THE TRAINING PROGRAM IN NEPHROLOGY AT THE YALE UNIVERSITY SCHOOL OF MEDICINE

Postdoctoral training in nephrology at Yale University had its origins in the 1940s within the Section of Metabolism created by Dr. John Peters. Since 1972, a distinct nephrology training program has existed, which is currently directed by Dr. Peter Aronson. The goal of the program is the training of academic nephrologists, and 70% of our graduates hold full-time faculty appointments.

We offer a combined clinical/research fellowship that is 3 (or more) years in duration and includes 1 year of full-time clinical training and 2 (or more) years devoted to clinical or laboratory research. Clinical-only and research-only fellowships are also available. There are currently 17 nephrology fellows, of whom 3 are receiving clinical training and the others are involved in research activities. Clinical training is based at Yale-New Haven Hospital and the West Haven VA Medical Center. Clinical fellows gain expertise in the diagnosis and management of patients with a broad array of nephrologic disorders including fluid and electrolyte disturbances, glomerulonephritis, interstitial nephritis, hypertension, acute and chronic renal failure, and intoxications. Fellows also receive intensive training in the care of patients receiving renal homografts. Training in the outpatient practice of Nephrology emphasizes continuity of care.

The 17 full-time faculty of the Section of Nephrology have scientific interests in the areas of epithelial transport, hypertension, hereditary renal disease, gene regulation, immunobiology, and acute renal failure. Clinical investigation emphasizes renal transplantation, disorders of potassium homeostasis, anemia of renal insufficiency, and health care policy. Research training is supported by a training grant from the National Institutes of Health. Yale University School of Medicine is unique in having a large group of distinguished faculty outside of the Section of Nephrology whose research interests include the study of the kidney and who also serve as research mentors for nephrology trainees. This provides fellows with access to a broad range of research projects within the fields of biostatistics, genetics, transplantation biology, physiology, and cell biology.

Posttransplant Erythrocytosis: Case Report and Review of Newer Treatment Modalities

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ABSTRACT
A case of posttransplant erythrocytosis in a 51-year-old diabetic man is described. This problem, which can occur in 5 to 15% of renal transplant patients, can result from a contracted plasma volume (diuretics, pressure natriuresis, or glycosuria) or from a true elevation in red blood cell mass. Once the diagnosis of true erythrocytosis is made by a radiolabeled red blood cell mass study, secondary causes such as hypoxia, liver disease, polycythemia rubra vera, renal artery stenosis, and cystic kidney disease should be excluded. Posttransplant erythrocytosis has only been observed in renal transplant recipients and appears to be more frequent with cyclosporine compared with azathioprine therapy. An inappropriately high level of erythropoietin has been described in some, but not all patients, suggesting stimulation of erythropoietin production as the mecha-
Posttransplant erythrocytosis is a well-known phenomenon in renal transplant recipients, occurring in approximately 5 to 15% of patients. Although usually transient and benign, erythrocytosis can follow a protracted course and, in some instances, precipitate thromboembolic complications. The underlying etiology of posttransplant erythrocytosis has been the subject of much investigation and is thought to be a failure of the normal regulation of erythropoietin production and perhaps erythroid stem cell response. In the following review, we discuss the possible mechanism of erythropoietin production with emphasis on newer modalities to treat the phenomenon.

**TABLE 1. Clinical data**

<table>
<thead>
<tr>
<th>Time Posttransplant</th>
<th>Hb (g/dL)</th>
<th>Hct (%)</th>
<th>MCV (fL)</th>
<th>BUN (mg/dL)</th>
<th>Creat (mg/dL)</th>
<th>Pred (mg/day)</th>
<th>Cs (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 wk</td>
<td>15</td>
<td>45</td>
<td>79</td>
<td>28</td>
<td>1.5</td>
<td>30</td>
<td>1000</td>
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<tr>
<td>1 month</td>
<td>16</td>
<td>50</td>
<td>79</td>
<td>33</td>
<td>1.5</td>
<td>25</td>
<td>750</td>
</tr>
<tr>
<td>3 months</td>
<td>15.5</td>
<td>51</td>
<td>77</td>
<td>32</td>
<td>1.5</td>
<td>17.5</td>
<td>400</td>
</tr>
<tr>
<td>6 months</td>
<td>16</td>
<td>54</td>
<td>72</td>
<td>23</td>
<td>1.3</td>
<td>15</td>
<td>300</td>
</tr>
<tr>
<td>12 months</td>
<td>14</td>
<td>51</td>
<td>67</td>
<td>32</td>
<td>1.7</td>
<td>10</td>
<td>250</td>
</tr>
<tr>
<td>18 months</td>
<td>14</td>
<td>47</td>
<td>75</td>
<td>25</td>
<td>1.6</td>
<td>10</td>
<td>250</td>
</tr>
<tr>
<td>24 months</td>
<td>16</td>
<td>53</td>
<td>79</td>
<td>28</td>
<td>1.4</td>
<td>10</td>
<td>200</td>
</tr>
</tbody>
</table>

Abbreviations: Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; Creat, creatinine; Pred, prednisone dose; Cs, cyclosporine dose.

**CASE REPORT**

J.A., a 51-yr-old man with type I diabetes mellitus, received a cadaveric renal transplant in August 1989. He had been on continuous ambulatory peritoneal dialysis for 1½ yr before this. Initial immunosuppression consisted of a single dose of methylprednisolone (500 mg) given in the operating room followed by a tapering dose of prednisone beginning on the first postoperative day, down to 10 mg/day at 1 yr. Cyclosporine was administered as a continuous iv infusion at 3 mg/kg per day until day 3, when an oral dose was begun to maintain specific RIA whole-blood trough levels between 150 and 250 ng/mL. The patient was originally placed on furosemide (40 mg/day), but this was discontinued at 3 months without any change in hematocrit. As can be seen by Table 1, his hemoglobin and hematocrit increased steadily after the transplant. He became symptomatic of erythrocytosis with headache and dizziness at 6 months posttransplant, at which time he received his first phlebotomy. Red blood cell mass, drawn after biweekly phlebotomies were initiated, was elevated at 34 mg/kg (normal, 23 to 33), and calculated blood volume was normal. Renal artery stenosis was excluded with a Doppler ultrasound of the transplanted kidney. Erythropoietin levels (measured by RIA) ranged between 16 and 47 mU/mL (normal, 8 to 21 mU/mL). He required phlebotomy once or twice a month in order to keep his hematocrit below 52. During this time, he developed severe iron deficiency with a serum ferritin level <7 ng/mL, an iron level of 8 mg/dL, and a total iron binding capacity level of 286 mg/dL. At 1 yr posttransplant, his mean corpuscular volume had dropped to 67 fL and he developed chelitis, which responded to the initiation of oral iron therapy. With iron therapy, he required phlebotomy more frequently, usually at weekly intervals. At 1½ yr after the transplant, theophylline therapy was started in an attempt to decrease adenosine-mediated erythropoietin production. However, the patient was unable to tolerate the drug without experiencing gas-
trointestinal symptoms and eventually refused to take it. The patient is now 2 yr posttransplant and continues to require frequent phlebotomy to avoid symptomatic erythrocytosis.

DISCUSSION

Our patient exemplifies a particularly severe case of posttransplant erythrocytosis. He has a true increase in red blood cell mass with elevated erythropoietin levels without any secondary cause such as renal artery stenosis. Furthermore, his increase in red blood cell production was not arrested with the development of severe iron deficiency. His erythrocytosis appeared to be due to unsuppressed erythropoietin production, but he was unable to decrease erythropoietin synthesis with theophylline because of intolerable gastrointestinal symptoms.

Post–renal transplant elevation of red blood cell mass and hematocrit is a well-described phenomenon in transplant recipients. The incidence varies in selected reports from 5 to 15% (1–6) to as high as 22% in one report (3). The onset of erythrocytosis can occur at several points in the posttransplant period ranging from 1 month up to 90 months (1,4,7). Although most cases of erythrocytosis are transient and benign, prolonged elevations of the hematocrit for longer than 5 yr have been described (1,7,8). Many transplant patients with transient erythrocytosis have an elevated hematocrit on the basis of decreased plasma volume rather than elevated red blood cell mass (2,8). The best examples of this phenomena include patients treated with diuretics, hypertensives with a pressure natriuresis, and diabetics with glycosuria, all of whom develop plasma volume contraction (2,8). Hence, the number of transplant patients with true erythrocytosis, defined as an elevated hematocrit and red blood cell mass, is significantly less than the figures quoted in series where the distinction was not made. When red blood cell mass was measured in patients with posttransplant erythrocytosis, the number with true erythrocytosis varied between 5 and 10% of all transplants (3,8,9).

The underlying etiology of erythrocytosis in those patients with a true increase in red blood cell mass is thought to be a failure of the normal regulation of erythropoietin production (4) or an altered sensitivity of erythroid stem cells to erythropoietin. Several factors to explain the pathogenesis have been suggested. Factors that have been implicated as etiologic include erythropoietin production from the transplant kidney as a result of renal artery stenosis, allograft rejection, or cyclosporine-induced renal ischemia, as well as native kidney erythropoietin synthesis in the setting of cystic disease (inherited or acquired), hydronephrosis, or chronic ischemia (1,10–12). Investigation of the remnant kidney as a culprit in erythropoietin production with resultant posttransplant erythrocytosis has inspired the use of remnant nephrectomy to cure the patient with persistent and long-standing erythrocytosis. Friman et al. performed bilateral nephrectomy on 22 patients with erythrocytosis of 13 months' mean duration (13). All but two of the subjects maintained normal blood counts at median follow-up time of 36 months. Of interest, seven of the patients had polycystic kidney disease whereas five had diabetic renal disease as the cause of ESRD. Both of these conditions are associated with the development of posttransplant erythrocytosis in some series and may in part explain the good response to remnant nephrectomy (1,5). Hepatic erythropoietin production, resolution of uremia-associated hyperparathyroidism, and use of androgenic steroids have also been cited as potential causes of posttransplant erythrocytosis (1,14,15). Indeed, there appears to be an association between erythrocytosis and the type of immunosuppression agent used. Posttransplant erythrocytosis appears to develop more frequently in cyclosporine-treated patients (9.4%) versus azathioprine-treated patients (3.7%) when evaluated in a prospective, randomized fashion (7). Furthermore, Besarab et al. noted an earlier onset of reticulocytosis in patients destined to develop erythrocytosis who were treated with cyclosporine as compared with azathioprine (6). The mechanism underlying erythrocytosis in cyclosporine-treated patients versus azathioprine-treated patients was thought to be twofold. First, azathioprine, via its myelosuppressant effect, inhibited red blood cell production at the level of the stem cell. Second, cyclosporine was able to stimulate erythropoietin production, via induction of renal hypoxia, through its effect on afferent arteriolar vasoconstriction and allow red blood cell precursors to mature as a result of its nonmyelosuppressive properties (7). A direct effect of cyclosporine on primitive red blood cell precursors to enhance erythrocytosis is also plausible (5).

Most recently, Qunibi et al. have implicated three factors as predictive of erythrocytosis in the posttransplant setting (9). These include (1) the level of serum creatinine at the onset of erythrocytosis; (2) the type of immunosuppression used; and (3) the duration of dialysis pretransplant. The probability of erythrocytosis increased as the creatinine value decreased, as time on dialysis pretransplant increased, and with double (prednisone and azathioprine or prednisone and cyclosporine) versus triple (prednisone, azathioprine, and cyclosporine) immunosuppression therapy. In this series, the overall incidence of erythrocytosis in the posttransplant period was 34% with double therapy versus 10.4% with triple therapy. The authors did not clarify whether the dose of cyclosporine was greater in patients on double versus triple therapy to explain these findings. They concluded that posttransplant erythrocytosis tended to develop in patients with better allo-
graft function and less immunosuppression. In contrast to the findings reported by Qunibi and colleagues, a randomized prospective trial comparing double- and triple-drug therapy in primary cadaveric renal transplants failed to show a dramatic difference in hematocrit between the two groups (15). Mean hematocrits were significantly but only mildly higher in double-drug therapy (43.3 ± 0.7) as compared with triple-drug therapy (41.1 ± 0.8) at 1 yr posttransplant. In that study, there was no significant difference in cyclosporine or steroid dosage between the two groups after 3 months posttransplant. It may be that the frequency of erythrocytosis is higher with double versus triple therapy if the dose of cyclosporine is higher, although this conclusion is not stated by either author (3, 1.5). In either case, the frequency of erythrocytosis as reported by Qunibi et al. is much higher than that described in other reports.

Many patients with posttransplant erythrocytosis have either an elevated erythropoietin level, as was seen in our patient, or a level higher than expected for the prevailing hematocrit. Indeed, over 30% of renal transplant patients monitored for more than 2.5 months will stabilize at erythropoietin levels higher than normal, although only 13% will ultimately develop erythrocytosis (16). Whether a malfunction in the erythropoietin-hematocrit feedback circuit explains all cases of posttransplant erythrocytosis or whether increased sensitivity to the action of erythropoietin also contributes to the mechanism deserves further study.

Specific therapy for posttransplant erythrocytosis and the need for close follow-up depends on the exact cause identified. An outline for a potential work-up is presented in Table 2. The idea is to distinguish true increases in red blood cell mass from cases of erythrocytosis due to contracted plasma volume. Once true posttransplant erythrocytosis is diagnosed, secondary causes of polycythemia should then be excluded. Erythropoietin levels are usually elevated or at least not suppressed for the level of the hematocrit in most patients with posttransplant erythrocytosis.

A serious complication of erythrocytosis is an increased incidence of thrombotic events, including phlebitis, cerebrovascular accident, and pulmonary embolism, which have been observed in some but not all series (1.7). In view of the potential thromboembolic complications associated with erythrocytosis, which can follow a prolonged course as seen in our patient, it is imperative to maintain a hematocrit below 50 to 55%. Therefore, patients who receive diuretics benefit from the discontinuation of these medications, whereas adequate blood pressure and glucose control in hypertensives and diabetics, respectively, allows correction of excessive extracellular fluid loss. In patients with documented red blood cell mass expansion without a treatable secondary cause, phlebotomy remains the most effective modality to lower the hematocrit but requires frequent monitoring, invasive needle punctures, and the risk of iron deficiency anemia, as developed in our patient.

Bakris et al. introduced oral theophylline as an effective intervention for the elevated hematocrit and red blood cell mass in renal transplant patients (9). Adenosine, formed from the degradation of ATP during hypoxia, stimulates erythropoietin production via stimulation of A2 adenosine receptors with subsequent activation of adenylate cyclase, formation of cAMP, and phosphorylation of enzymes (17,18). Theophylline, at a dose of 8 mg/kg per day, can nonspecifically antagonize the effect of adenosine at the A2 receptor and inhibit erythropoietin production. In the study of Bakris et al., eight transplant patients with baseline hematocrits of 5.0 ± 0.4 and erythropoietin levels of 60 ± 14 U/L were successfully treated within a 2-month period with reduction to levels of 0.46 ± 0.03 and 9 ± 7 U/L, respectively. Recovery upon withholding of theophylline to baseline values occurred within 8 wk, whereas rechallenge decreased levels to similarly noted reductions again within 2 months. Associated side effects included headache, nervousness, insomnia, and worsening hypertension. Our patient could not tolerate theophylline because of intolerable gastrointestinal symptoms even at low doses. Such symptoms may also limit its efficacy in other patients.

More recently, angiotensin-converting enzyme inhibitors (ACEI) have been reported to lower the hematocrit in both chronic hemodialysis patients and renal transplant recipients treated for hypertension (18,19). Hirakata et al. reported the development of significant anemia in 9 of 12 stable, hypertensive chronic hemodialysis patients treated with captopril.

**TABLE 2. Steps in the evaluation of posttransplant erythrocytosis**

<table>
<thead>
<tr>
<th>Measure Red Blood Cell Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>If elevated, proceed to Step II</td>
</tr>
<tr>
<td>If not elevated, discontinue diuretic, control hypertension or hyperglycemia to correct the &quot;spurious erythrocytosis&quot;</td>
</tr>
</tbody>
</table>

| Arterial Blood Gas or O2 Saturation; Liver Function Test; Feel for Spleen |
| To rule out polycythemia due to hypoxia, liver disease, or polycythemia vera |
| Doppler Ultrasound of the Kidney Transplant and Native Kidneys |
| To rule out secondary polycythemia due to renal artery stenosis or cystic kidneys |

| Measure Erythropoietin Level |
| Elevated or at least not suppressed in posttransplant erythrocytosis |
PPl
ATP cAMP
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(mean dose, 27.6 mg/day) with no other obvious cause for a decrease in the hemoglobin, hematocrit, and red blood cell count (18). Upon discontinuation of captopril, the patients’ hematologic parameters returned to baseline within 4 months and remained stable when monitored for up to 10 months. Of interest, two of the three patients who did not develop anemia were receiving the anabolic steroid methenolone enanthate (Decadurabolin; Organon, West Orange, NJ; 100 mg/wk), which is thought to improve erythropoiesis via an increased erythropoietin production or stimulation of bone marrow cells. Similarly, Vlahakos et al. observed progressive anemia unrelated to other etiologies in renal transplant recipients treated with enalapril at a mean dose of 9.0 ± 2.4 mg/day (19). Thirty-seven percent (10 of 27) of the posttransplant recipients were well matched with patients who did not become anemic except for their baseline hematocrit (0.42 ± 0.01 in the anemic group versus 0.36 ± 0.02 in the nonanemic group). Anemia developed in the first group (hematocrit, 0.42 ± 0.01 to 0.33 ± 0.01) within 12.3 ± 0.9 wk after the administration of enalapril. Discontinuation of the medication brought about an increase in hematocrit to nearly baseline levels (0.40 ± 0.01) within a mean of 9.1 ± 0.7 wk. The authors offered no explanation as to why some but not all transplant patients developed anemia with enalapril.

More recently, the effect of ACEI has been used to treat posttransplant erythrocytosis. Islam and co-workers prospectively treated seven erythrocytotic transplant recipients with 75 mg/day of captopril with impressive results (20). They were able to demonstrate a significant reduction in red blood cell mass (42 ± 4 versus 31 ± 5 mL/kg), red blood cell count (64.9 ± 3 versus 49.8 ± 9 x 10⁶/mm³), hematocrit (56.4 ± 4.6 versus 44.7 ± 5%), and hemoglobin (18.1 ± 1.5 versus 15 ± 1.6 g/dL) within 5 to 45 days of the commencement of captopril therapy. Erythropoietin levels, however, did not decrease significantly (23 ± 9 versus 18.6 ± 4 mU/mL) with captopril therapy. Follow-up ranging from 1.5 to 6.8 months revealed maintenance of this hematologic effect. There were no serious complications related to therapy with either of these ACEI, and no cases of hyperkalemia or deterioration in renal function were observed. Similar results have been observed in 12 patients treated with enalapril at doses starting at 2.5 to 5 mg/day with titration as necessary for blood pressure control (21). A decrease in hematocrit from 0.57 ± 0.01 to 0.47 ± 0.01 within 1 to 9 months was noted. Therapy was tolerated well with no evidence of renal deterioration or occurrence of hyperkalemia. Follow-up by this same group at 1 yr revealed maintenance of a lowered hematocrit (0.46 ± 0.01) with enalapril at doses between 2.5 and 10 mg/day and no evidence of toxicity (21).

If posttransplant erythrocytosis is related to unopposed erythropoietin production, treatment of this phenomenon depends on understanding the mechanism of erythropoietin production. The major source of erythropoietin production in humans is the kidney, whereas the liver, especially the Kupffer cell, is the primary extrarenal site of production (22). Liver production of erythropoietin is prominent in situations where hepatic injury or ischemia occurs. Fisher’s model for renal erythropoietin production postulates that hypoxia at the level of the kidney for whatever cause (anemic, ischemic, or hypobaric) initiates a cascade of events triggered by oxygen deprivation, which stimulates synthesis and/or secretion of erythropoietin (22). Hypoxia stimulates erythropoietin production via the adenylate cyclase cascade (Figure 1). Regardless of the proximate cause, hypoxia initiates the generation of adenosine, prostaglandins (PG) (specifically, PGE₂, PGF₂, and 6-keto-PGE₁), and β-adrenergic agonists (23,24). Each of these factors then acts through its specific receptor to activate a stimulatory G protein that increases adenylate cyclase activity and subsequent generation of cAMP.

Figure 1. Steps in erythropoietin (EPO) synthesis and the level at which the ACEI, theophylline, and propranolol may act to decrease erythropoietin production. Gs, stimulatory G protein; RBC, red blood cell; AII, angiotensin II; Pi, orthophosphate; PPI, pyrophosphate.

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adenosine receptor (Figure 1). In addition, nonselective adrenergic agonists act via \(\alpha_2\) adenosine receptors, whereas \(\beta\)-adrenergic agonists act via \(\beta_2\) adrenergic receptors. Although PG activate adenylate cyclase, their specific receptor is not known but may be a \(\beta_2\) receptor or the result of stimulation of a \(\beta\)-adrenergic mediator (23). It is likely that hypoxia acts to increase erythropoietin via multiple mediators depending on the degree of the hypoxic stimulus. In view of the major role adenylate cyclase plays in erythropoietin production, it is logical that theophylline has been shown to blunt posttransplant erythrocytosis via inhibition of the \(\alpha_2\) adenosine receptor (Figure 1). In addition, nonselective \(\beta\)-adrenergic blockers (propranolol) have been shown to reduce erythropoiesis in animals and may be useful to reduce the hematocrit in the erythrocytic transplant recipient via inhibition of the \(\beta_2\) receptor (25).

It is less clear how erythropoietin is modulated by the renin-angiotensin system. Early animal data supported a role for both angiotensin and angiotensin II, via induction of renal hypoxia, in the stimulation of erythropoietin production (26). Hepatic production of erythropoietin in anephric rats infused with angiotensin II supported a role for the liver in erythropoiesis (27). We can only speculate that ACEI may act to improve renal and/or hepatic blood flow and shut off hypoxia-induced erythropoietin production (Figure 1). It is unlikely that ACEI act by modulation of PG synthesis because data demonstrate that PG stimulation occurs with captopril but not with enalapril (28). Other possible mechanisms include inhibition of the effect of angiotensin II on red blood cell precursors, inhibition of erythropoietin’s effect on stem cells, or increased levels of bradykinin formed during blockade of kinin degradation. Currently, there are no data to support these mechanisms.

In summary, most cases of posttransplant erythrocytosis appear to be due to contraction of the plasma volume. In cases where a true increase in red blood cell mass is documented, disordered regulation of erythropoietin feedback appears to be the mechanism. As outlined in Table 3, a number of therapeutic options are now available to treat this phenomenon. Drugs that inhibit the synthesis of erythropoietin such as theophylline and the ACEI have been used and appear to be safe in the transplant population. Propranolol may have a role in this setting but requires further investigation. However, phlebotomy remains the mainstay of therapy when the patient is symptomatic or when the addition of another new drug is problematic. Last, in patients with prolonged erythrocytosis unresponsive to conservative therapy, bilateral nephrectomy of the remnant kidneys may provide cure for the erythrocytosis.

<table>
<thead>
<tr>
<th><strong>Spurious Erythrocytosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Control hypertension</td>
</tr>
<tr>
<td>Control hyperglycemia/glycosuria</td>
</tr>
</tbody>
</table>

**True Erythrocytosis (Increase in Red Blood Cell Mass)**

**Medical therapy**
- Phlebotomy (hematocrit < 50 to 55)
- Captopril (75 mg/day) (20)
- Enalapril (2.5 to 10 mg/day) (21)
- Theophylline (8 mg/kg per day) (9)
- Propranolol (? dose)
- Native kidney nephrectomy (13)

**REFERENCES**


THE EFFECTS OF WATER IMMERSION

... if the blood be thus driven (by the bath) from the external and internal parts, what becomes of the blood? The heart and great vessels, it would seem, must be burdened. Such is to a degree the case; and it is perhaps the stimulus of this fullness and distention or its action on the elasticity of those great vessels and the heart that constitutes the reaction (which leads forth the urine in abundant effusion). Such overloading of the heart and great organs would be dangerous in every case if the volume of the blood remained the same.

Philadelphia: Lloyd P.
Smith Press; 1847.