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Polycythæmia in Neoplastic Diseases

Polycythæmia secondary to hypoxia – respiratory, cardiac or altitude – is a well-known entity, and is characterized by increased production of red cells without changes in white cells, platelets or of the myeloid reticulum stroma. Polycythæmia vera, a separate disease process, was recognized by Vaquez (1895), Cabot (1899) and Russell (1902) before Osler's earlier writings in the field (1903) and the distinguishing features of this disease now include splenomegaly, increase in circulating white cells and platelets, the frequent finding of an elevation of leucocyte alkaline phosphatase, and a not infrequent termination of the disease in an acute leukæmia. Most would regard the condition as a benign neoplasm of bone marrow tissue, showing a tendency to malignant transition, and it is entirely distinct from polycythæmia secondary to anoxia in which only the red cell precursors are involved. In clinical practice, however, difficulties do arise as with early stages of polycythæmia vera, the proliferation may be most prominent in the erythroid series without splenic enlargement or myeloid changes. The possibility of confusion between polycythæmia vera and polycythæmia secondary to hypoxia clearly arises in such cases, but rather more intriguing possibilities have emerged from observations of the association of such erythrocytosis, not only with hypoxia, but with a variety of renal disorders and with certain tumours. In many cases now, correction of the renal disorder, or removal of the tumour has led to remission of the polycythæmia.

Erythrocytosis with Renal Lesions

Probably the earliest association of renal lesions with erythrocytosis was that described by Gaisböck (1922) under the title 'polycythæmia hypertonica'. He recognized the existence of polycythæmia in patients with a variety of renal lesions, but in some instances may have been dealing with patients suffering from thrombotic lesions in the kidney, secondary to polycythæmia itself, for in untreated polycythæmia with greatly increased blood viscosity arterial thromboses are not uncommon. However, Fairley (1945) reported 2 cases of marked polycythæmia associated with renal carcinoma in which removal of the tumour was followed by regression of the polycythæmia; some 15 cases have now been reported in detail in which this sequence has been observed. Over 70 cases have been reported in which severe polycythæmia was associated with a renal tumour – both carcinoma and adenoma. Cooper & Tuttle (1957), Gardner & Freymann (1958) and subsequently many others reported that erythroeytosis might occur with simple hydronephrosis and renal cysts, and that resection of the affected kidney was followed by cure of the erythrocytosis.

Erythrocytosis with Tumours of other Organs

Carpenter *et al.* (1943) reported the occurrence of erythrocytosis in association with cystic hæmangioblastoma of the cerebellum, a report subsequently confirmed by Walker (1945). Since that time some 42 such cases have been reported in the literature, and in 6, reviewed by Donati *et al.* (1963), the erythrocytosis was shown to undergo sustained remission following removal of the tumour. The frequency with which such erythrocytosis occurs in patients with the tumour is unknown, but is probably as high as 30–50% (Meredith & Hennigar 1954) if careful hæmatological assessment is carried out before surgery.

Thomson & Marson (1953) reported erythrocytosis associated with a massive uterine fibroid, remitting after removal of the tumour; in a further 9 cases reported since that date, erythrocytosis of marked severity has been found to remit after removal of the tumour.

Erythrocytosis has been reported in association with hepatoma (McFadzean *et al.* 1958) although here cure following removal of the tumour has not been described. One case of hamartoma of the liver with severe erythrocytosis has been reported (Joseph *et al.* 1962) in which resection of the hamartoma was followed by complete remission of the erythrocytosis.

Humoral Mechanism of Hypoxic Polycythæmia

Over the past twelve years, a considerable body of evidence has been amassed indicating that under physiological conditions red cell production is regulated by the hormone 'erythropoietin'. This hormone is mucoprotein in nature and has been only partially purified. Its action on the bone marrow is to stimulate normoblast proliferation, having no effect on leucocyte or platelet production. It is difficult to demonstrate with certainty in normal plasma, but is present in greatly increased amounts in conditions of severe anæmia; it may also be demonstrated in plasma under conditions of hypoxia and the final stimulus to its secretion, in all probability, is a low tissue oxygen tension at certain critical sites. The hormone may be recovered from many tissues, but the studies of Jacobson *et al.* (1957) suggest that the kidney is the major site of production in the body under conditions of anæmia. The distribution of erythropoietin in the kidney differs from that of renin and the renal tubular epithelium appears to be the most likely site of secretion (Penington 1963).

Assays of erythropoietin in plasma have been bedevilled by problems of specificity. Early reports (Linman & Bethell 1957) that the plasma of patients with both primary and secondary

polycythæmia contains a humoral stimulator of erythropoiesis have not been confirmed, and it would appear that the only specific assay preparation for erythropoietin is one in which a secretion of the hormone has been suppressed in the recipient animal by the induction of polycythæmia. Using such a preparation, a marked increase in erythropoietin may be demonstrated in the plasma in most subjects with erythrocytosis secondary to hypoxia whereas no such increase is found in polycythæmia vera (Penington 1961, Noyes *et al.* 1962, Lange & Gallagher 1962). A marked variation in bone marrow response to erythropoietin stimulation is observed in respiratory anoxia, the reasons for this being obscure (Freedman & Penington 1963).

The hæmatological evidence and results of bio-assay studies point, therefore, to the polycythæmia of hypoxia being mediated by the physiological regulator of red cell production, erythropoietin. Assay procedures are relatively crude, however, and it is important to note that in some patients with polycythæmia secondary to anoxia, it is not always possible to demonstrate a significant increase in concentration of erythropoietin above normal (Noyes *et al.* 1962, Freedman & Penington 1963). In all probability an increase of the order of twofold over the normal level is the least that can be detected as a positive assay result, and in some subjects lesser increases are capable of producing polycythæmia. Marked variation in marrow response may be a factor of great importance.

Humoral Mechanism in Renal and Tumour Polycythæmia

Polycythæmia with hydronephrosis and renal cysts: Gurney (1960), Rosse *et al.* (1963), Penington (1962) and others have reported an increase in plasma erythropoietin in some subjects with erythrocytosis associated with renal cysts and hydronephrosis. The same authors have reported erythropoietic activity in cyst fluid suggesting that the cyst wall might be the site of production of the hormone. However, Rosse *et al.* (1963) have reported a study of the erythropoietic activity of fluid from renal cysts in patients without polycythæmia, with polycythæmia vera and with pure erythrocytosis; erythropoietic activity was found in some instances in all three groups. Increase in plasma erythropoietin cannot be demonstrated in all such subjects, even though removal of the renal lesion is followed by remission of the erythrocytosis, and in one patient studied by Gurney (1960), in whom erythropoietin could be shown in the plasma, and remission followed nephrectomy, there was a recurrence of polycythæmia, but on this occasion with splenomegaly – apparently a typical polycythæmia vera.

Table 1
Assays of erythropoietin in polycythæmia

Diagnosis	*No. of cases*	*Material assayed*	*Result of assay*
Polycythæmia vera	4	Plasma	Negative
	1	Plasma	Weak positive ($P<0.05$)
Respiratory polycythæmia	10	Plasma	Positive ($P<0.01$)
	1	Plasma	Weak positive ($P<0.05$)
Polycythæmia vera with renal cyst	1	Plasma	Weak positive ($P<0.05$)
		Cyst fluid	Weak positive ($P<0.05$)
Erythrocytosis with:			
(1) Hydronephrosis	1	Plasma	Weak positive ($P<0.05$)
	1	Plasma, Urine	Negative
(2) Renal cysts	2	Plasma	Positive ($P<0.01$)
(3) Renal carcinoma	1	Plasma, Tumour extract	Positive ($P<0.01$)
	1	Plasma and tumour	Negative
(4) Cerebellar hæmangioblastoma	2	Plasma	Negative
	1	Cyst fluid	Negative
(5) Massive uterine fibroma	2	Plasma and tumour	Negative
(6) Hepatoma	1	Plasma	Negative

It appears, therefore, that benign renal lesions may be associated with an increase in erythropoietin secretion which may cause erythrocytosis or aggravate a coexistent polycythæmia vera (Table 1).

Polycythæmia with renal carcinoma: In a number of instances (Lange & Gallagher 1962, Penington 1962) increase in erythropoietin in plasma has been demonstrated in patients with erythrocytosis associated with renal carcinoma, and erythropoietin has been recovered from the tumour (Hewlett *et al.* 1960, Gurney 1962, Penington 1962). The small but significant number of cases in which removal of the tumour has been followed by prolonged remission of the erythrocytosis suggests that secretion of the hormone by the tumour may indeed cause the erythrocytosis. Renal carcinoma is commonly associated with pyrexia, presumably from tumour necrosis, and some degree of leucocytosis or thrombocytosis might be expected by this means. However, estimates of the frequency of polycythæmia in renal carcinoma vary widely, and certainly many of the reported cases bear all the hall-marks of polycythæmia vera. The incidence of erythrocytosis secondary to renal carcinoma may be as low as 1 %.

Erythrocytosis with cerebellar hæmangioblastoma: Waldmann *et al.* (1961) have reported a case in which erythropoietin – identified both chemically and enzymically – was found in a high concentration in the cyst fluid of a patient with erythro-

cytosis associated with cerebellar hæmangioblastoma. No increase in plasma erythropoietin could be demonstrated in this patient, or in 2 subjects with this condition studied by the author (Table 1). However, it must be emphasized that slight increase in secretion rates or possibly loss of diurnal secretion rhythm might be sufficient over a period of months to lead to a significant erythrocytosis.

Erythrocytosis and massive uterine fibroid: Erythropoietin studies in this syndrome have been uniformly negative. Vandenburg & Vasu (1963) failed to demonstrate the hormone in either plasma or tumour of one case, and the author has obtained similarly negative assays for erythropoietin in 2 cases. However, in one a crude saline extract of the tumour has been found to stimulate iron utilization in normal rats although containing no erythropoietin (unpublished results) and the possibility remains that uterine fibroids may contain a factor influencing secretion of erythropoietin, or influencing the bone marrow by some other means.

Erythrocytosis with hepatoma: Donati *et al.* (1963) have reported increase of erythropoietin in the plasma of one subject with erythrocytosis associated with hepatoma. In the one subject studied by the author, no significant increase of erythropoietin in plasma was detected, but the positive result of Donati and his colleagues does strongly suggest that this form of erythrocytosis is mediated by erythropoietin.

Erythrocytosis with phæochromocytoma: Waldmann & Bradley (1961) demonstrated erythropoiesis-stimulating activity in the plasma and tumour tissue of a boy with severe erythrocytosis and mild thrombocytosis associated with a widely metastasized phæochromocytoma. It is of some importance to note that the assay for erythropoietin was not carried out in the specific polycythæmic animal, and noradrenaline could have influenced the results obtained in the preparation used (Penington 1963). It seems probable, but not certain, that this tumour may produce erythrocytosis through secretion of erythropoietin.

Conclusion

Early studies of humoral mechanisms in polycythæmia were bedevilled by problems of specificity of bio-assay systems. However, it now appears certain that polycythæmia vera and hypoxic polycythæmia differ in respect of humoral stimulation of bone marrow, the latter being mediated by the hormone erythropoietin. In recent years a third group of polcythæmias has emerged in which erythrocytosis is secondary to one of a variety of tumours or to a benign space-occupying lesion of the kidney. In this third group, many reported studies, including those of the author, suggest that the mechanism of stimulation of the bone marrow is via the physiological regulating hormone, erythropoietin. However, bio-assays for the hormone are not yet sufficiently sensitive to be of routine use in the diagnosis of renal and tumour erythrocytosis. Table 2 summarizes the present state of our knowledge relating erythrocytosis to tumours.

Table 2
Erythrocytosis due to tumours

Tumour	*Surgical 'cure' of erythrocytosis*	*Erythropoietin*	
		In plasma	*From tumour*
Renal carcinoma	Yes	Yes	Yes
Renal adenoma	Yes	–	–
Cerebellar hæmangioblastoma	Yes	No	Yes
Massive uterine fibroid	Yes	No	No
Hamartoma of liver	Yes	–	–
Carcinoma of liver	–	Yes	No
Phæochromocytoma	–	(Yes)	(Yes)

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