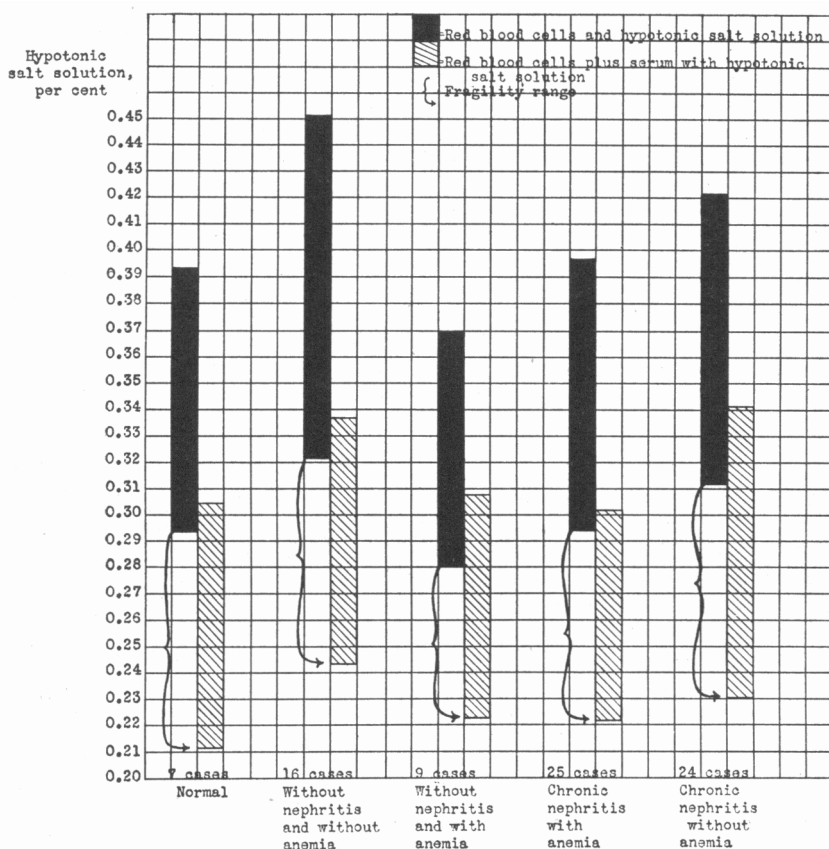


Fig. 2.—The average protection afforded by the blood serum against hemolysis by hypotonic salt solution in five types of cases.

blood cells. This property of serum seems to be fairly constant, except for the anemias of the hemolytic type as has been shown by Clark and Evans. In the anemia of chronic nephritis serum does not show definite decrease in antihemolytic power. In two cases of uremia, a few days before death, the serum exhibited marked antihemolytic properties which increased until death. In cases of chronic nephritis in which the

blood serum was tested daily change was not noticed during the development of anemia.

The results of this study would indicate that the anemia of chronic nephritis is not concerned with lack of protective power of the serum. Studies of the nature of this protective property of serum would indicate that the action depended on the colloidal property of the serum. Conditions which upset or disturbed the colloidal mechanism also produced changes in this protective action; heating, freezing, and shaking of the serum produced diminution of this action. After dialysis of the serum the dialysate and the residue both showed loss of this property. The dialysate and the residue were evaporated to their original volume to maintain the original salt concentration. The membrane did not show protective action. These findings also correspond to the conclusions reached by Clark and Evans.

It has been shown by Eppinger¹⁸ that excessive hemolysis usually occurs when the bile contains abnormally large amounts of urobilin and

TABLE 2.—ANTIHEMOLYTIC PROPERTY OF SERUM

Type	Cases	Average Protection Against Hemolysis, per Cent Less Salt
Normal.....	7	0.083
Without nephritis and anemia.....	16	0.077
Without nephritis but with anemia *.....	9	0.058
Chronic nephritis with anemia.....	25	0.07
Chronic nephritis without anemia.....	24	0.08

* Three cases of primary anemia are included.

urobilinogen. Quantitative examination of the duodenal contents, as utilized by Schneider¹⁹ in the hemolytic anemias, shows large amounts of urobilin and urobilinogen. Giffin, Sanford, and Szlapka²⁰ have shown that average values for urobilin and urobilinogen in hemolytic jaundice are 2,050 and 1,100 units, respectively. In cases of pernicious anemia the average value for urobilin was 1856.5 and for urobilinogen 1604.5 units. Table 3 gives average values obtained in cases of anemia of nephritis 600 units of urobilin and absence of urobilinogen in all cases except one. These findings correspond to those ordinarily found in secondary anemia.

18. Eppinger, H.: Zur Pathologie der Milzfunktion, Berl. klin. Wchnschr. **1**:1509-1572-2409, 1913.

19. Schneider, J. P.: The Hematopoietic-Hemolytic Index: a Proposed Determination Helpful in the Differential Diagnosis of Types of Pernicious Anemia Amenable to Cure by Splenectomy, Jour.-Lancet **37**:105, 1917; Further Quantitative Study of the Duodenal Blood Derived Pigments, Arch. Int. Med. **19**:156 (Feb.) 1917.

20. Giffin, H. Z.; Sanford, A. H., and Szlapka, T. L.: The Estimation of Urobilin and Urobilinogen in the Duodenal Contents, Am. J. M. Sc. **155**:562, 1918.

Hemolysis occurs constantly in the body, but there is no exact method of determining the normal rate of hemolysis. However, in the hemolytic anemias in which hemolysis is excessive, its recognition by clinical and laboratory means is usually possible. Such means, as applied in this study, have indicated that blood is not excessively destroyed in the anemia of chronic nephritis.

Defective blood formation is probably the important factor in the cause and maintenance of the anemia of chronic nephritis. This premise is supported by lack of evidence of abnormal blood destruction and

TABLE 3.—FINDINGS IN CHRONIC NEPHRITIS WITH ANEMIA

Cases	Hemo- globin, per Cent.	Erythrocytes			Leukocytes				Eosino- phils, per Cent.	Baso- phils, per Cent.	Duodenal Contents	
		Mil- lions	Re- ticu- lated	Nu- cle- ated	Num- ber	Poly- morpho- nuclears, per Cent.	Small Lympho- cytes, per Cent.	Large Mono- nuclears, per Cent.			Uro- bilin- ogen, Units	Uro- bilin, Units
A354982	39	2.31	...	0	7,400	64.5	24.5	10.5	3.5	0.5	0	400
A356822	68	3.74	0.2	0	7,400	60.0	30.0	4.0	3.5	2.5	200	600
A334085	42	2.69	0.3	0	7,700	71.0	19.0	8.5	3.0	...	0	200
A371812	62	4.05	1.3	0	12,000	58.8	33.5	5.0	1.5	1.5	0	400
A361797	53	3.20	0.2	0	4,530	55.0	38.7	4.2	1.0	1.0	0	600
A130794	44	2.52	0.1	1 cell	8,200	63.5	29.5	4.0	2.5	0.5	0	1,000
A123990	60	3.43	...	0	6,800	59.0	33.0	2.0	4.5	1.5	0	600
A374848	56	3.31	1.7	0	5,200	67.5	26.0	4.0	2.0	0.5	0	800
A364350	54	3.02	0.3	0	8,400	70.0	23.5	3.5	2.5	0.5
A380765	67	3.66	1.5	...	18,800	87.0	11.5	...	1.5	...	0	1,000
A384638	42	2.30	0.4	0	5,700	80.5	14.5	2.5	2.0	0.5	0	600

TABLE 4.—BLOOD COUNTS IN CHRONIC NEPHRITIS

	Hemo- globin, per Cent.	Erythro- cytes, Millions	Leuko- cytes	Color Index, per Cent.	Poly- morpho- nuclear Leukocytes, per Cent.	Lym- pho- cytes, per Cent.	Large Mono- nuclear Leukocytes, per Cent.	Eosino- phils, per Cent.	Baso- phils, per Cent.
Chronic nephritis with anemia (105 cases).....	56	3.31	9,020	0.8+	69.1*	23.6	4.8	1.9	0.3
Chronic nephritis without anemia (79 cases)†.....	75	4.22	8,160	?	63.6*	26.5	6.3	3.4	0.4

* Differential counts are the average of thirty-four cases.

† In three cases blood counts were not recorded.

by the fact that the blood picture of anemia of chronic nephritis corresponds to that of simple chronic anemia.

The erythrocytes of stained smears of the blood in cases of anemia of nephritis usually are moderately reduced in size; marked variation in the size is rarely noted. Poikilocytosis is rare, and achromia is usually mild. The incidence of reticulated red blood cells and of polychromatophilia is markedly low. Table 3 gives the average blood findings in eleven cases of the 105 in which the anemia of nephritis was severe. The low percentage of nucleated red cells and reticulated cells points to lack of action or sluggish action of regeneration by the bone marrow. Table 4 gives the average blood findings of two groups

of cases, 105 of chronic nephritis with anemia and seventy-nine without anemia. The average hemoglobin in the group with anemia was 56 per cent., which corresponds closely to the finding of DaCosta. No essential difference was noted in the leukocyte count in the two groups. In patients with anemia the per cent. of polymorphonuclear leukocytes averaged 5.6 higher and the lymphocytes 2.8 lower than in patients without anemia.

The platelet count in eight cases of chronic nephritis with severe anemia averaged 152,000, a condition which may have some bearing on the hemorrhagic tendency in some of the more severe cases of chronic nephritis with anemia.

As will be shown, the rate of development of the anemia, its lack of response to therapeutic measures, transfusion, arsenic, and iron, bear out this conclusion of defective hematopoiesis. When the anemia has been maintained for a considerable period, the bone marrow seems to establish a constant low threshold of activity for the individual. In this group of anemias of nephritis, cases were studied in which the bone marrow functioned fairly satisfactorily at from 40 to 50 per cent. of its normal activity level. Benzene produces a somewhat similar type of anemia. Minot²¹ described a case observed for three years, in which a satisfactory functioning level for the bone marrow was maintained at 80 per cent. of normal. In the more severe types of nephritic anemia, some of the features of an aplastic type are more in evidence, that is, absolute lack of response to treatment, and complete absence of immature and regenerative types of red cells. This group can be designated as secondary aplastic anemias of chronic nephritis.

INADEQUATE HEMATOPOIESIS

It is obviously impossible in this paper to attempt to review the causes of defective formation of blood, for the great majority of anemias are concerned with defective blood formation. The anemias of malignant disease, chronic sepsis, and other chronic pathologic processes concern the hematopoietic system directly; little is known regarding the mechanism involved. The bone marrow suffers in certain metabolic diseases, such as myxedema, in which the blood picture is often extremely confusing. Poor hygienic condition is the cause of mild anemia, although the pallor of the skin in this type may not indicate an actual decrease of blood elements.

In any chronic disease in which alteration of the blood picture is so common as in chronic nephritis, the question of defective diet deserves consideration. Patients with this disease often have been underfed

21. Minot, G. R.: Clinical Discussion of the Anemias, Oxford Med. **2**:589, 1920.

qualitatively and quantitatively for long periods. The chronic loss of albumin through the urine constitutes a loss of nitrogen to the organism, and its possible bearing on the production of anemia has been suggested. The retention of water in the blood and tissue have been made the explanation for the anemia of chronic nephritis. Not sufficient evidence is available to prove that hydremia or loss of albumin can cause a definite anemia.

The presence of a toxin or toxic agent in chronic nephritis has been assumed in order to explain the multiple tissue injury. As to whether this toxin is a known substance, and as the result of the renal damage appears in the blood in amounts sufficiently increased to cause injury to the bone marrow has never been proved. The possibility that this unknown agent, a hypothetic toxin, damages the bone marrow concomitantly with other vascular tissue must be considered.

Defective Diet.—The majority of cases of chronic nephritis are recognized, and in lieu of more specific treatment a dietary regime is instituted involving considerable restrictions. The following warrant consideration relative to blood changes: (1) the effects of fasting, (2) a prolonged low caloric diet, and (3) a prolonged low protein diet. A large volume of clinical and experimental evidence is available to help decide this question of the results of defective diet on the blood. Heidenhain,²² Panum²³ and Voit²⁴ have shown that loss of body weight and decrease of blood in fasting animals are proportional, normal values thus being maintained for hemoglobin and erythrocytes. Ash²⁵ has shown that, in general, the blood is distinctly resistant to the effects of inanition. Complete abstinence from food for long periods, at least thirty-one days, does not cause deleterious effects on the blood. There is slight actual loss of hemoglobin, more marked during the second ten days. Fasting does not cause any striking loss of hemoglobin and erythrocytes from the blood.

Blood changes in low diets have been studied by von Hösslin.²⁶ The studies of Benedict²⁷ and his collaborators revealed slight changes

22. Heidenhain, R. P. H.: *Disquisitiones Criticae et Experimentales de Sanguinis Quantitate in Mammalium Corpore Exstantis*. Halis, Gebauerio-Schwetschkianis, 1857. Quoted by Grawitz.

23. Panum, P. L.: Experimentelle Untersuchungen über die Veränderungen der Mengenverhältnisse des Blutes und seiner Bestandtheile durch die Inanition. *Arch. f. path. Anat. u. Physiol.* **29**:241, 1864.

24. Voit, C.: Ueber die Verschiedenheit der Eiweisszersetzung beim Hungern. *Ztschr. f. Biol.* **2**:307, 1866. Voit, C.: Gewichte der Organe eines wohlgenährten und eines hungernden Hundes, *Ztschr. f. Biol.* **12**:510, 1893.

25. Ash, J. E.: The Blood in Inanition, *Arch. Int. Med.* **14**:8 (July) 1914.

26. von Hösslin, H.: Ueber den Einfluss ungenügender Ernährung auf die Beschaffenheit des Blutes, München. med. Wchnschr. **37**:654-673, 1890.

27. Benedict, F. G.; Miles, W. R.; Roth, P., and Smith, H. M.: *Human Vitality and Efficiency under Prolonged Restricted Diet*, Washington, Carnegie Inst. Pub. No. 280, p. 701, 1919.

in blood findings after underfeeding. Minot studied the blood of two groups of men, *A* and *B*, receiving diets containing approximately 35 and 50 per cent. of normal caloric requirements. (Squad *A* had undergone a previous 10 per cent. loss in weight). Hemoglobin decreased slightly in both groups, four points in the former and slightly less in the latter. Minot concluded that further continuance of the experiments would not have produced further changes.

Von Hösslin has also studied the effects of low protein diet. One dog received an "albumin poor" diet and another of similar weight and age, received an exclusive albumin diet. The former showed a slight decrease of erythrocytes and hemoglobin after seven months. Chittenden's²⁸ experiments on healthy men with low protein diets (averaging from 45 to 53 gm. of protein) for periods averaging five months, showed a slight increase of erythrocytes and no change in hemoglobin or leukocytes. Von Hösslin concluded that in qualitatively deficient diets diminished iron content is responsible for the slight changes in the hemoglobin. Anemia has been noted in infants following the exclusive use of milk diets and Häusermann²⁹ has reported an analogous case in a young man, aged 18, who had always lived exclusively on milk. Erythrocyte counts were normal, but the hemoglobin had been reduced to 60 per cent. (Gowers' instrument).

Vinson's observations on anemia in hysterical dysphagia are of great interest. In these cases marked decreases in hemoglobin are found with no change in the number of erythrocytes. The recovery of hemoglobin to normal after resumption of vegetable and fruit diet is striking. The low color index and rapid recovery on a diet of fresh foods suggest some disturbance in the metabolism of iron.

As an effect of defective diets, hemoglobin is reduced only slightly, and even more equivocal changes occur in the erythrocytes. It must be kept in mind, however, that these experiments were made on healthy animals and robust men; diet may have a different action in the presence of disease or the effects of diet on the bone marrow may be modified or accentuated by disease. This cannot be ascertained since it is impossible to assign to each the exact part played in the production of anemia.

Hooper and Whipple³⁰ have shown that in the "simple anemia" (secondary to hemorrhage) of dogs the blood regeneration is more

28. Chittenden, R. H.: *Physiological Economy in Nutrition*. New York, F. A. Stokes Co., 1905, p. 478.

29. Häusermann, E.: *Die Assimilation des Eisens*, Ztschr. f. physiol. Chem. **23**:555, 1897.

30. Hooper, C. W., and Whipple, G. H.: *Blood Regeneration After Simple Anemia*, Am. J. Physiol. **45**:573, 1918.

rapid when carbohydrate diets are given. There is no reason to assume that such is the case in chronic nephritis. The deficiency of calories in low protein diets is made up by marked increase in carbohydrates. Our routine diet for nephritic patients of 1,500 calories and 40 gm. protein contains approximately 1,100 calories of carbohydrates. On the basis of Hooper and Whipple's observations in the blood regeneration after hemorrhage, this diet should favor rather than retard recovery in anemia of nephritis. The recovery response in the anemia of nephritis has an apparently different basis, as will be shown later.

In order to ascertain the effect of diet in the production and maintenance of anemia in chronic nephritis, twenty patients were selected at random from those referred to our service during 1921; ten with hypertension of more severe grades without renal insufficiency, and ten with chronic glomerular nephritis. The diet of the twenty patients averaged 1,500 calories and contained 40 gm. protein. As far as possible, the time element was the same in both groups, average time in the hospital was more than thirty days, and before admission both groups had been almost entirely restricted in calories and protein for from six months to one year. For a basis of comparison as far as dietetic restrictions were concerned, the conditions were fairly comparable in the two groups. In the cases of hypertension without renal insufficiency blood counts below 4,000,000 and hemoglobin less than 70 per cent. were found in three cases, explained by severe epistaxis and tonsillectomy three weeks previously. In the third case the cause of the anemia was not found. In the cases of nephritis anemia was found in eight, explanation of which will be given later. It would seem that there is insufficient evidence to ascribe the anemia of chronic nephritis to any definite metabolic effect of faulty diet. We have no evidence, either experimental or clinical, to show that after anemia is established in chronic nephritis deficient diet markedly influences the rate of formation of blood. This assumption is more logical than the assumption that diet per se can cause definite anemia.

Estimations of the basal metabolic rates were made in ten patients with chronic nephritis and anemia. The rates of all except one were within the limits of normal $+ 15$ and $- 15$ per cent. The basal metabolic rate of one patient with chronic nephritis and marked anemia was $+ 18$ per cent.

Loss of Albumin Through the Urine.—Prolonged loss of albumin through the urine in chronic nephritis has been noted as a possible agent in the cause of anemia of nephritis. Dieballa maintained that rarely is sufficient nitrogen lost in this manner to cause a negative nitrogen balance. If present, this negative balance is easily corrected by an

increase of protein diet. Dieballa and von Ketly³¹ observed a protein loss of 24 gm. through the urine. Epstein³² reported a case in which the loss of protein through the urine averaged from 18.5 to 26.2 gm. He says that excessive amounts of albumin in the urine for long periods undoubtedly have a marked effect on the body proteins, which would be more pronounced if combined with a low protein diet. The effects noted, however, have been decrease of serum albumin and increase of water in the blood. Epstein believes that this depletion of albumin of the blood explains edema in certain types of nephropathies. Evidence has not been presented, however, that excessive loss of albumin through the urine can cause anemia.

In order to determine whether or not the blood of patients with marked albuminuria shows anemia, twenty-four cases were studied, including cases of orthostatic albuminuria, chronic nephrosis, passive congestion with albuminuria, and focal nephritis. All cases in which there were complicating factors, such as loss of blood or chronic infection, were excluded. In Table 5 are shown the hemoglobin percentages,

TABLE 5.—RELATION OF LOSS OF ALBUMIN IN THE URINE TO HEMOGLOBIN AND ERYTHROCYTES

Cases With Marked Albuminuria	Number	Approximate Daily Loss of Albumin in Urine, Gm.	Hemoglobin, per Cent.	Erythrocytes, Millions
Focal nephritis.....	10	7.7	76.9	4.47
Orthostatic albuminuria.....	5	7.5	70.4	4.15
Chronic passive congestion....	5	6.5	81.0	4.82
Nephrosis.....	4	9.0	72.0	4.45

erythrocyte counts, and approximate loss of albumin through the urine. The diets in these groups were fairly constant, averaging from 40 to 50 gm. protein. The nitrogen balances were not determined. Previous to hospitalization the food intake had been variable. In several, the protein had been extremely low. In these cases a decrease in hemoglobin or erythrocytes was not shown. It seems reasonable to assume that albumin loss per se has no bearing on anemia in chronic nephritis.

Hydremia and Plethora.—Grawitz says that with circulatory stasis in chronic interstitial nephritis, the water content of blood increases or decreases. If blood is diluted, low values for hemoglobin and erythrocytes are found. Hammerschlag,³³ on the contrary, asserts that rarely is hydremia found in chronic interstitial nephritis and that in

31. Dieballa, G., and von Kétly, L.: Ueber die Wechselbeziehung von Albuminurie, Hydrämie und Hydrops bei Brightekern, *Deutsch. Arch. f. klin. Med.* **61**:76, 1898.

32. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for Its Alleviation, *Am. J. M. Sc.* **154**:638, 1917.

33. Hammerschlag, A.: Ueber Hydrämie, *Ztschr. f. klin. Med.* **21**:475, 1892.

the parenchymatous types, fluctuations in the specific gravity of the blood were extremely variable, changes being noted during increasing or decreasing edema. Krehl³⁴ says that hydremia is present in nephritis. Von Norden³⁵ is not convinced that such is the case. Labbé and Salomon³⁶ cite a case of severe anemia in which the erythrocytes increased from 500,000 to 2,542,000 coincidentally as peripheral edema disappeared. They conclude that hydremia can produce severe anemia and may be the cause of certain cases of so-called primary anemia. Mosenthal³⁷ says that hydremia actually exists in every case of renal edema and that albumin of the blood diminishes and specific gravity decreases.

Obviously unanimity of opinion does not exist regarding the existence of hydremia in chronic nephritis, and the rôle of so-called dilution anemia.

In certain types of nephritis serum albumin is relatively decreased. Epstein has emphasized this point in nephrosis. He believes the excessive loss of albumin through the urine is directly responsible for impoverishment of this colloid. Hammerschlag partly agrees with Epstein. Butterfield³⁸ and his associates have shown that the dry residue and protein contents of the serum of chronic nephritis with edema are definitely decreased, averaging 2.27 per cent. less than normal. Widal, Benard and Vaucher,³⁹ using the refractometric method, find in nephritis with edema, albumin of the blood to be diminished in proportion to the peripheral edema. In azotemic patients, hydremia was not found unless retention of chlorids was demonstrable in the blood. Thus, it seems fairly certain that there has been shown a relative decrease in serum albumin in chronic nephritis occurring more commonly in the group with edema. If blood volume were constant, it would be necessary to assume that this is replaced by water. There is no basis, however, for assuming that differences of 2, 4, or even 6 per cent. in water content of the serum can produce anemia, if blood volume is not increased. Slight fluctuations in hemoglobin and erythrocytes would reflect this slight dilution. To assume the produc-

34. Krehl, L.: *The Principles of Clinical Pathology*, Philadelphia, J. B. Lippincott & Co., 1905, p. 156.

35. von Noorden, K. H.: *Metabolism and Practical Medicine*. Chicago, W. T. Keener Co., 2:13, 1907.

36. Labbé, M., and Salomon: *Anémie pernicieuse progressive et nephrite chronique*, Bull. et mém. Soc. méd. d. hôp. de Par., 21:83, 1904.

37. Mosenthal, H. O.: *Renal Edema*, Biochem. Bull. 1:320, 1911.

38. Butterfield, E. E.; Erdwurm, F., and Braddock, W. H.: *The Differentiation of Nephropathies, Cardiopathies and Allied Conditions*, Am. J. M. Sc. 151:63, 1916.

39. Widal, F.; Benard, R., and Vaucher, E.: *L'hydrémie chez les brightiques et les cardiaques oedémateux; son étude à l'aide de la méthode refractométrique; comparaison de ses variations à celles du poids*, Semaine méd. 31:49, 1911.

tion of a definite anemia, plethora must be present. Data regarding blood volume in edema are rather meager; however, there are sufficient to indicate that probably blood volume is not greater in chronic nephritis with edema. Keith, Rowntree and Geraghty,⁴⁰ using their dye method, found that following a loss in weight of 11 kg. (edema fluid) in a case of chronic nephritis with marked edema, plasma volume did not change. After a loss in weight of 14 kg. (edema fluid) in a patient with cardiac disease, the total plasma volume was relatively higher. Bock,⁴¹ using the same method, found, in three cases of edema, that the relation of plasma volume to body weight was undisturbed; plasma volume was unchanged after loss in weight of 13.5 kg. (edema fluid). In our studies of hydremia and its relation to the anemia of chronic nephritis, it was concluded that the blood volume shows no constant increase, that is, plethora is not present.⁴² On this basis we are justified in assuming that the possible increase in water content of the blood is not sufficient to produce a so-called relative anemia. (We prefer to delay final judgment until these studies are completed.) For the present we are

TABLE 6.—EDEMA IN ONE HUNDRED CASES OF ANEMIA OF NEPHRITIS

Edema	Present, per Cent.	Absent, per Cent.
Trace.....	22	78
Moderate.....	11	89
Marked.....	3	97

convinced that hydremia is incapable of producing anemia of chronic nephritis to the degree observed in this study.

The incidence of anemia and edema is shown in Table 6. Marked edema was present in 3 per cent. of the cases of anemia.

Hemogenetic Toxin.—In studying the presence of a hemogenetic toxin as a factor in the production of anemia of nephritis the following points are considered: Is this toxin one of the normal metabolic products retained in the blood in excessive amounts, or is it an unknown toxic agent directly responsible for the renal injury?

Each of the nitrogenous constituents of the blood classed as non-protein has been tested for toxicity experimentally and clinically. Urea is mildly toxic, as has been shown by Hewlett⁴³ and his associates, producing symptoms of toxemia only if the concentration rises to 160

40. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* **16**:547, 1915.

41. Bock, A. V.: The Constancy of the Volume of the Blood Plasma, *Arch. Int. Med.* **27**:83 (Jan.) 1921.

42. A comprehensive study is being carried out relative to hydremia and will be included in a separate report.

43. Hewlett, A. W.; Gilbert, Q. O., and Wickett, A. D.: The Toxic Effects of Urea on Normal Individuals, *Arch. Int. Med.* **18**:636, 1916.

or 245 mg. for each 100 c.c. of blood. Rowntree's⁴⁴ similar experiments have shown that toxic symptoms can be produced when the urea nitrogen of the blood exceeds 30 mg. As Wells⁴⁵ has noted, however, the effect produced by high concentration of urea in the blood for comparatively short periods is entirely different from that caused by high concentration for days and weeks. Evidence is not available from many studies of the toxicity of urea that indicates that this substance in the blood in excessive amounts can cause anemia. The other nonprotein nitrogenous constituents have been investigated as to toxicity in relation to uremia and to hematopoiesis.

Clinical observations have thrown considerable light on the relationship between increased concentration of certain fractions of the nonprotein nitrogen in the blood and anemia. This relationship was analyzed in a series of cases of anemia of nephritis and found to be fairly close (Table 7). Anemia was present in 90 per cent. of the cases of chronic glomerular nephritis, in which blood urea exceeded 50 mg. for each 100 c.c. and in which blood creatinin exceeded 2 mg. for each 100 c.c.

TABLE 7.—RELATION OF BLOOD UREA, BLOOD CREATININ, AND NEURORETINITIS TO ANEMIA OF CHRONIC NEPHRITIS

Number		Anemia Present		Anemia Absent	
		Cases	Per Cent.	Cases	Per Cent.
105	Blood urea more than 50 mg. (retention).....	94	90	11	10
59	Blood creatinin more than 2 mg. (retention)....	56	94	3	6
41	Neuroretinitis (retention)	37	90	4	10
79	Blood urea normal (nonretention).....	8	10	71	90

It would seem that some close parallel exists between the retention of urea and creatinin and the anemia of nephritis. However, if injury to the bone marrow is caused in this manner, increased concentration of urea or creatinin would be present in every case of anemia of nephritis and the development of anemia would always be preceded by augmented values for these substances in the blood. Data presented in Table 8 indicate that these conditions are not fulfilled. In this case, renal insufficiency manifested itself by marked retinal injury, diminution of renal function, and elevated blood pressure; urea or creatinin, did not increase and the anemia developed after a lapse of time, as has been noted in all cases observed. The renal damage did not produce augmented amounts of nitrogen in the blood, but casts, erythrocytes and increased amount of albumin appeared in the urine. The bone

44. Rowntree, L. G.: Uremia, Etiology, Types and Diagnosis, J. Iowa State M. Soc. 7:1, 1917.

45. Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Co., 1918

marrow was injured, however, as shown by the definite decrease in hemoglobin and erythrocytes. There was also an increase of peripheral edema. The same sequence of events was observed in a similar case. Apparently, then, elevated urea and creatinin values are not essential to the cause of anemia of nephritis. Other nitrogenous constituents of the blood have been partially investigated. Retention of uric acid showed no constancy in its relation to anemia. The estimations of the ammonia nitrogen fraction have been unsatisfactory. Foster⁴⁶ reported an increase in the ammonia nitrogen up to 2.2 mg. for each 100 c.c. in the blood of half of his uremic patients. Our work has shown no such increase in patients with chronic nephritis and anemia. Estimation of amino-nitrogen of the blood in several cases of anemia of chronic nephritis showed no constant increase; the unidentified portion or rest nitrogen was not increased. Bock reports increased amino-nitrogen in the blood in cases of nephritis and in other conditions, hyperthyroidism and cirrhosis of the liver.

Further work is necessary before any conclusion can be reached with regard to the hemotoxic rôle of the ammonia fraction. Wells was of the opinion that the anemia of nephritis may be due to the hemolytic action of retained products of metabolism, in which the ammonium compounds are important. This study would seem to show, however, that if the ammonium compounds are concerned in the production of this anemia, the mechanism of hemolysis is not acting.

Investigations of the inorganic bases in the blood of patients with chronic nephritis did not reveal parallel changes in the sodium, potassium, magnesium and calcium contents.⁴⁷ Phosphorus was increased in cases of uremia with acidosis, as has been shown by Marriott and Howland,⁴⁸ and Denis and Minot.⁴⁹

Relationship was not observed between anemia and either chlorids or carbon dioxid combining power of the plasma.

Unknown Toxic Agent.—A study of the development of anemia in chronic nephritis suggests an unknown agent as the cause of the anemia. The clinical course of the disease is extremely variable and confusing. As cases are more closely observed and more intensely studied, certain features of the disease stand out. In many cases of chronic glomerular nephritis, two phases of the disease are noted: (1) latent or compen-

46. Foster, N. B.: Uremia. III. The Nonprotein Nitrogen of Blood, Arch. Int. Med. **15**:356 (April) 1915.

47. Unpublished work of McVicker, Ross and Barrio.

48. Marriott, W. McK., and Howland, J.: Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, Arch. Int. Med. **18**:708, 1916.

49. Denis, W., and Minot, A. S.: A Study of Phosphate Retention from the Standpoint of Blood Analysis, Arch. Int. Med. **26**:99 (July) 1921.

sated periods, and (2) active or decompensated periods. During a compensated period, renal function is deficient in some respects, but adequate for the individual to "carry on." Moderate disturbance of various kidney functions occur. Concentration and excretion of water may show impairment. The presence of albumin and casts in the urine reveal structural damage. Renal function is usually decreased and blood pressure increased. The retina and heart may show definite injury. Patients in this stage of the disease may or may not have anemia. Anemia was not present in eight cases studied during the period of renal break. Following the effect or toxic action of some unknown substance, which, in many cases is undoubtedly infectious in origin, the decompensation period supervenes. Further impairment of renal function is shown by appearance of casts, erythrocytes and increased amounts of albumin in the urine, decreased phenolsulphonephthalein excretion, and augmented amounts of nitrogen in the blood.

Retinal, cardiac, and vascular injuries are usually revealed by the clinical investigation. If, in this phase of the disease, the blood counts and hemoglobin estimations are repeated frequently, it will be found that after a certain period definite decreases are noted. In the cases studied, the length of this period was variable but averaged from four to six weeks. The degree of this decrease in hemoglobin and erythrocytes seems to depend largely on the severity of the toxic action. In several cases the anemia and renal insufficiency were not progressive or severe. The values for nitrogen of the blood dropped rather quickly and increased values for phenolsulphonephthalein excretion were observed within a short time. In the cases in which injury was more severe and renal insufficiency progressive, the hemoglobin and erythrocytes were similarly affected (Fig. 3).

The latency in the development of the anemia can be explained on the basis of its bone marrow origin. The circulating erythrocytes are not destroyed. Excessive hemolysis is not present. The normal replacement of erythrocytes is slower after injury to the bone marrow. As the circulating cells die and replacement is slow, a lapse of time is natural before anemia is evident.

As the life of erythrocytes has been given by different workers to be from ten to thirty days, the time of appearance of the anemia would necessarily fall within this period. Ashby's⁵⁰ work would seem to indicate that the transfused cells live for longer periods. Probably the time necessary for the appearance of the anemia would depend to a large degree on the severity of injury to the bone marrow.

50. Ashby, W.: Study of Transfused Blood. I. The Periodicity in Eliminative Activity Shown by the Organism, *J. Exper. M.* **34**:127, 1921.

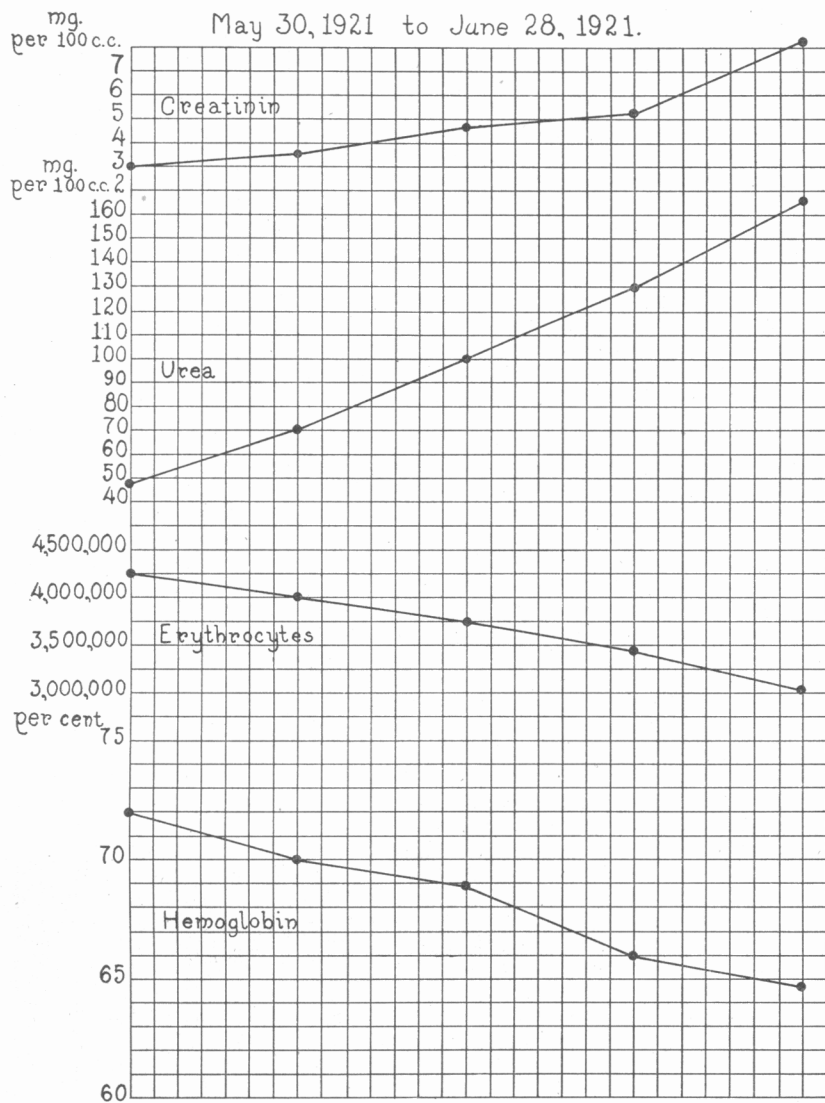


Fig. 3 (Case A 359322).—Blood findings during development of renal insufficiency. The renal injury was severe and progressive. The anemia followed a similar course.

The recovery of the hemopoietic function is not parallel to recovery of renal function. In the case charted in Figure 4 it will be noted that values for urea and creatinin, high during the period of renal insufficiency, had returned to normal before the anemia was evident. Two months later, blood values had not yet returned to their previous level.

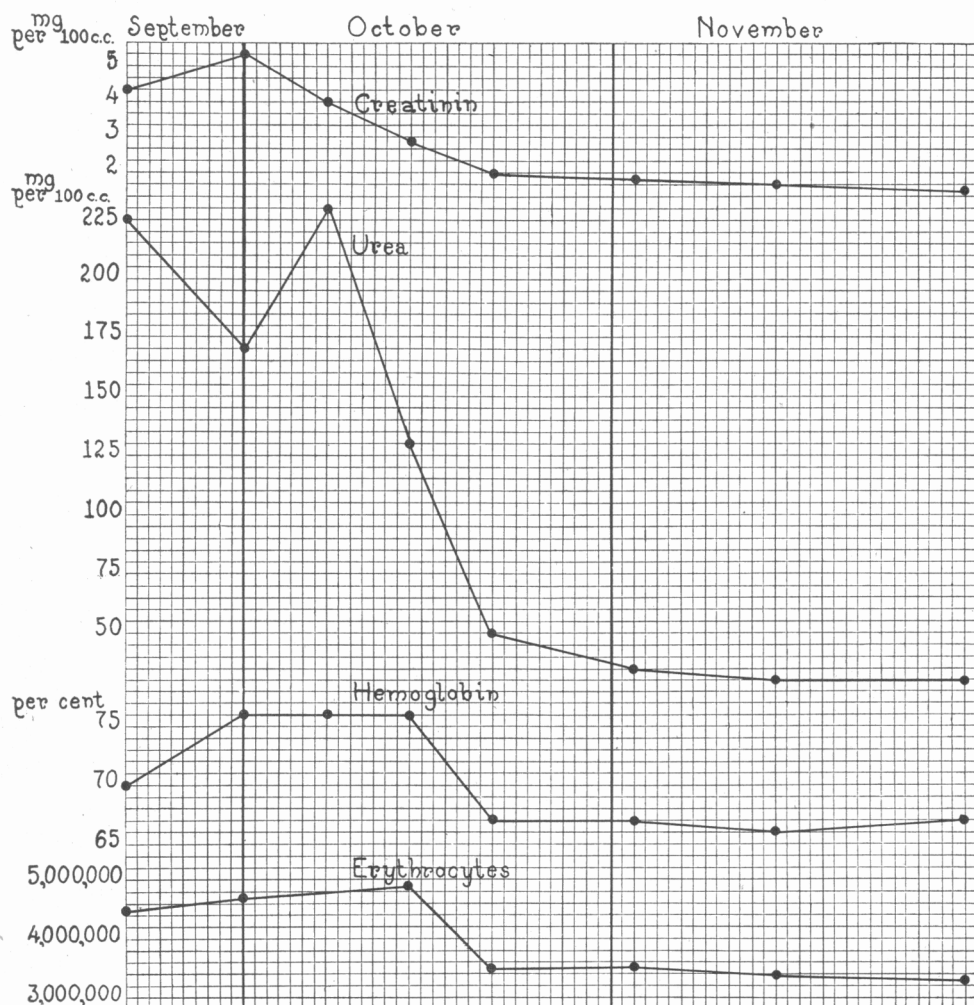


Fig. 4 (Case A 297046).—Blood findings during and following a period of renal insufficiency. Urea and creatinin returned to normal before anemia was evident.

In Figure 5 it will be seen that anemia developed following the renal break. A year later, hemoglobin and erythrocytes had not returned to normal. At this time the patient presented the picture of chronic nephritis of the compensated or latent period. It would be expected

that the next period of renal insufficiency would lower the hemoglobin and erythrocytes still farther. If the patient survived several renal breaks anemia would become more severe, reaching a degree often seen in severe chronic nephritis. In two cases recently studied, the bone marrow exhibited marked irritation, as shown by sharp increase in reticulated cells, accompanied by sharp recovery of the hemoglobin and erythrocyte values. These recoveries took place without parallel improvement of renal function. In one case, 7 per cent. reticulated red cells were found during this period of improvement. We have no

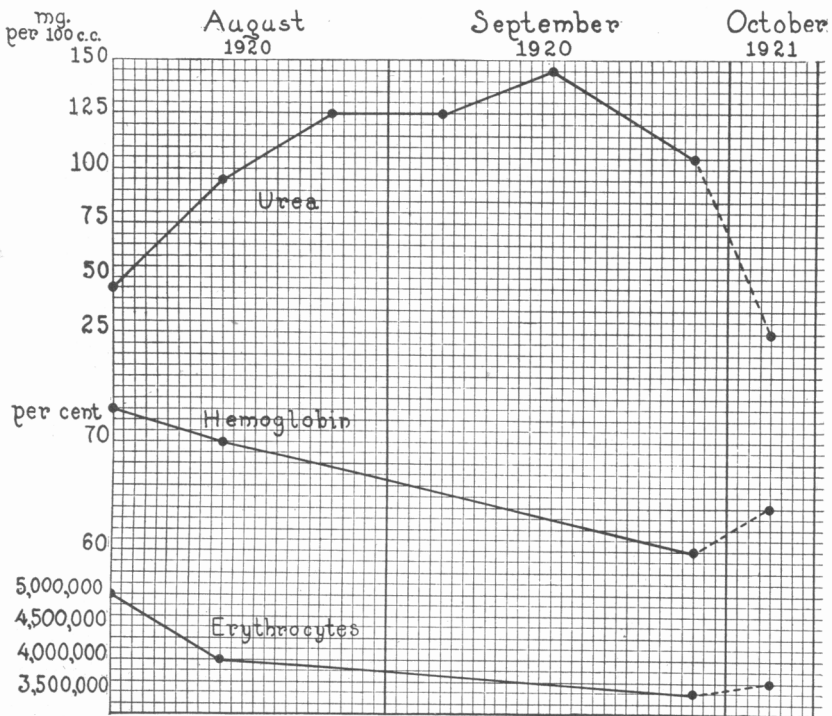


Fig. 5 (Case A 166657).—Blood findings during and after a renal break. Hemoglobin and erythrocyte values had not returned to normal one year later.

explanation of the cause of these sharp remissions in the anemia of chronic nephritis. They are exceptional. The recovery on the part of the bone marrow in the usual case is extremely gradual, or lacking. A clear cut case has not been observed which would show that the bone marrow has escaped injury following a phase of renal insufficiency. Several cases were observed during hospitalization for a period of three to four weeks following the onset of renal break. Subsequent inquiry regarding the progress of the case brought out the fact that the patient became pale and anemic as would be expected, according to clinical and laboratory findings.

The close relationship between elevated values for blood creatinin and anemia has a practical significance. In Table 9 are tabulated twenty cases of chronic nephritis in which creatinin values of 5 mg. and over, for each 100 c.c. were present. In all cases, anemia was present. The

TABLE 8.—CASE A 183454, CHRONIC GLOMERULAR NEPHRITIS; EVIDENCE OF RENAL RETINAL, AND BONE-MARROW INJURY

Date	Blood Urea, per Cent.	Blood Creatinin, per Cent.	Phenol-sulphone-phthal- ein, per Cent.	Blood Pressure	Fundi	Edema	Hemo- globin, per Cent.	Erythro- cytes, Millions	Remarks
3/14/19	18	...	45	180/125	Negative	Trace	81	General condi- tion good
1/ 8/20	42	...	45	Negative	85	5.04	Period of renal compensation
7/14/20	58	1.6	..	170/110	Negative	Moderate	75	5.24	
8/24/20	14	...	45	Trace	84	5.00	
10/28/20	30	1.39	40	160/105	One small hemorrhage	75	4.56	
11/26/20	25	1.4	45	164/118	80	5.16	
12/29/20	42	...	45	81		
2/23/21	29	1.33							
4/29/21	55	1.58							
12/ 5/21	37	1.8	15	220/150	Exudate and hemorrhage	Moder- ate	72	4.12	Mild nasopharn- geal infection followed by "renal break"
12/14/21	33	2.1	15	180/130	Moderate			
12/21/21	30	1.9	20	234/140	70	3.96	
12/23/21	30	1.0	20	Macular star			
1/ 2/22	30	1.8	Macular star	Trace			
1/20/22	40	1.6	25	168/118	Right pro- gressive change	Trace	67	3.60	

TABLE 9.—CREATININ RETENTION IN TWENTY CASES OF CHRONIC GLOMERULAR NEPHRITIS

Case	Creatinin, Mg. for Each 100 C.c.		Hemoglobin, per Cent.		Erythrocytes, Millions		Remarks
	Low	High	High	Low	High	Low	
A374849	4.4	7.2	59	55	3.31	3.00	Death four months later
A307422	8.35	10.4	..	40	2.64	Death ten days later
A354032	5.1	7.5	..	35	1.65	Death eight months later
A350322	3.3	7.0	70	67	4.06	3.63	Death three months later
A350944	17.1	18.1	37	36	1.90	1.83	Death six days later
A380765	3.3	9.8	67	67	3.68	3.66	Death one month later
A379161	15.0	16.0	..	56	3.38	Death ten days later
A312332	...	6.0	..	57	3.18	Still living
A311764	9.0	9.0	38	38	2.60	2.14	Death one month later
A339309	...	5.0	..	55	3.08	Death one month later
A343930	4.2	12.5	50	48	3.64	3.27	Death six months later
A334085	6.8	11.4	42	37	2.81	2.34	Still living
A363227	...	10.0	..	45	2.46	Death four months later
A153126	...	8.5	..	25	2.01	Death six months later
A342192	4.9	6.0	..	54	3.32	Death five months later
A323566	7.5	9.3	29	28	1.94	1.66	Death
A316817	...	6.0	..	46	2.73	Death four months later
A204193	2.5	5.0	65	54	4.60	3.25	Death ten months later
A342192	4.9	7.2	74	54	4.80	3.32	Death four months later
A353465	19.0	22.6	29	27	1.84	1.50	Death fourteen days later

Average creatinin, 8.8 mg. for each 100 c.c.; average hemoglobin, 48.5 per cent.; average erythrocytes, 2,960,000.

average hemoglobin values and red cell counts are given. As will be noted, reports were obtained in nineteen cases in which death followed within a period of eighteen months. Anemia in chronic nephritis of the group, such as we have defined, has then, a definite prognostic

value, approximately that of creatinin retention, when values for hemoglobin and erythrocytes approximate the averages given in Table 8. A larger group of cases are in course of investigation with the object of establishing prognostic values for anemia of chronic nephritis.

SUMMARY

The anemia of uncomplicated chronic nephritis was studied from several standpoints. Cases were not included in which blood loss had occurred. Hemolysis could not be demonstrated as a cause of this type of anemia. The conclusion is reached that this anemia is due to decreased function of the bone marrow. Qualitatively or quantitatively defective diets and loss of albumin through the urine are not important etiologic factors. The rôle of hydremia is not clear. Evidence is presented that hydremia is not a factor in the production of anemia in this series of cases. The relationship of various constituents of the blood to the anemia of chronic nephritis was studied; constancy of relation was not found. A close parallelism was found between anemia and augmented urea and creatinin values, although etiologic relationship could not be established. Neuroretinitis and anemia of chronic nephritis also were found to be closely related. In a group of cases studied during the development of renal insufficiency, anemia developed four to six weeks after the onset of the renal injury. The tardiness of the anemia is explained on the basis of decreased formation of erythrocytes. The recovery of bone marrow function was studied and it was found that as a rule, recovery is slow, depending to a large extent on the severity of the injury. After repeated injuries to the bone marrow, anemia becomes more severe and takes on certain characteristics of a hypoplastic or aplastic type of anemia. The injury to the bone marrow concerns only its erythrogenetic function. Leukocyto-genesis is not involved.

This conception of the causation of nephritic anemia throws additional light on this disease. Chronic nephritis should be viewed from the standpoint of a constitutional disease. Renal injury is only one phase of this widespread toxic damage. The retinal, cardiac and vascular tissues, and hematopoietic system are also definitely injured. All of these tissues may be involved in the toxic process, or one or more may escape.⁵¹ This study of anemia of nephritis would seem to indicate that the bone marrow participates almost invariably in this toxic process. Exceptions to this phenomenon have not been found. Possibly further study may modify this conception. The close parallel-

51. Atchley, D. W.: A Study of Eight Cases of Acute Nephritis, *Arch. Int. Med.* **22**:370 (Sept.) 1918. Atchley has suggested a similar explanation of acute glomerular nephritis.

ism between urea and creatinin retentions and the anemia of chronic nephritis can be explained from the fact that the majority of patients seen in the hospital are in the stage of renal insufficiency. If these patients were examined later, nitrogen values within normal limits would be found, but the anemia would still be present (Fig. 5). In other words, it would depend on whether this comparison of nitrogen retention and anemia was made in the compensated or decompensated stage of the disease.

This study has not thrown additional light on the cause of the production of this widespread constitutional injury. In several cases, however, the period of renal insufficiency, the active phase, directly followed infections of the nasopharynx.

The prognostic value of anemia in chronic nephritis seems to be definitely shown.

CONCLUSIONS

1. Evidence is presented to show that the anemia of uncomplicated chronic nephritis develops in the absence of blood loss, and this anemia is not due to excessive hemolysis.

2. Proof is not at hand to indicate that this type of anemia is due to increased concentration in the blood of any known nitrogenous substance.

3. Evidence is presented which indicates that the bone marrow suffers damage concomitantly with renal, retinal and cardiac tissues.

4. Chronic nephritis is a constitutional disease; accumulating evidence points to primary vascular injury of widespread distribution, renal, cardiac, and retinal tissues and the bone marrow tissues reveal secondary effects of vascular disease.

5. The unknown agent causing renal insufficiency is probably the etiologic factor in the disturbance of hematopoiesis, in other words, a common cause is present.

6. The anemia of chronic nephritis, if present to the degree indicated, has a prognostic value similar to that of creatinin retention.