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Erythropoiesis in Anephric Man*

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Recent progress in the understanding of the physiology of erythropoiesis has led to definition of the kidney's importance as a source of erythropoietin. Although Erslev (1, 2) did not document erythropoietin production in rabbit kidney *in vivo*, Jacobson, Goldwasser, Fried, and Plzak (3), Reissmann, Nomura, Gunn, and Brosius (4), and Naets and Heuse (5, 6) clearly managed to define the kidney as an important regulator of erythropoiesis in rats and dogs. The studies in the dog were very convincing, for Naets (5) described nearly total and permanent erythroid aplasia after bilateral nephrectomy.

Increasing ability to manage chronic renal failure and the renoprival state, by both renal transplantation and intermittent, long-term hemodialysis, has offered the opportunity to examine the possible role of the kidney in human erythropoiesis. Several uremic patients have undergone bilateral nephrectomy, remaining renoprival for from 2 to over 400 days before suitable homotransplantation could be performed. One individual, in whom a solitary kidney was accidentally removed, was subsequently transferred to the Peter Bent Brigham Hospital and studied before transplantation. In addition, erythropoiesis was measured in two patients who were considered for, but did not undergo, bilateral nephrectomy. The

erythropoietic status of these uremic and anephric individuals forms the basis of this report, the results of which fail to demonstrate complete dependence of erythropoiesis on the presence of renal tissue in man.

Methods

1) *Patients.* A total of six patients was investigated (Table I). All were hospitalized at the Peter Bent Brigham Hospital. Four patients were maintained in the renoprival state for periods of 2 to 420 days. Patients 1 and 2 had bilateral nephrectomy in preparation for renal transplantation. In the former, nephrectomy was carried out in separate stages. Patient 3 underwent bilateral nephrectomy in separate stages because of accelerated, unrelenting hypertension associated with chronic pyelonephritis. Patient 4, previously nonazotemic, was accidentally rendered renoprival by removal of a solitary kidney. He was transferred to the Peter Bent Brigham for a renal homograft. Patients 5 and 6 were studied with both kidneys *in situ*, while being maintained on a chronic hemodialysis program.

2) *Treatment.* Hemodialysis, required by all patients with the exception of Patient 1, who was maintained by peritoneal lavage, was generally carried out twice weekly. Patient 3 was hemodialyzed for several hours five mornings each week. Dialysis was performed utilizing the Travenol twin coil artificial kidney. Frequently only one coil was used, eliminating the need for exogenous blood. The number of hours of dialysis and the bath composition were dependent upon the individual patient's need. Dietary salt, water, and protein were individually varied. In general, moderate protein and sodium restrictions were imposed, and all patients kept their fluid intake below 1 L per day.

3) *Hematologic investigations.* Hematopoiesis was investigated during the anephric state in four of the patients. The diseased kidneys of Patients 5 and 6 remained *in situ*. Hematocrit, hemoglobin concentration, reticulocyte percentage, leukocyte count, and platelet count (phase) were measured with standard techniques (7). Plasma iron turnover and red cell production rates were estimated with Fe^{59} by techniques previously described (8). *In vivo* external scanning studies of Fe^{59} localization in liver, spleen, and sacrum, and Cr^{51} red cell survival studies were performed in four patients.

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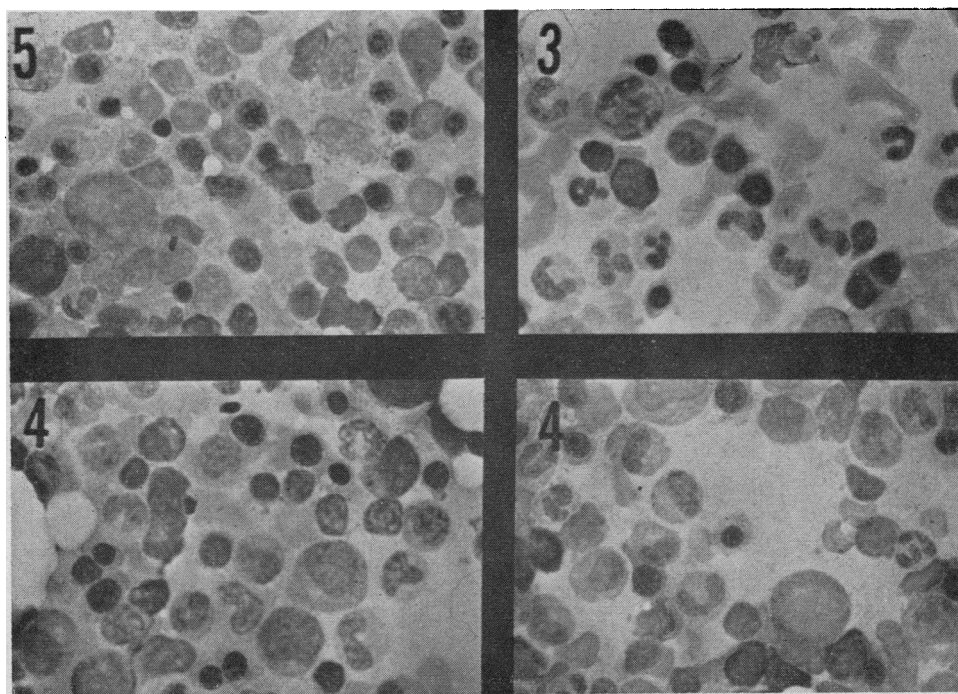


FIG. 1. SELECTED OIL IMMERSION VIEWS OF THE BONE MARROW ASPIRATES FROM PATIENT 5, WHOSE DISEASED KIDNEYS REMAINED IN SITU; PATIENT 3, 28 DAYS AFTER NEPHRECTOMY; AND PATIENT 4, 11 (left) AND 131 (right) DAYS AFTER NEPHRECTOMY. Erythroid precursors are easily demonstrable.

The time between hemodialyses was never greater than 7 days; therefore the Cr^{sc} survival measurements cannot be considered accurate.

Bone marrow aspirates were stained with the Jenner-Giemsa technique as well as with ferrocyanide, the latter for estimate of iron stores.

4) *Effects of hypoxia.* Attempts to provide controlled hypoxic stimulation of erythropoiesis in Patients 3 and 4, by exposure to a gas mixture of low oxygen tension, were unsuccessful. The patients were unable to tolerate the confinement necessary to complete these studies. Hypoxia was induced in Patient 3 by an intercurrent illness, and estimates of erythropoiesis were performed before, during, and after this event (see Results).

5) *Erythropoietin assays.* Plasma erythropoietin levels were estimated both at rest and before and after the induction of anoxia. Alcoholic extracts (9) of 100-ml samples of plasma were assayed in polycythemic mice (10). Both Fe^{59} uptake by circulating erythrocytes and the reticulocyte responses were measured. In neither bioassay system were the erythropoietic activities of these plasma extracts greater than those of control plasma extracts or of saline.

Results

1) The peripheral blood counts of the patients at the time of their initial bone marrow and isotope studies are shown in Table II.

TABLE I
Azotemia and kidney weight

Patient	Age	Sex	Disease	Renoprival period	Blood urea nitrogen	Total kidney weight	Duration of azotemia before initial study
				days	mg/100 ml	g	
1	36	M	Glomerulonephritis	2	112	240	8 mo
2	17	F	Glomerulonephritis	30	40-100	130	7 yr
3	35	M	Pyelonephritis	420	30-70	200	20 yr
4	34	M	No prior renal disease	145	25-175		10 days
5	29	M	Pyelonephritis		50-125	125 (autopsy)	3 yr
6	45	M	Glomerulonephritis		50-125		6 yr

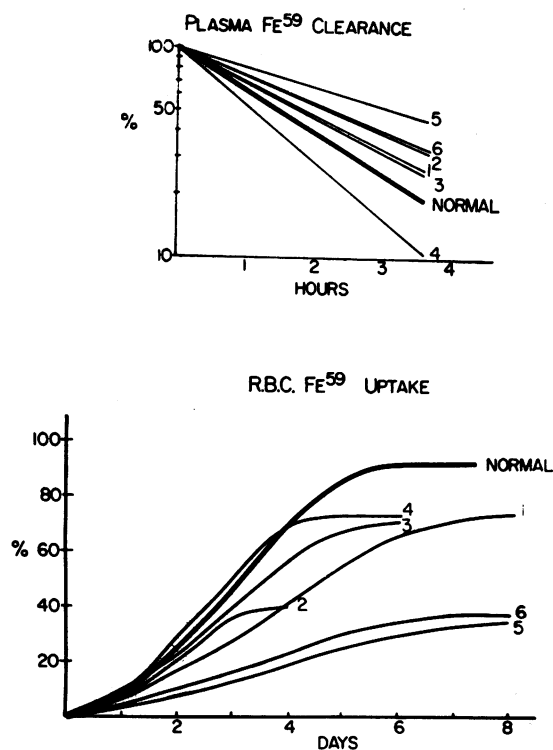


FIG. 2. THE PLASMA Fe^{59} CLEARANCE AND RED CELL Fe^{59} UPTAKE CURVES IN THE ANEPHRIC AND UREMIC PATIENTS. Heavy lines denote the average normal values usually observed.

2) Cytologic examinations of bone marrow from these patients were not of predictive value when related to measurements of effective red cell production with Fe^{59} . Some selected oil immersion fields from Patients 3, 4, and 5 are shown in Figure 1. Contrary to results in dogs (5, 6, 11), erythroid cells were apparent in all of the preparations, but the marrow smears of these patients tended to be hypoplastic. The marrow iron stores were uniformly increased.

3) Table III presents the data derived from the studies with Fe^{59} and Cr^{51} . Figure 2 portrays the plasma Fe^{59} clearance and red cell Fe^{59} uptake curves. Figure 3 shows the results of *in vivo* scanning of liver, spleen, and sacrum in Patients 2, 3, 4, and 5. These data are in no way distinctive from data derived from similar examinations of uremic individuals (12). Erythropoiesis was suppressed, but the degree of suppression of erythrocyte production was certainly no more striking than that observed in patients with chronic renal disease. In fact, Patient 5, whose kidneys remained *in situ*, had one of the poorest red cell production rates of the group. In addition, Patient 4, who had been uremic for only 10 days, had an increased rate of erythropoiesis that failed to compensate for his short erythrocyte survival. It should be emphasized that the patients had lost varying amounts of their body fat; this alteration in body composition might result in some overestimation of the red cell production rate expressed as milliliters per kilogram per day.

The results of serial studies of Patient 3 showed that this anephric patient could enhance his rate of erythropoiesis. Two attempts were made to examine the effects of hypoxia in this patient. The first, on days 119 and 120 after nephrectomy, was a controlled study that was poorly tolerated by the patient. Hypoxia was intermittent. No effect on plasma or red cell iron turnover could be demonstrated, nor were plasma erythropoietin levels affected. On day 329, 1 week before the next measurement, the patient underwent subtotal gastrectomy because of persistent hemorrhage from a duodenal ulcer. He received 16 U of blood. On day 334 he became progressively hyperpneic and dyspneic; his arterial PO_2 and hemoglobin

TABLE II
Hematologic data

Patient	Days post-nephrectomy	Hematocrit	Hemoglobin	Leukocytes	Platelets	Reticulocytes	Blood urea nitrogen
		%	g/100 ml	/mm ³	/mm ³	%	mg/100 ml
1	2	28	8.7	23,075		1.0	91
2	16	25	7.5	8,562	112,000	0.8	24
3	27	27	9.2	11,400	232,500	2.2	89
4	9	21	6.7	13,523		3.0	166
5		19	5.7	6,540	240,000	0.5	91
6		22	7.0	4,344	345,000	1.0	104

TABLE III
Erythrokinetics

Patient	Days post-nephrectomy	Plasma				Red cells				Arterial oxygen				
		Iron $\mu\text{g}/100\text{ ml}$	Iron-binding capacity $\mu\text{g}/100\text{ ml}$	Iron turnover $\text{mg}/\text{kg}/\text{day}$	Fe^{59} $t_{1/2}$ hours	Volume ml/kg	Fe^{59} uptake %	Production $\text{ml}/\text{kg}/\text{day}$	Renewal $\%/ \text{day}$	Volume ml/kg	Cr^{51} $t_{1/2}$ days	Hemato- crit %	Po_2 mm Hg	Satu- ration %
1	2	68		0.29	1.92	49	70	0.20	1.15	17.4		26		
	16	86	262	0.37	2.24	57.5	39	0.14	0.74	19		25		
2	28	56	284	0.31	1.92	63	74	0.23	1.12	21.0	25	25		
	119	135	414	0.44	2.88	56	48	0.21	1.04	20.6	27	27	96	98
	120	113	396	0.44	2.78	56	48	0.21	1.04	20.6	27	27	53	88
3	223										13	21		
	336	160	240	1.01	1.75	67	45*	0.46	1.5	31.4		32	47	83.2
	363	66	456	0.52	1.1	51.7	69	0.36	1.8	20.6		28.5		
4	11	112	282	0.74	1.08	43	75	0.56	3.3	16.9	14	28		
	47	64	420	0.33	1.75	54				23		30		
	70					45				13.7		23		
5	131	66	252	0.54	1.2	59	68	0.37	1.7	21.6		27.5		
		146	231	0.34	3.4	48.5	36	0.12	0.93	13.2	13	21.4		
6		166	240	0.66	2.5	60	35	0.23	1.15	20	16	25		
	Normal	50-150	150-300	0.25-0.35	1.2-2	35-45	80-100	0.22-0.32	0.8-1.0	25-32	26-35			

* In 4 days.

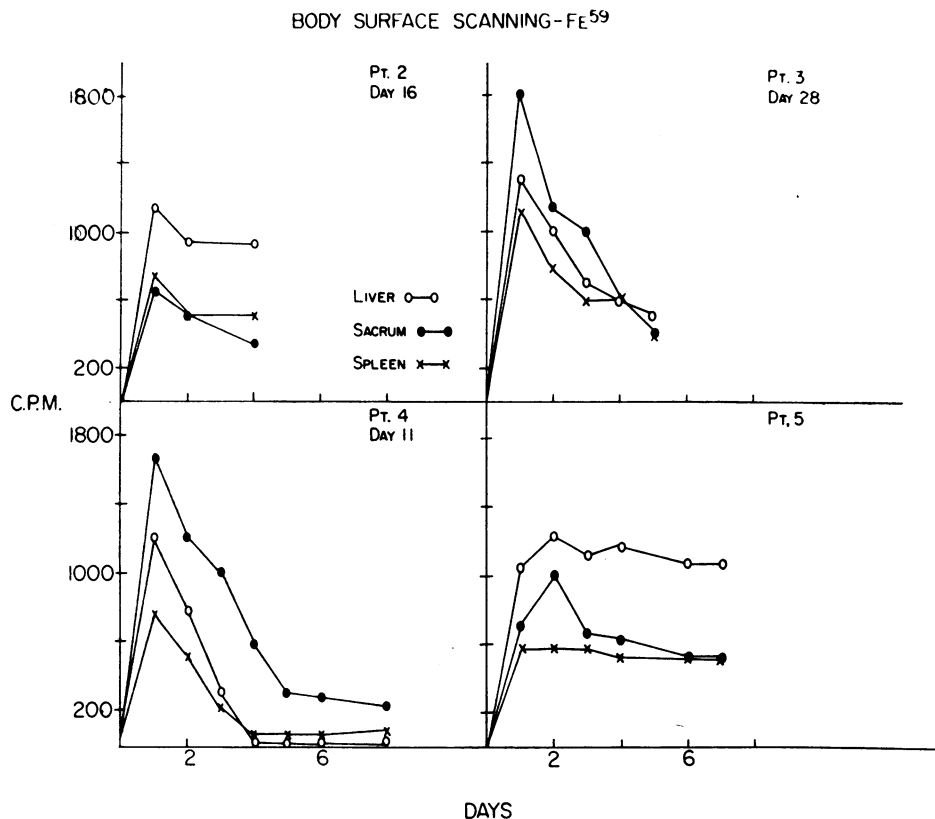


FIG. 3. BODY SURFACE SCANNING OF Fe^{59} RADIOACTIVITY OVER THE LIVER, SPLEEN, AND SACRUM OF PATIENTS 2, 3, 4, AND 5. COUNTS ARE CORRECTED FOR THE RADIOACTIVITY DUE TO BLOOD FLOW.

oxygen saturation were at the low levels recorded in Table III. The cause of this disorder was not determined. The measurements of erythropoiesis on day 336 were performed approximately 30 hours after onset of these symptoms and revealed a marked increase in red cell production over previous recorded values. No erythropoietin activity was detected in his plasma. It is important to stress that the high red cell volume measured on day 336 resulted from transfusion therapy. In addition, the higher estimate of red cell production resulted from the increased plasma volume, which was associated with a noteworthy increase in the serum iron concentration and a faster rate of disappearance of Fe^{59} from the plasma. The hypoxia gradually improved. On day 363, after 2 weeks of freedom from respiratory symptoms, erythropoiesis was studied once again. The red cell production had declined somewhat but not to the levels previously measured in this patient. On renoprival day 398, this patient de-

veloped severe pericardial tamponade due to a bloody uremic pericardial effusion. This hypoxic stimulus persisted for 24 hours, until it was relieved by partial pericardectomy. Reticulocyte counts of 8 to 10% were observed during the first two postoperative days.

Examination of red cell production was repeated in Patient 4 on renoprival day 131. This study was accompanied by a bone marrow examination and was carried out 2 weeks after the patient's last transfusion. In addition, he had been dialyzed for the previous 2 weeks on the artificial kidney without bank blood priming of the coil. Since the turnover time of exogenously administered erythropoietin is thought to be no greater than 1 to 2 days (13) and may be much more rapid (9), it is very unlikely that any exogenous erythropoietin was available to the patient during this study. The bone marrow was somewhat hypoplastic, but the myelopoietic:erythropoietic ratio was 3:1, and the measurement of red cell

production with Fe^{59} revealed a slightly increased rate of red cell production.

The results of the bone marrow and ferrokinetic measurements in Patient 6, whose kidneys remained *in situ*, were similar to those of the anephric patients.

Discussion

The kidney appears to be an important source of erythropoietin in dogs, rabbits, and rats (3-6, 11, 14). Goldfarb and Tobian (15), who have reviewed the rodent juxtaglomerular apparatus as a source of erythropoietin, postulate the existence of at least two rodent renal erythropoietins. Erythropoietic function has been ascribed (16) and denied (17) to angiotensin II. The growing literature describing erythrocytosis in association with renal cysts and tumors (18-20) also supports the importance of the kidney as a source of this hormone. On the contrary, reports concerning erythrocytosis with or without increased erythropoietin production in association with cerebellar and hepatic tumors in man (21, 22) indicate that extrarenal neoplastic tissues may also influence erythropoiesis. Erslev's studies of the rabbit (1, 2) firmly demonstrate lack of dependence of erythropoiesis on the kidney in this animal. In addition, studies of erythropoietic activities in non-neoplastic extrarenal tissue extracts (23, 24) and of erythropoietic responses in anephric rabbits and rats (24, 25) have been interpreted to indicate a less restricted site of erythropoietin synthesis and broader control of erythropoiesis. Indeed, recent evidence indicates that certain products of red cell hemolysis may themselves contribute to stimulation of erythropoiesis (26).

None of our patients had detectable erythropoietin in extracts of their plasma. However, the development of more sensitive methods might reveal its presence. Gallagher, McCarthy, and Lange (27) and Naets and Heuse (6) have also noted that anemic uremics usually have no erythropoietin detectable in their plasma. Although these workers interpret their data to support the view that "the erythroid failure of uremia is due to inability of the diseased kidney to produce erythropoietin" (27), it is clear that many other plasma inhibitors created in the uremic syndrome

may combine to reduce the detectable erythropoietin in a crude plasma extract. In addition, serious interference with the morphology of HeLa (28) and bone marrow cells (29), as well as chemical interference with erythrocyte metabolism in uremia (30-32), has been described.

Although Choremis, Megas, Liaromati, and Michael (33) maintain that marrow erythroblastopenia occurs in cases of acute glomerulonephritis without azotemia, review of their cases reveals only two such patients, and one of these was only mildly anemic. Moreover, the relationship between azotemia and erythropoiesis is highly variable. Some patients are observed with acute renal cortical necrosis, marked azotemia, and hemolytic anemia with reticulocyte counts as high as 15 to 30%. Others with mild azotemia are anemic due to depressed erythropoiesis. In addition, Van Dyke, Keighley, and Lawrence (34) have studied one patient with mild anemia secondary to chronic glomerulonephritis. This patient failed to exhibit an erythropoietic response to a 3-day course of erythropoietin at a dose that was considered large enough to produce a significant erythropoietic response in normal individuals.

The results of study of the anephric men described here, and of a similar study performed several years ago by Rees and his co-workers (35), support a broad view of the regulation of erythropoiesis in man. The Cr^{51} measurements, although brief, agreed with previous findings of hemolysis in uremia and particularly in the renoprival state (36). The Fe^{59} studies showed that the anephric patients, in common with other uremics, all exhibited relative bone marrow failure in that they did not maintain an adequate marrow response to the shortened erythrocyte survival and low total red cell volume. But it must be emphasized that the anephric patients produced red cells as well as do uremic individuals whose kidneys remain *in situ*. Furthermore, anephric man may increase his red cell production rate well above normal, as demonstrated by Patients 3 and 4. These facts provide strong evidence against complete dependence on renal tissue for red cell production in man. It should also be noted that the anephric patients maintained adequate circulating leukocytes and platelets.

Our studies do not settle the question of the source of erythropoietin, since the hormone was not detected at any time. If erythropoietin is necessary for any erythropoiesis in man, the kidney is certainly not its sole source. On the other hand, erythropoietin may not be necessary for the stimulation of the rates of erythropoiesis observed in these patients.

The studies of anephric patients with long histories of chronic uremia must be interpreted cautiously. The fact that in these patients erythropoiesis was no worse than in severe chronic uremics, such as Patients 5 and 6, should be evaluated in the light of the physiological significance of nephrectomy in such patients. A review of the total kidney weight (Table I) and renal morphology of the chronic uremics and of the renoprival chronic uremics reveals that the surgeon usually removed mere remnants of renal tissue. These anephric patients had performed a gradual and partial autonephrectomy during the years before surgery. If the kidney is a prime source of erythropoietin, whatever secondary sources of erythropoietin might have been available were allowed adequate time to rise. On the contrary, Patient 4 and the patient studied by Rees and his colleagues (35) had been entirely normal before nephrectomy. The increased rate of erythropoiesis observed shortly after nephrectomy in these patients militates more strongly against an exclusive renal role than do the results in the other patients.

Summary

Erythropoiesis has been measured in four renoprival patients. These patients maintained hemoglobin concentrations within the range of 7 to 9 g per 100 ml of blood in the presence of mild hemolysis. Further, the response of one patient to hypoxia, although diminished, persisted in the absence of the kidney. In another patient, an increased rate of red cell production was noted. It follows that man is not totally dependent upon a renal source of erythropoietin for his red cell production.

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