ERYTHROPOIETIN IN ACUTE ERYTHROBLASTOPENIA OF SICKLE CELL ANEMIA

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In 1948 Owren made a significant observation in hereditary spherocytosis. He noted a temporary bone marrow hypoplasia predominantly involving the erythroid elements and applied the term "aplastic crisis" to this condition.[1]

Following Owren's observation, aplastic crises were also demonstrated in other types of hemolytic conditions, namely sickle cell anemia, thalassemia major, paroxysmal nocturnal hemoglobinuria, acquired hemolytic anemia, hereditary elliptocytosis, and congenital nonspherocytic hemolytic anemia.[2,3] Similar crises have also been observed in hematologically normal individuals, precipitated by infection, drug toxicity, and allergy.[3,4] "Acute erythroblastopenia" should be the term of choice as real pancytopenic states are exceedingly rare.[5]

Such a crisis in sickle cell anemia was first described by Singer, et al.[6] It was considered a rare event in this disease, and indeed, until 1960, there were only 14 reports of aplastic crisis in sickle cell anemia.[3] Approximately 27 additional cases have appeared in the literature since that time.

The purpose of the present report is to describe two more cases of sickle cell anemia with acute erythroblastopenia, and particularly to stress erythropoietin levels that to our knowledge have not previously been reported during such crises.

Material and Method

The study consisted of the determination of erythropoietin levels in two cases of sickle cell anemia during acute erythroblastopenia. The clinical and laboratory data regarding the erythroblastopenic crises are summarized in Tables 1 and 2.

From Ankara University Faculty of Medicine, Ankara, Turkey, The patients were seen at St. Louis Children's Hospital, St. Louis, Missouri, U.S.A.

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TABLE 1
CLINICAL DATA IN ERYTHOBLASTIC CRISES

Case	Age	Race/Sex	Previous Illnesses	Presenting Symptoms
1	5 1/2	N/M	Upper respiratory infection 2 weeks before	Fever 38.50 Marked Pallor Lethargy Incoherence No infection diagnosed
2	7	N/M	Tonsillitis 2 weeks before	Fever 39° Pallor Listlessness Pneumoccol URI

TABLE 2
LABORATORY DATA

Case	Hb gm.%	Hct. %	Retic. %	WBC	Platelets	Bilirubin mg.% Total/ Direct	Bone Marrow	
							M.E	remarks
1	4.5	14	0.4	13.105	Numerous on films	1.5/0.4	70:1	Markedly depressed erythropoiesis a few giant proerythroblasts present.
in 2 days	3.3	10	0	—	"	—		
2	3.8	13	0.1	14. 101	"	0.67/0.27	16:1	Normocellular, depressed erythropoiesis slight increase in plasma cells.

Method: Blood specimens were collected from the patients and heparinized. The plasma was removed and kept frozen until used. Plasma was assayed without further treatment and erythropoietin was measured by the Fe^{59} red cell incorporation method using starved Sprague-Dawley rats weighing 150 to 200 grams.[8] Ten rats were used for each assay: five as controls and five as test animals. Twenty-four and 48 hours after the onset of fasting, the rats were injected subcutaneously with 0.5 ml of the test plasma.[9] Control animals were injected with 0.5 ml of saline solution. Twenty-four hours after the second injection, one microcurie of Fe^{59} in the form of ferrous citrate was injected intravenously into a tail vein. Eighteen hours later, a blood sample was taken from the heart, under light anesthesia, and counted in a well type scintillation counter. The per cent of Fe^{59} incorporated into the red blood cells was calculated, assuming a blood volume of five per cent of body weight, and the results were expressed

as the average per cent uptake of Fe^{59} by the animals in each assay. The same method was used for determination of urinary erythropoietin levels.

Results and Discussion

Erythroblastopenic crises are usually self-limiting and last briefly from seven to fourteen days.[1,2] In hematologically normal persons such crises result in only mild anemia which may go unnoticed. However, an abrupt cessation of red cell production may prove fatal[1] in the presence of pre-existing hemolysis. Therefore, early recognition of an erythroblastopenic crisis in sickle cell anemia and in other hemolytic anemias is of clinical importance. The patients whose cases are reported here were admitted to the hospital and made complete recoveries as indicated by the increase in reticulocytes on the eighth and seventh days after admission respectively (Figures 1 and 2).

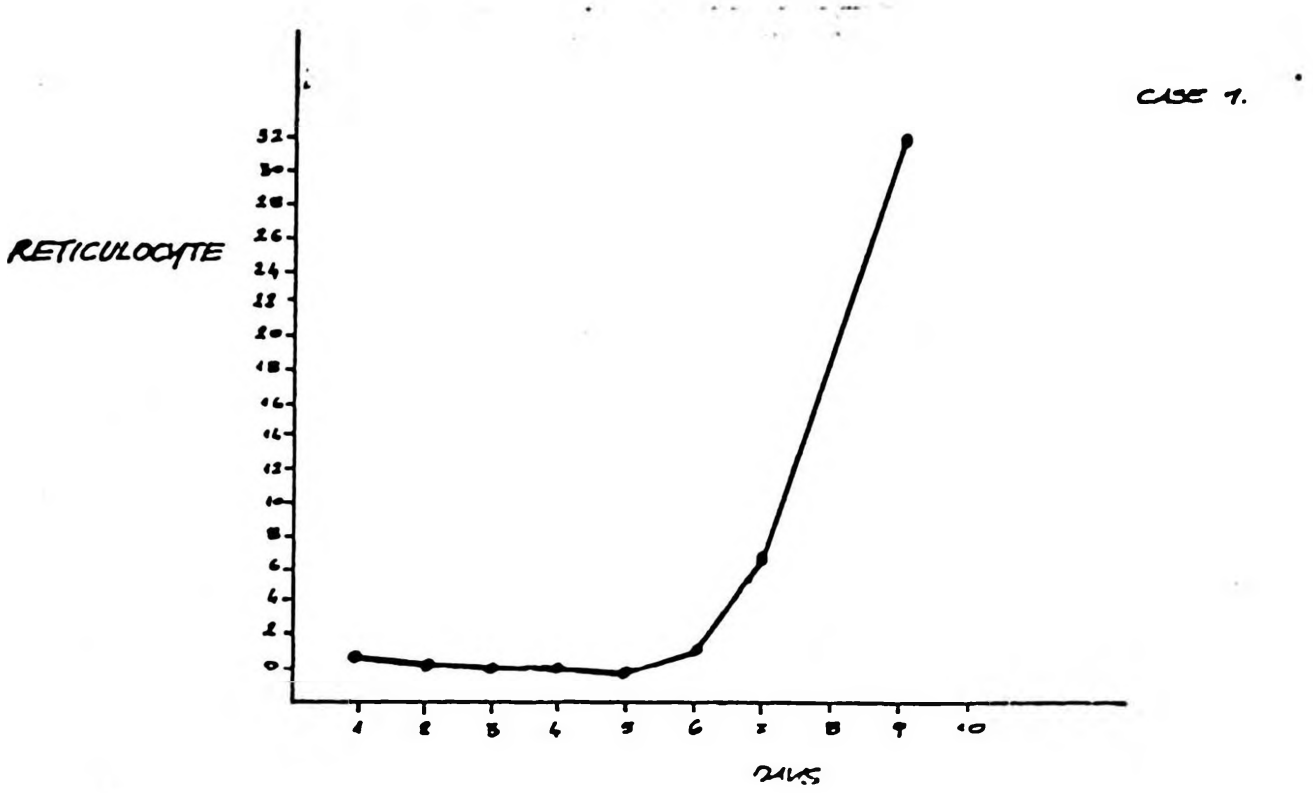

Figure 1.

The concept of humoral control of erythropoiesis has now been generally accepted.[10,11] Erythropoietin has been studied in nearly all types of anemias. Consistently high levels of erythropoietin were observed in aplastic and hypoplastic anemias.[9,12,14]

Although Jones, et al[1,5] were able to demonstrate erythropoietin in 12 of 16 plasma samples from patients with sickle cell anemia,

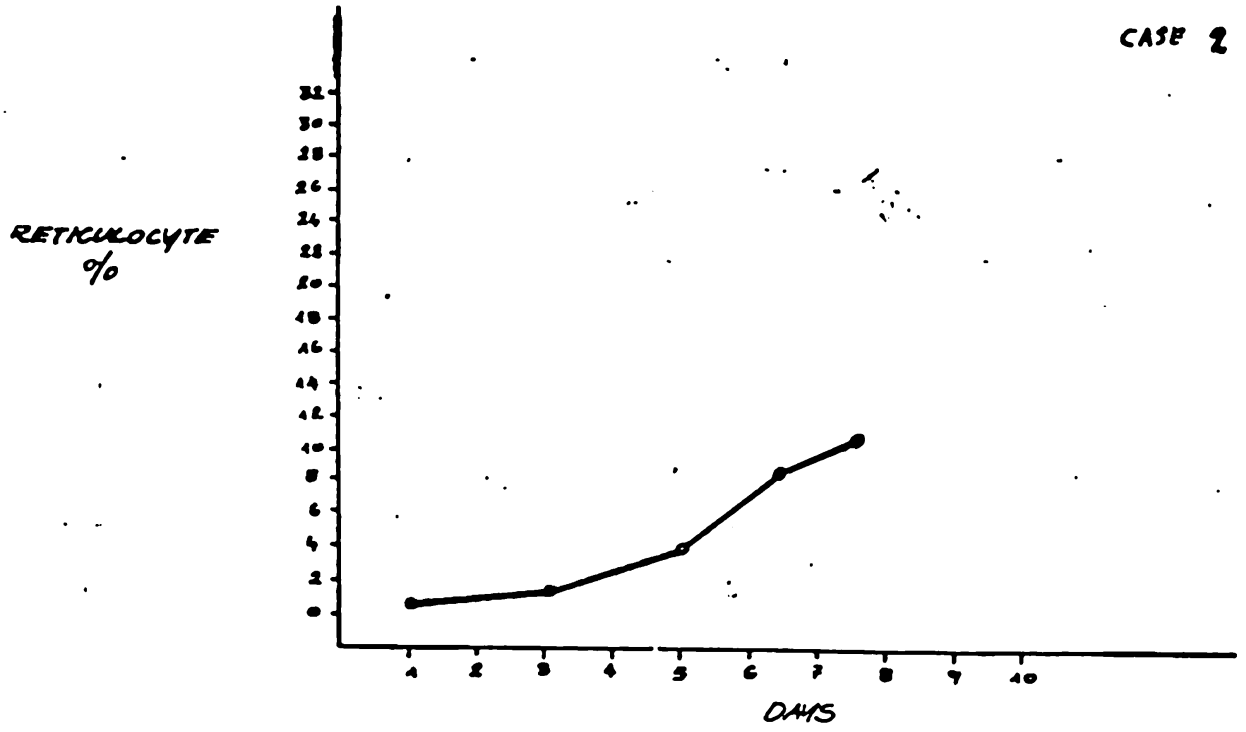

Figure 2.

none of these patients had aplastic crisis. We, however, have had the unique opportunity of studying erythropoietin throughout the course of the crisis.

Erythropoietin levels in the plasma and urine of our first patient, before and after transfusion, are shown in Figure 3. Two pre-transfusion plasma erythropoietin level determinations were found to be significantly elevated (9.9 % and 10.3 %, respectively), as compared to the control (3.5 %). Increased urinary erythropoietin levels were similarly detected before transfusion in this case. Two post-transfusion erythropoietin determinations were made which indicated a fifty per cent drop compared to the pre-transfusion levels (5.6 % and 5.3 %). It should be noted that in this case there was complete deprivation of erythroid elements in the marrow. The second patient, who had less severe erythroid aplasia, did not show a similar rise in erythropoietin levels in either plasma or urine (Figure 4).

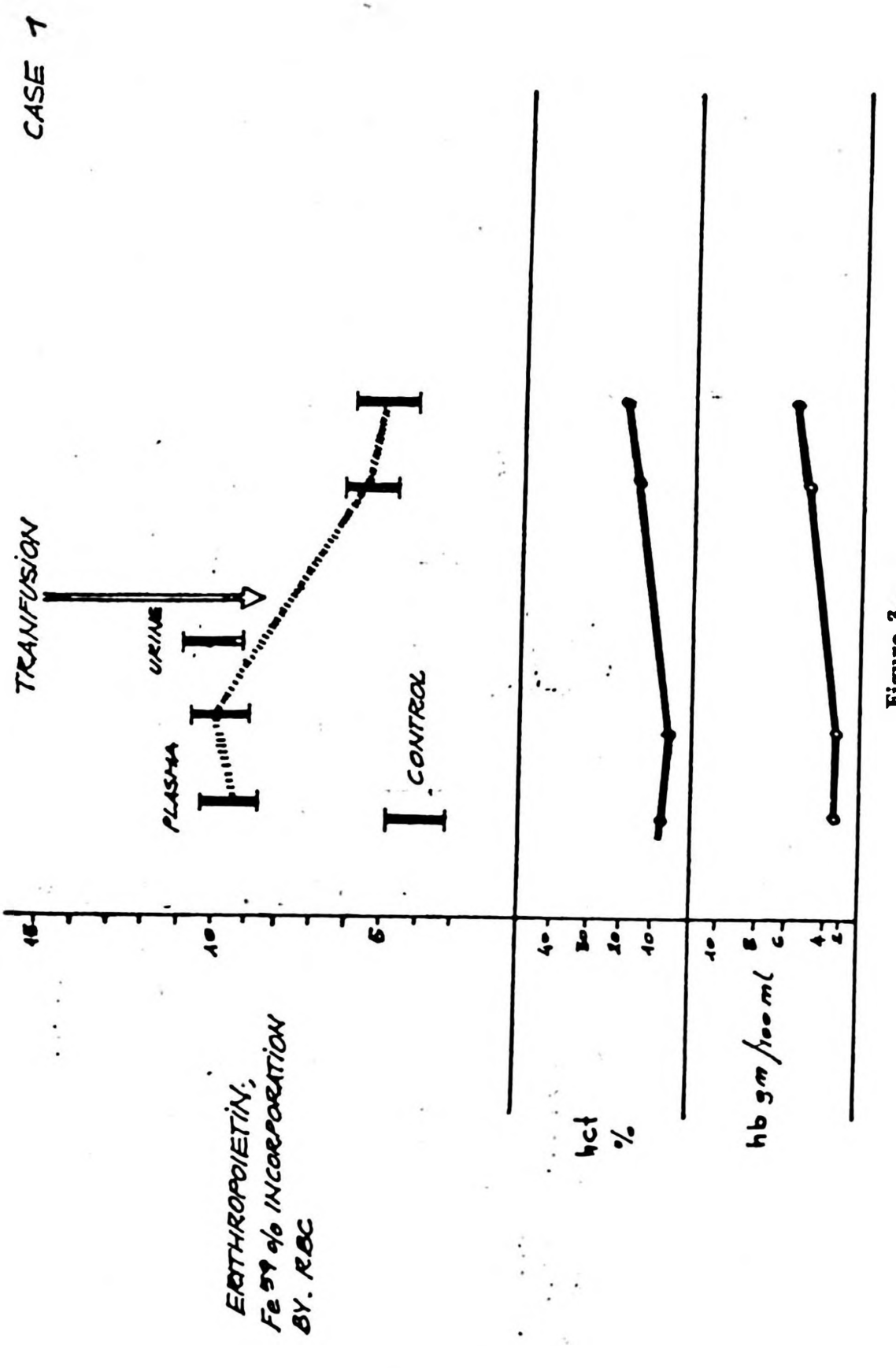
CASE 1
TRANFUSION
URINE
PLASMA
CONTROL
ERYTHROPOIETIN;
Fe 59 % INCORPORATION
BY. RBC
hct
%
hb gm/100 ml

Figure 3.

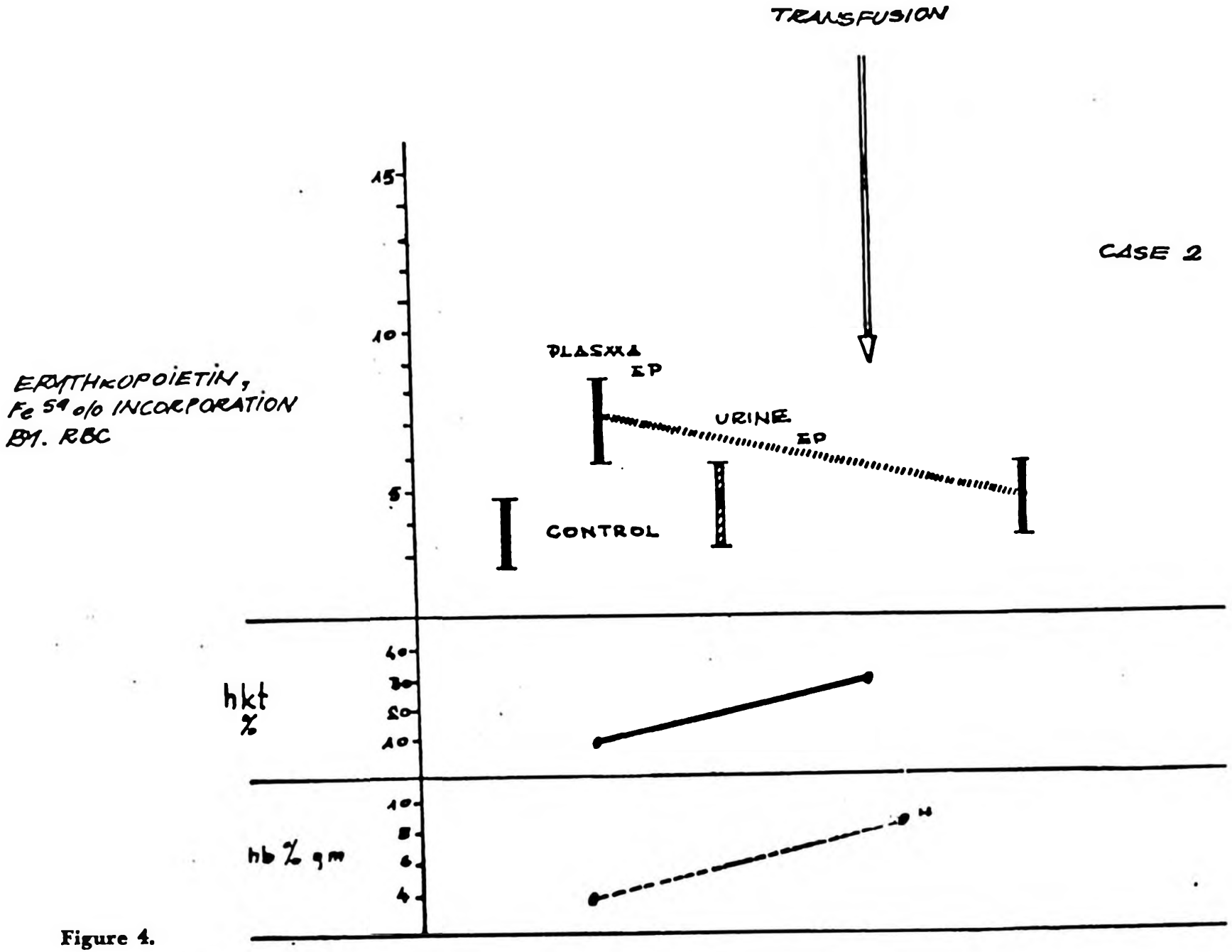
TRANSFUSION
CASE 2
ERYTHROPOIETIN,
Fe 59 o/o INCORPORATION
BM. RBC
15
10
5
PLASMA
EP
URINE
EP
CONTROL
hkt
%
40
30
20
10
hb % gm
10
8
6
4
H

Figure 4.

It is of particular interest that the severity of anemia was about the same in our two patients. The difference in the erythropoietin levels, therefore, can be explained on the basis of the degree of erythroid aplasia in the marrow. This is in agreement with the concept that erythropoietin is utilized by the bone marrow and that the plasma level reflects the balance between production and utilization.[11] In other words the functional state of the marrow appears to be a more important factor for erythropoietin than does the severity of the anemic stimulus in these cases. Lack of urinary eythropoietin in the second case indicates that unless the plasma level increases and perhaps exceeds a certain threshold, erythropoietin will not appear in the urine.

The decrease in plasma erythropoietin levels in our patients after transfusion was similar to that reported in several cases by others.[16,17]

Conclusion

Erythroblastopenic crisis in sickle cell anemia seems to be remarkably similar to real aplastic anemia in regard to erythropoietin; thus, such a crisis can not be explained on the basis of lack of erythropoietin.

The rise of erythropoietin in plasma and in urine appears to be more closely related to the erythroid activity in the marrow than to the severity of the anemia.

Summary

Plasma and urinary erythropoietin have been determined in two patients with sickle cell anemia and erythroblastopenic crisis. The erythropoietic activity could be demonstrated in both of the children. The role of erythroid activity and the severity of the anemia on erythropoietin levels are discussed.

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