THE PATHOGENESIS OF ANEMIA IN ACUTE GLOMERULONEPHRITIS. ESTIMATIONS OF BLOOD PRODUCTION AND BLOOD DESTRUCTION IN A CASE RECEIVING MASSIVE TRANSFUSIONS*

By Charles P. Emerson, M.D.

Anemia is one of the familiar manifestations of Bright's disease and a frequent complication of uremia, irrespective of the etiologic factors responsible for renal failure. A peculiarly intimate association exists between anemia and glomerulonephritis, in relation to which this hematologic sign is of diagnostic and prognostic importance. Conclusions regarding its pathogenesis are based on the experience of numerous investigators, who have emphasized the consistent lack of signs indicating excessive blood loss or blood destruction, and have succeeded in correlating the occurrence and severity of this anemia with the degree and duration of associated azotemia. Hence, the anemia associated with nitrogen retention is generally regarded as an example of erythropoietic failure. Furthermore, its refractoriness to erythropoietic stimulation with iron or liver therapy has been interpreted as evidence that blood production in patients with renal decompensation is retarded in consequence of "toxic inhibition of the bone marrow" by retained nitrogenous metabolic products.

This hypothesis, although possibly correct, as a premise mainly deduced through analogy, by inference and by exclusion bears particular scrutiny, little or no evidence of a positive and unequivocal sort having been marshalled in its support. The toxic metabolite presumed to be implicated has thus far escaped identification, and of all of the numerous chemical agents recognized as bone marrow depressants there is none known to exert comparable effects on the bone marrow or peripheral blood.

Finally, it may be objected that the hematologic data cited from case reports in support of this concept, including descriptions of reticulocytosis and alterations of bone marrow histology, in some instances suggest an enhancement, rather than a depression, of erythropoietic activity in patients with nephritis and anemia.

Transfusion studies, designed to permit an estimation of the survival of injected donor red cells, have contributed valuable information relative to the pathogenesis of various types of anemia, particularly those associated with certain hemolytic syndromes. This technic of investigation, employing serial measurements of the circulating blood volume in addition to selective agglutination counts, was applied in the study of a patient with an initial attack of early acute glomerulonephritis, who, presenting signs of moderate azotemia and progressive anemia, was adjudged particularly suitable as a subject for detailed hematologic investigation. Data were accordingly obtained which served as a basis for the relative evaluation of blood production, blood loss and blood destruction as factors possibly implicated in the development of his anemia. Appreciating the limited significance of the results obtained, which, pending confirmation from comparable investigations can

*The data utilized in this case report were obtained while on active duty with the Fifth (U.S.) General Hospital in the European Theater of Operations.
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hardly be evaluated in relation to other patients with Bright’s disease, the observations are nevertheless considered of sufficient interest to warrant description in the form of an individual case report.

CASE HISTORY AND INITIAL OBSERVATIONS*

A 27-year-old, white, American enlisted soldier was admitted to the hospital complaining of progressive swelling of the legs. Two months before entry he had contracted an acute pharyngitis which completely subsided in the course of several days. Thereafter he experienced persistent weakness and unusual fatigability. Two weeks before admission he became aware of painless swelling of his lower extremities, which increased, and, together with symptoms of general malaise, headaches and anorexia, occasioned his entry to the hospital.

The physical findings on admission were those of a well-developed male with pallid complexion and obvious pitting edema of the lower extremities. His body temperature was normal; arterial pressure 190/130 mm. Hg; height 168 cm.; weight 73.4 Kg. (35 Kg. in excess of his average weight prior to the present illness).

Initial laboratory data. Urinalysis: Specific gravity 1.015, albumin 4+, sediment (uncentrifuged) containing 15–20 r.b.c., 2–4 w.b.c. and numerous casts, granular and cellular per high power field. Blood hemoglobin concentration, 13.1 Gm. per cent; red cell count, 3.98 million per cu. mm.; hematocrit reading, 36.7; leukocytes, 8,200 per cu. mm., with normal differential count; platelets, 194,000 per cu. mm. Erythrocyte osmotic fragility normal; sedimentation rate (Westergren) 17 mm. in one hour. Blood urea nitrogen concentration, 2.5 mg. per cent; total serum protein concentration, 4.4 Gm. per cent. Bleeding time (Duke) 34 minutes; clotting time (Lee-White) 84 minutes. Stool examinations were negative for occult blood. The initial throat culture contained beta hemolytic streptococci, this organism failing to be demonstrated on re-examination after eight days.

METHODS OF STUDY

The patient was observed for a period of fifty days during which he was essentially at complete bed rest, maintained on a dietary regime restricted solely with respect to its sodium content. Penicillin, 120,000 units daily, was administered intramuscularly from the fourth to the thirteenth day. Otherwise, apart from transfusions and albumin injections subsequently to be specified, no therapeutic agents, hemopoietic, diuretic or antibacterial, were employed.

Daily observations included measurements of the arterial pressure, body weight, fluid intake and urine volume. Urinalyses were performed daily, which included, after the eighth day, a quantitative (Esbach) estimation of the total urine albumin excretion. Blood hemoglobin concentrations and icterus indices were determined with Klett photometric technics. Blood urea nitrogen was measured colorimetrically after urease digestion and nesslerization, and total protein concentrations by the procedure of Phillips and Van Slyke.17 Plasma volume determinations, employing T-1824 dye, were performed by a modification18 of the method of Gibson and Evans.19 Calculations of the circulating red cell volume and total blood volume were based on the plasma volume and hematocrit values, these computations involving a correction factor of −15 per cent applied to the calculated red cell volume to compensate for the relatively constant disparity between the large vessel hematocrit and the total body hematocrit.20

Group-O donor blood, freshly drawn into acidified glucose-citrate anticoagulant

*Identifying initials of the patient have been deleted here and in the table and figures at the request of the Technical Information Office of the Surgeon General’s Office.
solution, was employed in the first course of transfusions; in preparation for the second series red cells from freshly obtained group-0 blood were washed once and resuspended in 0.85 per cent saline solution. At intervals following transfusions the concentration of donor cells was determined; from these data it was possible to calculate the total volume of circulating donor cells and group-A recipient's cells. Selective agglutination counts were performed by modifications of the Ashby technic, utilizing dried anti-A grouping serum, a procedure that has been successfully applied in other investigations and has recently been evaluated by Young.

![Graph](image)

Fig. 1. Hematologic, blood chemical, and clinical data on a case of acute glomerulonephritis receiving infusions of whole blood, red cells and albumin.

**Course**

The hematologic findings and metabolic data obtained in this case are charted in figure 1 which depicts the observed fluctuations in the hemoglobin concentration, red cell count, blood urea nitrogen, total serum protein concentration, fluid balance, total albumin excretion, body weight and systolic arterial pressure.

It was evident on the fifteenth day that the patient's anemia, which was of a normocytic, normochromic type, was progressing in severity, the hemoglobin concentration having decreased from 13.1 to 11.2 Gm. per cent and the hematocrit reading from 36.7 to 30.8 since admission to the hospital. Blood volume measurements (table 1 and figure 2) indicated a total circulating red cell volume of 1080 cc. representing a calculated deficit of approximately 900 cc. or 45 per cent, relative to
the expected volume for an average normal male of his stature. The total blood volume was likewise deficient (approximately 20 per cent), this decrease being en-

Table 1.—Blood Studies in the Course of Transfusion Therapy

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Values expected in normal male, ht. 168 cm. (10, 24)

Blood transusions

Fig. 1. The influence of blood transfusions on anemia associated with acute glomerulonephritis.
tracts had been insignificant, hematuria continuing to be of microscopic degree, and only an occasional stool containing a trace of occult blood during the entire period of observation.

**First transfusion series.** On the fifteenth, and again on the sixteenth hospital day the patient received group-O whole blood totalling 470 cc. of red cells and 650 cc. of plasma. A mild febrile reaction followed on each occasion and, at the conclusion of the second injection, he experienced transient severe lumbar aching pain. The spleen promptly became enlarged and remained palpable for two weeks. Hemoglobinemia and hemoglobinuria did not occur, but there developed for the first time a mild transient icterus, a relative decrease in urine output and an increase in albumin excretion.

Blood volume studies and selective agglutination counts performed on the day following the second transfusion demonstrated that, whereas the injected red cells had survived in toto, a destruction of the patient's group-A cells had occurred, this loss approximately equalling the volume of transfused erythrocytes (table 1 and fig. 2). Thereafter, during the nine day interval between the first and second series of transfusions, the red cell volume continued to diminish, the patient's cells decreasing by 100 cc. (15 per cent) and the donor cells by 120 cc. (27 per cent). This progression of anemia developed despite the onset of a persistent reticulocytosis which occurred abruptly following transfusion (fig. 2).

**Second transfusion series.** Between the twenty-fifth and twenty-ninth hospital days the patient was transfused with saline-washed group-O cells derived from 2000 cc. of whole blood, all plasma having been removed. The total red cell volume was thereby increased to 1610 cc., or approximately 80 per cent of the expected normal value. There was a recurrence of mild transient icterus which, on the basis of selective agglutination counts, was apparently due to the prompt destruction of those donor cells injected in the final transfusion. No destruction of patient's cells resulted and those donor cells remaining at the conclusion of this series of transfusions survived thereafter in normal fashion, less than 10 per cent being eliminated in the course of the ensuing two weeks. A progressive increase in the patient's circulating red cells was demonstrable after the twenty-fifth day, their total volume being 250 cc., or 45 per cent, greater on the forty-third day. Although no subjective symptoms were associated with the cell transfusions a definite increase in proteinuria was noted immediately thereafter, a phenomenon which had likewise followed the earlier transfusions of whole blood, and the subsequent administration of crystalline human albumin.

**DISCUSSION**

This report concerns a patient hospitalized early in an initial attack of acute glomerulonephritis with manifestations of arterial hypertension, hematuria, albuminuria and nitrogen retention, who was under continuous observation for fifty days. During the first observation period, when renal decompensation was maximal, although by no means marked, there developed a moderately severe normocytic normochromic anemia of a type commonly associated with nephritis. Two weeks following the appearance of dependent edema, the first clinical evidence of
his renal disease, the venous hematocrit reading was 36.7, a reduction of approximately 20 per cent; two weeks later the hematocrit was 30.8, approximately 30 per cent below normal, but the calculated deficit in total circulating red cell volume at this time was 45 per cent. Measurements of the plasma volume indicated that there had occurred no compensatory increase in the latter, and that the true severity of the anemia, judged solely on the basis of the red cell and hemoglobin concentrations, had been obscured as a result of a reduction in the total blood volume. Alterations of a similar character in patients with acute nephritis have been reported by Harris and Gibson.25

Rapid red cell depletion of the degree exhibited by this patient is difficult to explain solely on the basis of erythropoietic depression due to toxic inhibition of the bone marrow, to a metabolic defect, or to a nutritional deficiency. Even assuming a complete cessation of blood production the decline in the red cell volume occurred at approximately twice the expected rate26 of 0.8 to 1.0 per cent per day, unless this bone marrow aplasia is considered to have occurred at the time of the antecedent pharyngitis. The latter possibility can hardly be discarded, but such an hypothesis presumes that the initial observations of hematocrit and hemoglobin concentration were misleading, the plasma volume at that time being considerably lower than when first determined two weeks later, a supposition for which there is no basis. Complete bone marrow inactivity is in any case an improbable explanation for the observed anemia, on the grounds that the reticulocytes, although not numerous (1.2 per cent) before transfusion therapy, were nevertheless present. It is of interest that the presence of reticulocytes in the peripheral blood has consistently been described in case reports published in relation to this problem, whatever interpretations may have been adduced from the hematologic data obtained.

Significant blood loss having been adequately excluded during the entire period of observation, it is inferred that excessive and uncompensated blood destruction must have been responsible for the rapid development of anemia in this case. Observations following the first series of transfusions tended to confirm this evaluation of the mechanisms involved. The patient, blood group-A, received 1000 cc. of group-O whole blood in the course of twenty-four hours, a procedure which precipitated a mild hemolytic crisis, with prompt destruction of 430 cc. of his own cells. Inasmuch as the donor erythrocytes quantitatively replaced the destroyed recipient cells there occurred no significant change in the severity of the anemia. An important contributing factor in this response was unquestionably the presence of incompatible isoagglutinins in the injected donor blood, the hemolytic effect of which has been previously described. Unfortunately the titer of anti-A isoagglutinins in the injected material was not determined. It may be stated, however, that no instance has been observed21 in which a comparable degree of hemolysis was produced by the first transfusion of plasma or whole blood containing incompatible isoagglutinins in very high titer; hence this patient must have been unusually susceptible to the hemolytic effect of the "universal donor" blood he received. Of far greater significance are the observations pertaining to the subsequent fate of the normal donor erythrocytes which were eliminated at an average rate of 3 per cent per day, or more than three times the expected rate. Depletion of the patient's own
cell population also continued to be excessive (1.6 per cent per day) but their net loss occurred less rapidly, which may be explained on the basis of a sudden increase in blood production evidenced by a concomitant reticulocytosis (fig. 2).

This sudden and unexpected increase in reticulocytes, indicating enhanced erythropoietic activity immediately following transfusion, deserves particular mention. Immediately preceding this therapy the reticulocyte count was 1.2 per cent; immediately thereafter the percentage had increased to 13.8. The precise explanation for this phenomenon is not evident, but it is of interest that the peak reticulocytosis occurred prior to a further substantial reduction in the venous hematocrit or hemoglobin concentration; hence, the stimulus for increased bone marrow activity was not primarily an increase in bone marrow hypoxia. Moreover, inasmuch as it occurred at a time when the elevation of blood urea nitrogen was almost maximal, one is tempted to reject the hypothesis that the previous inadequacy of blood production was due to toxic inhibition of the bone marrow as a result of nitrogen retention or to other unexcreted metabolites. It is possible that the resumption of normal erythropoietic activity displayed at this time was related to the increased hemolysis provoked by the administration of incompatible isoagglutinins; that it occurred, not as a result of increased anemia, donor erythrocytes having been substituted almost quantitatively for the patient's hemolyzed red cells, but due to the stimulus of some hemopoietically effective material derived from the latter. Or the donor blood may have been the source of an erythropoietic agent, of which there had been a previous deficiency. Whatever the true explanation, blood formation proceeded thenceforth at an increased rate, although temporarily outpaced by blood destruction.

As a result of the second series of transfusions, involving the administration of plasma-free red cell suspensions, the patient's anemia was practically relieved. In the course of four days the hemoglobin concentration was increased from 9.3 to 15.3 Gm. per cent, and the hematocrit reading from 27.1 to 43.7; the total red cell volume was almost doubled. A significant proportion of the injected cells were hemolyzed in the process of their preparation, or were eliminated very promptly following the injection. Nevertheless the subsequent fate of this donor blood, which survived normally, together with data indicating a progressive increase in the patient's red cell population, suggest that abnormal blood destruction had ceased, and that blood formation was occurring at a normal rate. The factors responsible for this reversion to a normal hematologic status can not be positively identified on the basis of the available evidence. It is of interest, however, in view of the well known correlation between the anemia of renal disease and the degree of nitrogen retention, that during the first twenty hospital days when signs of increased blood destruction and impaired erythropoiesis were most prominent, the blood urea nitrogen concentration ranged from 25 to 34 mg. per cent (average 30 mg. per cent), whereas during the subsequent thirty days when erythropoiesis and hemolysis were normal the blood urea nitrogen did not exceed 20 mg. per cent (average value 17.5 mg. per cent.). No relationship was observed between the hematologic status and the grade of hematuria and proteinuria, or fluctuations in the total circulating protein.
A final comment is warranted regarding the influence of transfusion therapy on other manifestations of nephritis in this case. No evidence can be adduced that the course of the arterial hypertension, which was one of gradual improvement, was in any way affected by these maneuvers. Hematuria and albuminuria persisted without remission throughout the period of study. The transient elevations of total urinary albumin excretion following each series of transfusions, whether involving the injection of whole blood, washed red cells or purified albumin, presumably reflect an increased renal blood flow and glomerular filtration attending this therapy. Similar increases in proteinuria following the administration of albumin in cases of nephritis have been described by Thorn et al.\(^7\) The progressive improvement in renal function as measured by changes in body weight, indicating increasingly effective water and sodium clearance, is readily attributable to the natural course of this patient's disease, rather than to variations in the degree of anemia. Thus, there was less water retention on the twenty-fifth hospital day, when his body weight was 69 kilograms, his blood volume 3650 cc. and hematocrit 27.1, than on the fourteenth day when his body weight was 73 kilograms, blood volume 3960 cc. and hematocrit 30.8. Similar conclusions obtain with respect to the observed reduction, between the eighteenth and twenty-first days, in the blood urea nitrogen concentration, these data being obtained in a patient whose renal decompensation was never severe, and whose clinical course was entirely consistent with one of progressive spontaneous improvement.

**Summary and Conclusions**

1. A 27 year old patient with an initial episode of acute glomerulonephritis was observed over a fifty day period, studies being directed primarily in an attempt to define the mechanisms responsible for a rapidly developing anemia. Hematologic data, including serial blood volume measurements and selective agglutination counts were obtained before and after the introduction of massive transfusion therapy.

2. The administration of group-O whole blood containing incompatible anti-A isoagglutinins in the first series of transfusions failed to improve the anemia but initiated a sustained reticulocyte response. Following this therapy there was evidence of increased blood destruction involving both the recipient's and the normal donor erythrocytes.

3. Data obtained following a second series of transfusions employing plasma-free group-O red cells, administered during a recovery phase when renal function had improved, indicated that blood destruction had largely abated and that hematopoietic activity was normal.

4. Two factors of undetermined origin are believed to have been implicated in the pathogenesis of anemia in this case: one, the occurrence of abnormally rapid blood destruction, and the other, impairment of blood formation. Both phenomena were associated with the presence of nitrogen retention, despite which, however, a prompt erythropoietic response followed the transfusion of whole blood with quantitative replacement of patient's red cells with donor erythrocytes, suggesting that previous bone marrow inactivity was not attributable to "toxic suppression."
The author is greatly indebted to Dr. Richard V. Ebert, formerly Major, M.C., A.U.S., for his valuable assistance in the planning and conduct of this experimental case study.

ACKNOWLEDGMENT

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