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Polycythemia Secondary to a Pheochromocytoma with Production of an Erythropoiesis Stimulating Factor by the Tumor. (26957)

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Polycythemia has been noted in association with various neoplasms including renal tumors (1,2), cerebellar hemangioblastomas (3,4), uterine fibroids (5) and pheochromocytomas (6). Hematologically these patients have shown erythrocytosis with no associated splenomegaly or increases in the white cell or platelet count. The elevated hemoglobin and hematocrit returned to normal following resection of the tumors. An erythropoiesis stimulating factor (erythropoietin) has been demonstrated in a saline extract of a renal carcinoma (7) and in the fluid obtained from renal cysts (7,8) and cystic cerebellar hemangioblastomas in patients with associated erythemia (4).

In this report we describe a patient with polycythemia associated with pheochromocytoma tumors and demonstrate production of an erythropoiesis stimulating factor by the tumor.

Case summary. D. R., a 10-year-old white boy, was admitted to the Univ. of Maryland Hospital with a complaint of headache. Six months prior to admission the patient developed progressively severe headaches, drenching night sweats, and a 12 lb. weight loss. Two weeks prior to admission the blood pressure was elevated to 170/140 mm Hg.

On admission the patient was markedly plethoric. Blood pressure was 180/110 mm Hg in the upper extremities and 210/160 mm Hg in the lower extremities. A round non-tender walnut-size mass was found in the left flank just under the costal cage. There was no splenomegaly and the remainder of the physical examination was negative.

Laboratory data. The hematocrit was 65%, hemoglobin 21 g %, red cell count 8.3 million/mm^3, leucocytes 8000/mm^3, and platelet count 745,000/mm^3. The bone marrow showed marked erythroid hyperplasia. Total red cell volume was 40 cc/kg, 14 cc/kg above estimated normal value. Arterial oxygen saturation was 93%. Urinary catecholamine excretion determined on 2 occasions gave results of 792 and 1014 units.

At operation 4 tumor masses were removed, 2 from the left adrenal, one from the bifurcation of the aorta and one from the right adrenal. These tumors were microscopically identified as pheochromocytomata.

The patient gradually became normotensive and has been free of symtoms for the year following surgery. The blood data were as follows: hemoglobin 13.8 g %, hematocrit 39%, red cell count 4.65 million/mm^3, and red cell mass was 26 cc/kg. Catecholamine excretion was 4 units.

TABLE I. Erythropoietin Assay.

Material assayed*	Material assayed per inj. per rat	RBC Fe^{59} uptake % at 16-18 hr	Reticulocyte per 1000 RBC
Albumin control (12)	2 ml of 7%	6.0 ± 1.4	2 ± 1
Normal serum (12)	2 ml	6.4 ± 1.4	3 ± 1
Patient's " (12)	2 "	10.3 ± 3.5	—
Saline extract of tumor, non-dialyzable fraction (14)	.4 g of tumor tissue	15.2 ± 4.2	19 ± 5
Saline extract of tumor dialyzable fraction (14)	*Idem*	6.2 ± .9	—
Ether extract of tumor (6)	"	6.8 ± 2.1	—

* No. of rats utilized in assay is shown in parentheses.

Special studies. Methods. The erythropoiesis stimulating activity of the patient's serum and of a saline and lipid extract of a homogenate of the pheochromocytomata tumors was studied by a modification of the fasted rat assay for erythropoietin of Fried *et al.* (9). Normal serum, albumin, adrenaline*, cortisone† adrenocorticotropic hormone‡, testosterone§, and a saline extract of dog adrenal were assayed simultaneously as controls.

Tissues to be assayed were weighed, ground into a fine suspension in a Potter Elvejhem homogenizer and either saline or ether was added. After centrifugation the supernatant fluid was removed and used for assay.

Groups of 6 to 14, 140-160 g, female Sprague Dawley fasted rats were utilized as the recipient animals. The material to be assayed was injected subcutaneously 24 and 48 hours after onset of the fast and 0.5 μc of Fe^{59} was injected intraperitoneally at 80 hours. The rats were bled 16 to 18 hours after administration of the isotope and the hematocrit and incorporation of Fe^{59} into red blood cells determined assuming a blood volume of 5% of the body weight for all recipients.

Results. The results of the assay of erythropoiesis stimulating activity are shown in Tables I and II. On subcutaneous injection of the saline extract of tumor tissue, there was a significant stimulation of erythropoiesis in the fasted rat as shown by an elevated Fe^{59} incorporation into red cells and reticulocytosis compared to animals that received 2 ml of normal plasma or 5% albumin solution. The serum removed from the patient prior to operation also showed some erythropoiesis stimulating activity. The activity appears to be non-dialyzable and not soluble in ether. Groups of 6 rats given adrenocorticotrophic hormone, adrenalin, cortisone, testosterone, and a saline extract of normal dog adrenal had an 18 hour Fe^{59} incorporation comparable to normal serum. This differentiates the known erythropoietically active substances related to the adrenal from the active substances in the pheochromocytoma extract. No significant differences were noted in the mean hematocrit of the various groups studied, excluding the possibility that any of the agents administered were hemolytic.

TABLE II. Erythropoietin Assay.

Material assayed*	Material assayed/inj./rat	RBC Fe^{59} uptake % at 16-18 hr
Saline control (12)	2 ml of .9%	5.0 ± 1.4
Saline extract of normal dog adrenal (6)	.4 g of tissue	4.2 ± .9
Adrenalin (6)	1:1000 (.2 ml)	6.2 ± 1.4
Cortisone (6)	25 mg	5.6 ± 1.0
Testosterone (6)	25 "	5.1 ± 1.4
Adrenocorticotrophic hormone (6)	40 units	4.8 ± 1.2

* No. of rats utilized in assay is shown in parentheses.

* Parke, Davis & Co.
† Merck Sharp & Dohme Co.
‡ Wilson Laboratories, Inc.
§ Eli Lilly & Co.

Discussion. Polycythemia in childhood is most commonly associated with anoxia due to cardiac or pulmonary disease. Rare cases of congenital familial polycythemia and polycythemia vera have been reported in this age group (10). These causes of polycythemia may be excluded in the present case in view of the normal arterial oxygen saturation and the hematological response to tumor resection. Demonstration of an elevated total red cell volume indicates that this case represents true rather than relative or stress polycythemia where there is a normal total red cell volume but a significantly reduced plasma volume (11). The present studies suggest that the polycythemia seen in association with the pheochromocytoma tumors in this patient is the result of production by the tumor of a substance that stimulates erythropoiesis. The active material appears to be stable on freezing and thawing, not lipid soluble and nondialyzable.

Carnot and Deflandre (12) first suggested that red cell production by the marrow was controlled by a circulating stimulating substance. Recent studies from various laboratories have demonstrated the presence of such a hormone, erythropoietin, in serum and urine of anoxic and anemic animals and man (13). The work of Jacobson *et al.* (14) suggests that the kidney is the major or even sole site of production of erythropoiesis stimulating factors. Gurney (7) and Nixon *et al.* (8) have demonstrated production of erythropoiesis stimulating factors by renal cysts and a renal tumor in patients with associated polycythemia.

Erslev (15) and Mirand *et al.* (16) contend that there are extra-renal sites of erythropoietin production. The present study confirms this view indicating that erythropoiesis stimulating factors can be produced in extra-renal tissue (a pheochromocytoma) at least in pathological states.

Summary. 1. Erythropoiesis stimulating activity has been demonstrated in the saline extract of 4 pheochromocytoma tumors and the serum from a 10-year-old boy with hypertension and polycythemia. 2. The erythropoietically active material was nondialyzable and not lipid soluble.

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