The anemia of chronic renal failure

Overview and early erythropoietin experience

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■ One of the most important deficiency states associated with chronic renal failure is profound anemia. While it has been possible to identify differing types of anemia in patients receiving dialysis support, and thus correct the secondary causes, most patients continue to exhibit symptoms and signs of the anemic state. This review of the anemias associated with renal failure explores the diagnostic and therapeutic possibilities that may help the physician in evaluating the anemic patient with chronic renal failure. Also described is the early clinical experience with a new genetically engineered hormone, recombinant human erythropoietin (r-HuEPo), which has been under investigation for nearly two years at The Cleveland Clinic Foundation as part of a multi-center trial. An orderly approach to the anemic patient with renal dysfunction is suggested, and conjectures about the impact of newer therapies are made.

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PATIENTS with chronic renal failure usually have a series of symptoms that lead physicians to recommend support therapy. Patients' complaints of tiredness, lethargy, and lightheadedness classically have been interpreted as expression of the "uremic state." The association of anemia with failing renal function was both a laboratory and a clinical observation, and until very recently, this anemia was thought to be merely an expression of the effect of uremia on another organ system.

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Dialysis support and diagnostic workup of more severe varieties of the associated anemic condition was the only approach available to these patients. Drug manipulation, transfusions, and supplemental vitamin therapy were the only medical alternatives. With the recent testing of recombinant human erythropoietin (r-HuEPo) to treat the anemia associated with renal failure, a new step in therapy has been taken.

The various causes for this anemia still need to be identified although the underlying renal disease is chronic. A rational and cost-effective investigation of the etiology of the specific anemia will help direct appropriate therapy.

DEFINITION AND DIAGNOSIS

Beginning at a glomerular filtration rate of 40 mL/min and progressing toward dialysis, anemia will develop in patients who do not have adequate erythropoietin production (*Figure 1*). The average hematocrit

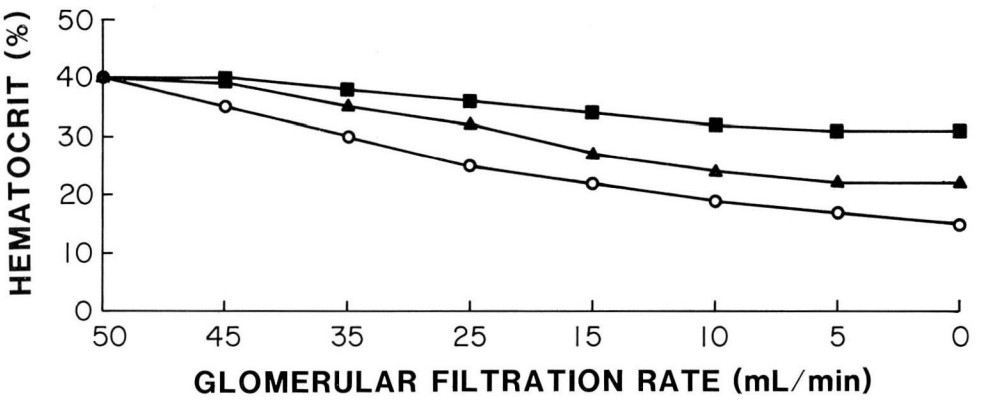

FIGURE 1. Progression of anemia according to etiology of ESRD (■–■ = polycystic disease; ▲–▲ = glomerular disease; 0–0 = interstitial disease).

TABLE 1
OVERVIEW OF RENAL FAILURE-ASSOCIATED ANEMIA

Etiology/ primary mechanism	RBC morphology laboratory testing	Preferred therapy
Chromic renal failure/ low relative EPo levels, uremic marrow blockade	Normochromic-normocytic/ normal and/or negative lab results	Dialysis, EPo infusions
Blood loss/ iron deficiency	Hypochromic-microcytic/ ↓ferritin ↓bone iron content ↓serum iron saturation	Supplemental iron intake
Aluminum overload/ blockade of iron uptake	Hypochromic-microcytic/ ↑serum aluminum ↑bone aluminum content ↑RBC aluminum content ↑desferrioxamine challenge	Desferrioxamine chelation
Vitamin deficiency/ defective hemoglobin formation	Normochromic-macrocytic/ ↓RBC/serum B12 levels ↓folate levels	Supplemental vitamin intake
RBC rupture/ drug, mechanical, idiopathic	Normochromic-normocytic/ helmet and/or ghost cells ↑methemalbumin ↑lactic dehydrogenase ↑plasma hemoglobin	Discontinue drug, correct equipment, stop toxin

of the typical dialysis patient will be 21%–23%. Approximately 15% of the hemodialysis population will require significant blood transfusion (>1 unit per month) to maintain a suitable RBC mass.

The requirements for blood may also change according to longevity on dialysis and the level of azotemic control.[1]

RBC morphology

Perhaps the best approach to understanding and diagnosing anemia in patients with renal failure is to classify the type of morphology associated with the process (*Table 1*). The vast majority of anemias are associated with chronic disease and as such will remain a *normochromic-normocytic* variety.[1] Burr cell formations and various abnormal RBC shapes associated with the uremic state are often present. Ghost cells or helmet cells, however, are quite infrequent in the patient with uncomplicated disease. Bone marrow aspirate also reveals a normocellular anatomy, usually with a normal myeloid-to-erythroid ratio.

Microcytic and/or hypochromic anemia generally denotes underlying iron deficiency. The marrow iron stores are usually low, and this is reflected in the serum ferritin levels of the patient who is not receiving transfusions. There is a problem in interpreting serum iron levels, iron binding capacity, and ferritin in the patient who receives multiple transfusions. Calculating the iron burden from one transfusion, there are approximately 200 mg of iron per unit of RBC infused. This iron load may be reflected in higher serum levels, yet the total burden of iron will be low. Since gastrointestinal absorption of iron is not decreased in the uremic state, the oral iron load will usually provide adequate iron. Parenteral iron supplementation should be used with caution since, in the absence of concurrent r-HuEPo therapy, the larger bolus of iron will generally flood the transport system.

If iron deficiency is not present and the morphology is microcytic, heavy-metal intoxication should be considered as a strong possibility. The anemia of aluminum intoxication has received much attention lately, and theories of aluminum-induced inhibition of delta-aminolevulinic acid dehydratase activity (similar to the anemia of lead intoxication) or its binding with transferrin, thus blocking iron incorporation, have been advanced.[2] There does not always seem to be a close correlation between serum aluminum levels and the degree of anemia. Recently nickel deficiency[3] and zinc deficiency, as well as zinc-induced copper deficiencies, have been implicated in several forms of *sideroblastic* anemias, and toxic effects of various drugs (isoniazid, chloramphenicol) or associated various neoplastic or inflammatory states are known etiological factors[4]

Megaloblastic anemias may also be encountered in uremic patients receiving dialytic support. The most frequent cause seems to be the lack of vitamin B12 or folic acid. While vitamin B12 deficiency is rare because dietary intake, albeit reduced, is usually adequate to cover the dialytic losses, vitamin supplementation is recommended. Folic acid loss during dialysis may result in a megaloblastic form of anemia. Since the most common dietary source of folic acid is fruits and vegetables, restriction or type of preparation of these foodstuffs because of their potassium content may also reduce dietary intake of this vitamin.

A number of drugs may either antagonize DNA synthesis directly or antagonize folate, and result in anemia. Obvious anti-metabolites (methotrexate, cyclophosphamide) used in the therapy of concurrent diseases or the not infrequently used anticonvulsants (phenytoin, phenobarbital) may easily be implicated in varying degrees of megaloblastic anemias.[5] Also, such states as pernicious anemia, although not common in chronic renal failure, should be considered when vitamin B12 deficiency is noted.

Early destruction of the RBC may be seen in renal failure and has been cited as a major cause of anemia in this patient group.[6] Cell hemolysis can be secondary to either intrinsic factors affecting the integrity of the cell membrane or extrinsic factors that enhance RBC destruction. The events may be either acute in onset or of a more chronic nature. In a small number of patients receiving chronic dialysis, a fall in RBC survival may be attributed to increased sequestration of erythrocytes by the spleen. Most patients undergoing hemodialysis have splenomegaly and thus the mere presence of a large spleen and worsening anemia should only arouse the suspicion of hypersplenism.

Adverse effects of various drugs should be considered in a patient with acute anemia. Drugs most frequently associated with hemolysis include alpha-methyldopa, penicillin, quinine, or quinidine. A positive reaction to the Coombs test in patients treated with alpha-methyldopa, associated with IgG but not C3 coating of the RBC, is all but diagnostic. The hapten-like effects of penicillin-associated anemia and the "innocent bystander" antibodies that adhere to the RBC membrane, fixing complement and thus causing hemolysis in quinine and quinidine toxicity, are rare iatrogenic etiologies.

Other physical or toxic effects that lead to RBC hemolysis and are more frequently noted in the dialysis population are due to various elements of the dialytic process itself or the preparation of the artificial kidney or the dialysate. Oxidants such as copper, chloramine, or nitrates in the dialysis solution will have adverse effects on RBC survival. For these reasons, the water supply to any dialysis facility should he thoroughly tested periodically and the water treated before mixing with dialysate concentrate for dialysis. The elimination of copper tubing and the use of carbon filters and either a deionizer and/or reverse osmosis in preparing the water for use in dialysis have greatly reduced the incidence of these forms of hemolytic anemias.

With the increasing use of dialyzer reprocessing and the continued practice of disinfection with formaldehyde, another potential source of acute hemolysis is the infusion of formaldehyde. In early reports, the development of an anti-N antibody in patients who were subjected to chronic formaldehyde exposure was noted to be much less frequent with lower predialysis formaldehyde concentrations in the reprocessed kidney.[7] There is no evidence that patients subjected to dialyzer reuse have any greater degree of anemia than their single-use counterparts. It is, however, important to assure the complete rinsing of the dialyzer so that the formaldehyde concentration of the infusate remains below 3 μg/mL.

Technical errors such as an overheated dialysis bath, a faulty blood pump, high forced blood flows through a small access needle (more frequent with the high-flux dialytic techniques), dialysis against water, or faulty extracorporeal lines are quite rare, having an estimated frequency of only 0.06% of all dialytic interventions.[8] Finally, the underlying pathologic state of the patient—autoimmune hemolysis from connective tissue disorders, enhanced hemolysis in the sickle-cell patient, or indirect effects of pneumococcal, staphylococcal, or *Escherichia coli* bacteremia—may also produce a clinically apparent anemia.

TABLE 2
FERROKINETICS: LABELED IRON INCORPORATION IN VARIOUS ANEMIAS

Disease state	^{59}Fe plasma disappearance	Fe inclusion
Normal	60–90 min	80–90%
Hypoplastic or low EPo	prolonged	low
Iron deficiency	rapid	complete
Hemolysis	rapid	early
Megaloblastic	rapid	low

Laboratory testing

While the basic consideration in the differential diagnosis of anemia is the RBC size, as measured by the mean corpuscular volume (MCV), automated flow cytometry has allowed instantaneous analysis not only of erythrocyte volume but also the coefficient of variation of the RBC volume distribution expressed as the RBC distribution width (RDW). Thus, the values for MCV (<80 fL = microcytosis, 80–100 fL = normocytosis, >100 fL = macrocytosis) and RDW (low = anisocytosis absent; high = anisocytosis present) will give the clinician an early idea of the type of anemia that is present. Direct review of the peripheral smear will still, however, give the greatest amount of information.

The deficiency states may be easily evaluated by either direct or indirect measurement of the element in question. Bone marrow iron content is perhaps the earliest indicator of iron deficiency anemia, while tissue iron contents do not correlate well with iron-overloaded states. Serum iron-binding capacity may aid in establishing the diagnosis of iron deficiency or overload, and serum ferritin will correlate well with total-body iron content. Adjusting the "normal values" for ferritin in chronic renal failure to >70 ng/mL, a lower serum value will indicate iron deficiency. The percent of transferrin saturation will also be a reliable indicator of the supply of iron to the developing RBC and can be used to differentiate deficiency from chronic disease as well as hypoproliferative states.

The biological assay standard for the measurement of erythropoietin levels remains the polycythemic mouse assay. This assay is, however, expensive, time-consuming, and technically involved, and cannot measure normal or subnormal levels, so that widespread laboratory availability is not practical. The development of in vitro testing using fetal mouse liver cultures, hemagglutination inhibition, or radioimmunoassay systems has been proposed. Since mouse liver and inhibition tests measure active substances and not pure erythropoietin, the bioassay is necessarily a confirmatory process, whereas the immunoassay has gained acceptance with the recent cloning of the erythropoietin gene and consequent availability of the hormone in sufficient quantity. Normal human serum levels of erythropoietin appear to be approximately 15 mU/mL (5–36.6 mU/mL) depending upon the assay method used.[9]

An estimate of the effectiveness of erythropoiesis may be obtained through ferrokinetic studies (*Table 2*). Radioactive iron (Fe-59) is first bound in vitro to plasma transferrin and subsequently injected into the patient. Serial peripheral blood samples are drawn to determine both the plasma half-life of the injected sample and the incorporation of the radiolabeled iron into the erythrocytes. The usual plasma half-life in normal people is 60–90 minutes, while 80%–90% of the injected dose is incorporated into RBCs within one week. In hypoplastic anemia and low effective erythropoietin states, plasma iron disappearance is slow, and incorporation of labeled iron into hemoglobin is also retarded. In iron deficiency, on the other hand, plasma clearance is rapid and iron incorporation is complete, while in hemolytic anemias removal and uptake are rapid but removal of the RBC from the peripheral blood is premature. In megaloblastic anemia plasma removal of the labeled iron will be rapid but uptake by the erythrocytes will be very slow and partial.

Serum vitamin B12 and erythrocyte folate levels are good indicators of biologically active concentrations of these substances in the patient with megaloblastic anemia. Radioimmunoassay techniques may also be used. Normal values, however, may vary among laboratories, with a general range of 200–900 pg/mL for vitamin B12 and 6–20 ng/mL for folic acid.

Laboratory documentation of hemolysis in the patient with chronic renal failure will follow the general outlines of that for other patients, with a few important exceptions. It must be remembered that these patients also have a decreased RBC production secondary to a relative lack of erythropoietin. Thus, the high reticulocyte counts thought to be the hallmark of the hemolytic process may not be as dramatic as in the patient without renal failure. The increase in unconjugated bilirubin and the low to absent haptoglobin are not as indicative of hemolysis in patients with chronic renal failure, and the elevation of lactate dehydrogenase is also a common finding without a major hemolytic process. Plasma hemoglobin and methemalbumin elevations are not frequently found and when present indicate significant intravascular hemolysis. Methemalbumin is greatly elevated in copper-, nitrate-, or chloramine-induced hemolysis, as well as in technical error resulting in RBC

destruction.

Tagging erythrocytes and following the incorporation and later destruction of these cells is the most precise method of evaluating RBC survival times. This method usually uses Cr-51 or DF P-32 to label the RBC; later various scanning techniques can be used to monitor the sequestration of labeled cells in various organs. The splenomegaly that frequently accompanies dialysis can be easily evaluated for its role in the development of anemia by this rather simple method. More elaborate testing of inherited or acquired structural abnormalities of the RBC membrane is usually not necessary.

THERAPY OF ANEMIA

General considerations

The vast majority of patients with chronic renal failure who are either receiving dialytic support or approaching the need for dialysis will have a normochromic, normocytic anemia, which will be normal on much of the testing described above. These patients will be dependent upon the nephrologist for establishing a rational regimen for treatment of their anemia. The points that are usually considered in establishing a hematocrit maintenance level are the age of the patient, transplant status, concurrent or complicating diseases, and lifestyle or work patterns. Generally, the younger patient will tolerate a lower hematocrit, while patients who are older and have accompanying coronary disease will usually be maintained at higher levels. Although a more pronounced level of anemia may be supported, the level of activity is generally higher among the younger population, and thus a slightly higher hematocrit needs to be established.

Once reversible causes of the anemia have been addressed, therapy is undertaken. The initial step with all patients is to enhance the natural production of erythrocytes through mechanical or pharmacological maneuvers. Although anemia per se is not an absolute indicator for the initiation of dialysis, once begun, the dialytic prescription should maintain the patient in as nonuremic a state as possible. With appropriate dietary control and using urea kinetic modeling to establish the dialysis frequency and dosage, patients should be held to mid-week BUN levels of <80 mg/100 mL or first-week levels of <100 mg/100 mL.[10] In many patients, starting dialysis will raise the hematocrit by as much as 5% to 8% over predialysis values, while dialysis will improve hematocrit in patients with chronic disease by another 2% to 3%.[11,12] This has actually been aided with widespread use of dialyzer recycling, where the artificial kidney is cleaned of residual blood a bit more aggressively than in the single-use situation. Simple changes in the basic technique of re-transfusion, along with minimizing blood drawing by using pediatric blood collection systems and eliminating unnecessary blood testing, will decrease iatrogenic blood losses.

Any decrease in the status of a patient's baseline hematocrit should lead to an investigation of blood loss, especially via the gastrointestinal tract. Testing stool for occult blood is a simple and effective method of identifying blood loss by this route and will also help interpret the accompanying sudden rise in BUN frequently seen in these patients. Widespread deterioration in the anemic patient should alert the physician to possible dialysate contamination caused by failure of the water treatment system or changes in water supply. Periodic water testing has been strongly recommended and should include not only raw water but also treated water. All dialytic procedures should be reviewed and any recent changes addressed (e.g. needle size, change in average blood flow or pumping equipment, change in dialysate supplier, etc.) as a possible cause for hemolysis.

Supplemental therapies should include vitamin B complex and folic acid. Since these are water-soluble substances and easily removed with dialysis, added losses are incurred. With the trend toward more restricted protein intake in the predialysis therapy of patients with chronic renal disease and more aggressive use of high-efficiency dialytic techniques once these patients require support, vitamin supplementation is all the more necessary.

Specific considerations

Establishing the state of iron balance and adding oral iron supplements while monitoring therapy by periodic serum ferritin determinations may be helpful. Oral iron therapy is preferred over parenteral in treating iron deficiency or maintaining iron stores and hematocrit. Intravenous delivery is preferred over the intramuscular route during the rare times that parenteral iron is administered. This preference is based on the greater ability to treat an anaphylactic reaction, if it occurs, with intravenous access and avoiding entry into the muscle of a patient receiving anticoagulation therapy in conjunction with dialysis therapy. It is also possible to overload the serum inadvertently with iron during parenteral administration and thus deposit iron into tissue while iron still needs to be incorporated into the hematopoietic system.[13] Both oral and parenteral administration have been used during r-HuEPo therapy in patients who required iron supplementation.

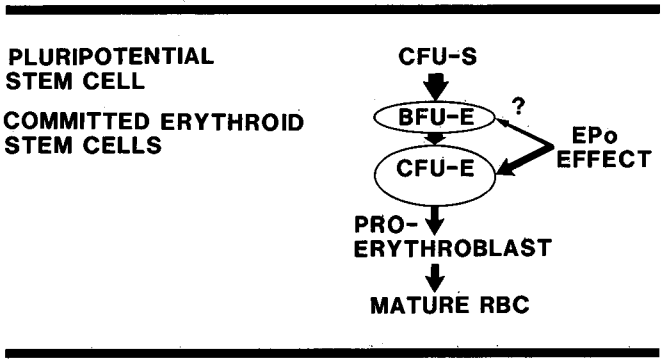

FIGURE 2. Target cells for erythropoietin (*EPo*) stimulation. *CFU-S* = colony-forming cell-stem; *BFU-E* = burst forming unit-erythroid; *CFU-E* = colony-forming unit-erythroid.

Another pharmacological approach to the anemia of renal patients is the use of androgens. The parenteral administration of nandrolone decanoate (200–300 mg IM per week) has been found to be effective in enhancing erythropoiesis in some patients receiving dialysis. Administration for three to six months and evaluation of changes in either the absolute hematocrit or transfusion requirement during this time will uncover those patients who will be helped and eliminate those patients who would find no benefit from this therapy. While the mechanism of action is thought to be the stimulation of erythropoietin synthesis, both renal and extrarenal, its use has been associated with other drug effects. The most apparent of these side effects are masculinizing changes (hirsutism, acne, muscle distribution) in the female and occasional priapism in the male. Both groups are prone to hepatic dysfunction, including cholestasis and liver function test abnormalities. If after six months of therapy there has been no improvement in the anemia, therapy should be discontinued.

The routine use of transfusions to maintain a specific hematocrit has been the treatment of choice for many patients on dialysis until recently. The type of blood used has fluctuated with availability and transplant protocol but usually consists of some form of washed, leukocyte-poor RBC infusion rather than whole blood. As pointed out earlier, each transfusion carries 200 mg of iron. This iron load may have enormous clinical consequences in patients who receive large amounts of blood. Patients receiving dialysis are prone to hemochromatosis with dysfunctional iron deposition in liver, heart, and other tissues. Patients will usually have elevated serum ferritin (>5000 μg/L), as well as clinical syndromes associated with specific organ dysfunction. Patients who receive multiple units at a single sitting will be more likely to have a depressed erythropoietin response to hypoxia than those who receive only one unit. Thus, patients who receive multiple units may well become dependent upon RBC infusions for maintenance and consequently be subjected to increased iron load. The proposed use of chelating agents to treat established iron overload has found only limited success. Desferrioxamine has been given in dosages of 40 to 90 mg/kg/wk in most protocols[14,15] and has been removed either via usual dialysis sessions or with hemofiltration. These interventions have met with mixed clinical results.

Another drawback to the liberal use of transfusions is the potential for transmission of disease. There have been great strides in the screening of blood for hepatitis B and more recently for acquired immunodeficiency syndrome (AIDS) associated virus (HIV); however, there has continued to be a moderately high incidence of non-A, non-B hepatitis among patients who receive multiple transfusions. Transplantation protocols have moved full circle, from discouraging transfusions because of the enhanced antibody production, to forced transfusions because of statistically significant improvement in cadaver graft survival among patients receiving multiple transfusions, and now to a more moderate transfusion policy. All patients should receive transfusions only when there is a clinical need. A frequent clinical situation in which the usual state of anemia improves is seen during liver cell regeneration. Liver parenchymal damage caused by viral hepatitis or drug toxicity with subsequent liver repair has been said to induce a transient elevation of the RBC mass. Patients with chronic hepatitis suffering ongoing liver cell destruction and regeneration will have a higher hematocrit than those without hepatitis. Nonrenal erythropoietin produced from liver cells has been suggested as the major component in the etiology of this phenomenon.[16]

The recent identification and cloning of the erythropoietin gene have made possible the production of adequate amounts of r-HuEPo for clinical investigation. Rat and sheep models of anemia associated with chronic renal failure have responded to hormonal infusions, and positive results in the correction of anemia have already been reported in early phase I and II human trials.[17,18] These results seem to support the theory that the inhibitory effect of some uremic toxins can be overcome by flooding the system with r-HuEPo.

Erythropoietin seems to have its major effect on the already committed line of the erythroid stem cell series. These burst-forming units later mature into colony-forming units and then through pro-erythroblasts and

reticulocytes into mature RBCs. The CFU-E cell types seem to be the ones affected by the r-HuEPo infusions, although there are also data to support an effect at other points in the cascade (*Figure 2*).

In the multicenter phase III human clinical trials recently reported,[19] we have noted an improvement in hemoglobin and hematocrit in all patients entered into the study. Through design, patients who were heavily transfusion-dependent were included, and their transfusion requirement was reduced to zero, while the hematocrit was maintained within the range of 34%–38%. There was an increased requirement for iron supplementation, similar to that reported in the phase I and II clinical trial,[18] but the earlier reported problems with high serum potassium levels were not observed. While the blood urea nitrogen and serum creatinine levels did rise, this reflected decreased dialyzer clearance, easily overcome by minor treatment adjustments.[20]

We noted increased diastolic blood pressures in approximately 30% of our patients. Generally, those patients who had a history of hypertension were more prone to having it reappear. While there have been reports of severe hypertension precipitating encephalopathy, we have found the hypertension to be medically treatable. We found no correlation between dose schedule or amount or total duration of treatment and the occurrence of hypertension. We have further studied the hemodynamics of this therapy[21] and are pursuing a broader look at its effect on vessels and heart activity.

Treatment response seems to follow a dose-dependent curve, as noted earlier,[18] and end-point hematocrit should probably be set at 35% to 38%. Treatment is given three times weekly, intravenously, at the conclusion of the hemodialysis run.[22] In all patients treated thus far, no untoward effects directly attributed to the hormone have been noted.

It is difficult to recommend surgery for anemia, but there are the rare patients with hypersplenism who would benefit from splenectomy. The diagnosis must be confirmed by RBC survival studies and evidence of splenic sequestration. This state is quite frequently accompanied by osteitis fibrosa, a consequence of hyperparathyroidism. Again, the recommendation of parathyroidectomy is not based on the level of anemia but rather on the level of bone involvement. While parathyroidectomy has been reported to be accompanied by an improvement in the state of anemia, we have not found that to be a frequent occurrence. There has not been any evidence of a direct toxic effect of parathyroid hormone on the hematopoietic system other than its effect of marrow fibrosis.[23] Therefore, elevated serum levels of parathyroid hormone will have much less significance, while a bone biopsy examination will be the preferred test.

Finally, improvement in the anemia may be associated with the use of different dialytic support systems. Continuous ambulatory peritoneal dialysis (CAPD) has been noted in our population to induce an early rise in the hematocrit of patients transferred from hemodialysis. This improvement was, however, short-lived, and hematocrits usually returned to baseline values within three to four months of continued therapy. There was also a similar improvement in RBC mass among those patients treated with hemofiltration. These therapies produce a greater clearance of the "middle molecular size" elements. Thus, there was speculation of an enhanced removal of some inhibitor. Since there has not been a universal agreement on the improvement of the anemia and any improvement has been short-lived, the validity of these theories is questioned.

Special situations may arise with the patient who is anatomically anephric rather than functionally anephric. There is a more profound anemia in the former group, probably due to the total lack of renal erythropoietin production and subsequent dependence upon nonrenal sources. These patients will usually have a higher transfusion requirement and are therefore more frequently at risk for iron overload or transfusion-related transmission of disease. We strongly recommend that nephrectomy be performed only with strict guidelines for very specific needs rather than as part of a general approach to a disease or preparation for renal transplantation. The endocrinological effects of an anatomically intact kidney outweigh any theoretical advantage to its indiscriminate removal.

SUMMARY

The anemia present in patients with chronic renal failure has been a well-recognized associated syndrome carrying its own morbidity. Much of the clinical expression of uremia—tiredness, lethargy, generalized malaise—may be the result of the anemia rather than the expression of some uremic toxin. The patients with less anemia, for example patients whose primary diagnosis is polycystic renal disease, better tolerate the end-stage uremic state than do other more anemic patients with chronic renal failure. Much of the cardiac dysfunction associated with uremia has also been related to anemia and shown to improve with correction of the hematocrit.

Since until recently there were no means to correct the underlying pathology for the anemia of chronic renal failure, attention had focused on the forms of anemia that were correctable. By minimizing blood loss and improving dialytic intervention, along with the use of anabolic steroids, chelating agents, and judicious blood transfusions, the anemic-uremic patient was able to continue to exist. The ability to correct this anemia totally through the replacement of the lacking hormone, erythropoietin, enhances the probability of further patient rehabilitation.

Since all the dialytic characteristics were developed for the anemic patient, will these also need to be restudied? Will the type of artificial kidney, the methods of dialytic support currently employed, or the equipment utilized need to be altered as the patient population begins to have a normal hematocrit? Will renal transplantation still offer the advantages over dialytic support once the chronic anemia is reversed? With the ability to treat some of the associated syndromes of the uremic state, the state of the patient with chronic renal failure is improving. With the correction of the anemia of renal disease, patients may begin to live on dialysis rather than merely exist in uremia.

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