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Polycythaemia

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Abstract
Though strictly speaking polycythaemia means an increase in all three formed elements in the peripheral blood the term is usually used to describe an increase above normal in the number of circulating red cells per unit volume of blood. The polycythaemia may be relative, due to a fall in the plasma volume, or true or absolute when the total number of red cells in the body, the red cell mass, is increased. Such an increase in the mass of circulating red cells could in theory be produced by a prolongation of the average life span of red cells beyond the normal value of about no days, or by an increased output of red cells by the haemopoietic system. Present evidence indicates that in the majority of true polvcythacinic syndromes, it is the latter which occurs (Pike 1958).

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POLYCYTHAEMIA

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Though strictly speaking polycythaemia means an increase in all three formed elements in the peripheral blood the term is usually used to describe an increase above normal in the number of circulating red cells per unit volume of blood. The polycythaemia may be relative, due to a fall in the plasma volume, or true or absolute when the total number of red cells in the body, the red cell mass, is increased. Such an increase in the mass of circulating red cells could in theory be produced by a prolongation of the average life span of red cells beyond the normal value of about 110 days, or by an increased output of red cells by the haemopoietic system. Present evidence indicates that in the majority of true polycythaemic syndromes, it is the latter which occurs (Pike 1958).

SOME COMMENTS ON AETIOLOGY AND PATHOGENESIS

Before discussing this further a brief word about the normal control of erythropoiesis would seem appropriate. In health the number of red cells in the blood stream remains remarkably constant and though it is known that endocrine secretions from the gonads, the thyroid and the suprarenals have considerable influence on this, they do not seem to supply the fundamental stimulus to erythropoiesis (Wintrobe 1961). For many years, however, clinical and experimental observations in man and animals have shown the importance of oxygen; thus oxygen lack has a stimulating effect and excess of oxygen depresses erythropoiesis. That this is not a direct effect on erythropoiesis was shown by the fact that in parabiotic rats erythropoiesis occurs in both rats even if only one of them is made anoxic (Reissmann 1960) and it can also be shown that the plasma of anaemic animals contains a factor capable of stimulating erythropoiesis. This and similar work supported earlier suggestions of the existence in the blood of a hormone-like substance capable of stimulating erythropoiesis. This factor, erythropoietin, is now usually accepted as the main humoral mechanism in the control of erythropoiesis. It has no effect on leucocytes and platelets. The main source of erythropoietin is probably the kidney but an extra renal site of this or a similar hormone, probably in the liver, exists also (Rosse and Waldmann 1962).

Under normal conditions it is presumed that the oxygen tension in the blood controls the release of erythropoietin which is capable of stimulating the marrow to produce red cells only. Any rise of the number of red cells above normal is counteracted by the tendency for such a change to depress the output of erythropoietin.

POLYCYTHAEMIA VERA

This is the earliest of these conditions to be described. Original descriptions are those of Vaquez (1892) and Osler (1903). In contrast to the other polycythaemic syndromes to be discussed, in the classical case there is evidence

of hyperplasia of all marrow elements, with leucocytosis and thrombocytosis in addition to erythrocytosis, and also splenomegaly.

The aetiology is a subject which gives rise to much discussion and though many would agree with the view put forward by Damashek (1954) that it is a relatively benign neoplasm, there has been a tendency to challenge this in the light of the recent progress made in the field of secondary polycythaemias (Pike 1958). The neoplastic concept classifies polycythaemia vera as one of the group of "myeloproliferative syndromes" which includes myelofibrosis, chronic myeloid leukaemia, primary thrombocythaemia and di Guglielmo's syndrome, all these conditions being thought to have common ancestry in the primitive multipotential mesenchymal cell. In favour of this concept is the fact that intermediate forms with features characteristic of several of the clinical entities constituting the group may be seen quite frequently in the same patient and that one condition may evolve into another (Lopas and Josephson, 1964). An increase in basophil granulocytes is a common feature in these conditions which also appear to respond to the same type of therapy. Much of the evidence in support of the myeloproliferative concept of the aetiology of polycythaemia vera it will be appreciated, is largely circumstantial and other aetiological possibilities will be mentioned later.

SECONDARY POLYCYTHAEMIA

In the light of the known physiological importance of oxygen in the control of erythropoiesis it is not surprising that a group of well defined conditions exist where tissue anoxia due to a low oxygen saturation in the blood results in polycythaemia. This may result from a low oxygen tension in the inspired air as occurs for example as part of the adaptive mechanism to high altitude. Pathological causes include various diseases of the lungs and heart, especially congenital cyanotic heart disease and arterio-venous shunts which allow unsaturated venous blood to enter the arterial circulation. Hypoventilation not necessarily due to lung disease as caused by extreme obesity or structural chest disease, may also cause secondary polycythaemia which may also result from the presence of abnormal blood pigments.

In 1945 Fairly described two cases of polycythaemia treated by removal of a renal carcinoma and subsequent developments have confirmed the association of polycythaemia with various well defined lesions of the kidney, benign and malignant tumours, cysts and hydronephrosis, and of other organs also, such as cerebellar haemangioblastoma, phaeochromocytoma, hepatoma and possibly certain uterine tumours (Pike 1958). The association is particularly strong with hypernephroma and polycythaemia will be found in about 30-50 per cent of patients suffering from this condition (Penington 1965). Raised levels of erythropoietin may be found in the plasma of patients with anoxic polycythaemia and in patients with renal lesions, cerebellar haemangioblastoma and phaeochromocytoma (Gurney 1965, Modan 1965).

Polycythaemia has also been noted to arise as a result of the action of various poisons. The best evidence for such a causation is the polycythaemia which may follow cobalt poisoning. This is not related to the erythrocytosis which may follow the treatment of pernicious anaemia. For further information on this subject the reader should consult a recent review by Modan (1965).

In the light of the known causes of secondary polycythaemia the possible roles of anoxia and erythropoietin in the aetiology of polycythaemia vera have been scrutinised recently and although anoxia seems to have been excluded without difficulty, the status of erythropoietin in polycythaemia vera remains undecided (Gurney 1965). If the red cell production in polycythaemia vera is due to primary proliferation in the bone marrow as suggested by the myeloproliferation concept of the disorder one would expect the serum levels of erythropoietin to be depressed in that condition. Unfortunately the measurement of erythropoietin depends on biological assay methods which are relatively crude. Thus anything less than a twofold rise in the circulating level of erythropoietin cannot be reliably detected and it is known that less than this is capable of producing polycythaemia (Penington 1965). It is also known that the sensitivity of different individuals to erythropoietin varies. Even the best methods at present available are only able to demonstrate equivocal levels in normal man. It seems therefore that present methods cannot definitely exclude raised erythropoietin levels in polycythaemia vera and certainly cannot demonstrate reduced levels. However, even if erythropoietin could be implicated as a causative feature of the erythrocytosis of polycythaemia vera, some other hormone would

have to be responsible for the leukocytosis and thrombocytosis commonly associated with that condition.

Another approach to the problem has been to see if there is any association between polycythaemia vera and any of the lesions known to be responsible for secondary polycythaemia. Delamore and Macdonald (1962) in a study of patients with polycythaemia vera, demonstrated no pyelographic abnormality but Brandt and his colleagues (1963) in a larger series of patients with polycythaemia vera found that 9 per cent of cases had significant lesions with included two renal carcinomas.

BENIGN ERYTHROCYTOSIS

In dealing with polycythaemia one is left with a group of patients with true polycythaemia without leukocytosis or thrombocytosis and without splenomegaly. In all respects the blood picture simulates that of secondary polycythaemia yet there is no clinical or laboratory evidence to support this. It has been suggested (Modan 1965) that this group should be classified separately. Some of these patients turn out to have polycythaemia vera and some perhaps to have polycythaemia secondary to an unrecognised cause. Most of the so-called cases of polycythaemia vera described in children belong in this group (Abildgaard et al 1964). Familial cases associated with splenomegaly can be classified here. Some individuals with erythrocytosis of this type may be cases with high normal blood counts. Apart from those patients who turn out to have polycythaemia vera, the main characteristic of this group of conditions is their benign course.

RELATIVE POLYCYTHAEMIA

In this condition the red cell values appear to be raised but are in fact normal or even reduced. The apparently high counts are the result of a considerably diminished plasma volume. In most cases the cause of this haemo-concentration such as burns, diuresis, dehydration, is obvious. In 1952 Lawrence and Berlin described a group of cases in which the red cell mass was normal and the plasma volume chronically depressed giving rise to apparent erythrocytosis. They called this polycythaemia of stress mainly because the haemo-concentration simulated that which occurs initially on being exposed to the stress of high altitude (Lawrence 1952). Damashek (1953) emphasised the association of this condition with anxiety and tension, vascular disease, hypertension and peptic ulceration. In that the association with stress is only inferred the condition is probably better labelled as pseudopolycythaemia; there is well documented evidence that it is not uncommon and certainly commoner than polycythaemia vera. It runs a more benign course and like polycythaemia vera is commoner in men.

It is likely that many of the cases of polycythaemia hypertonica which Gaisbock described belong to this group (Gaisbock 1922). This interesting group is the subject of two recent reviews where it was found that although some patients with the features of Gaisbock's syndrome had a true though mild polycythaemia, many had pseudopolycythaemia (Russell and Conley 1964; Hall 1965).

In the light of the preceding discussion the following classification somewhat modified after Modan (1965) is suggested.

TABLE I

True Polycythaemia

1. Polycythaemia vera.
2. Secondary Polycythaemia.
   (a) *Anoxic*
   - High altitude
   - Lung Disease
   - Heart Disease—congenital or acquired
   - Respiratory disease
   - Obesity
   - Abnormal haemoglobin pigments

   (b) *Humoral*
   - Renal
   - Cerebellar haemangioblastoma
   - Phaeochromocytoma
   - Uterine myoma (?)
   - Liver carcinoma
   - Endocrine—Cushing's syndrome
   - Others

   (c) *Chemical and Toxic*

3. Benign erythrocytosis
   - Idiopathic
   - Familial
   - Primary erythrocytosis of children
   - Normal variant.

Relative Polycythaemia

1. Fluid loss or diminished intake.
2. Pseudopolycythaemia or polycythaemia of stress.

DIAGNOSIS

Space does not permit a full description of the clinical features of these conditions. Certain diagnostic difficulties are worth discussion. The main problems which often arise can be stated as (a) Does the patient have polycythaemia and (b) if so, is this true or relative polycythaemia, and, if the former, is the physician dealing with polycythaemia vera or a secondary type?

Laboratory determinations will usually enable the diagnosis of polycythaemia to be made and a packed cell volume of > 55% (> 52% in the female) establishes the diagnosis. However, this may be masked in true polycythaemia by the fact that the red cells tend to be small. Determination of the red cell count will distinguish these cases. Occasionally the plasma volume may rise in proportion to the red cell mass masking both the rise in the red cell count and the packed cell volume. The reason for this may not be obvious but a not unusual cause is congestive cardiac failure. Bleeding, a common complication of polycythaemia vera for example where there is a bleeding tendency and where 10-15 per cent of patients have a peptic ulcer, may also mask the diagnosis. In difficult cases clinical suspicion may only be confirmed by an actual measurement of the red cell mass. The most popular method of doing this is with the use of the radioactive isotope chromium$_{51}$ (Mollison 1961).

If in association with polycythaemia there is leukocytosis, thrombocytosis, splenomegaly, hyperplasia of red and white cell and platelet precursors in the bone marrow and a raised leukocyte alkaline phosphatase, then the patient has polycythaemia vera. All cases are, however, not typical. Thus about 30 per cent of cases may have normal white and platelet counts and in a similar proportion the spleen is not palpable. The marrow is not always hyperplastic. It is in this group that the possibility that one is dealing with pseudopolycythaemia arises and once this has been excluded by determining the red cell mass, secondary polycythaemia is likely.

Though an anoxic polycythaemia is usually clinically obvious this is not always so and in particular a pulmonary arterio-venous shunt may be overlooked. Determination of the percentage oxygen saturation of the arterial blood is the only way of excluding this group with certainty. This should normally be not less than 97%. In older patients with polycythaemia vera levels of 93% have been described. There are some cases of polycythaemia vera however where unexplained levels of 91% have been found. A low level in this condition may occasionally be due to a throbotic complication in the central nervous system resulting in hypoventilation (Bader et al 1963). Intravenous pyelography and occasionally aortagraphy will be necessary to distinguish renal causes of polycythaemia and in fact in view of the findings of Brandt and his colleagues (1963) should be considered even in typical cases of polycythaemia vera. The leukocyte alkaline phosphatase is of considerable help in distinguishing vera from secondary types of polycythaemia. In the latter cases it is not raised. Infection should be remembered however as one of the commoner conditions giving rise to abnormally high levels (Hayhoe 1958). At present the determination of the circulating level of erythropoietin is too difficult and too insensitive to be used routinely in diagnosis but should be considered in selected cases.

Some cases will defeat all attempts at an accurate diagnosis particularly when facilities for red cell mass determination are not available. Observation over a period of time with perhaps appraisal of the response to careful venesection will help in most cases.

COURSE AND PROGNOSIS

Though cases of polycythaemia vera have been known to live for many years without complications, this is rare even with treatment. Vascular thrombosis is the most frequent complication and haemorrhage is not unusual although the precise mechanism for this is not understood. In that the disease is one of later life, affected subjects may die of an unrelated condition. The terminal picture of the disorder may be myelofibrosis, a leukaemoid reaction which resembles chronic myeloid leukaemia, or acute leukaemia. Untreated the mean survival is about five years from the time of diagnosis (Lancet 1965). The course of secondary polycythaemia depends largely on the underlying cause.

TREATMENT

Except in polycythaemia vera there is little evidence that therapy is required in the other conditions in this group. Even though the

blood viscosity will be raised in these there is little evidence that this alone requires therapy and thus, for example, vascular phenomena are said on the whole to be unusual in the secondary physiological polycythaemia of high altitude (Russell and Conley 1964). The situation may, however, be different where there is already a predisposition to vascular disease.

In polycythaemia vera some form of treatment is required. In particular treatment reduces the incidence of vascular accidents and the life expectancy is thought to be prolonged to about 13 years from the time of diagnosis (Massouredis and Lawrence 1957).

Venesection is the more frequently used form of treatment and by itself may produce a remission lasting several months. This is, however, unusual and when it is required more often than once in two months resort should be made to some other form of therapy. It is of particular value either alone or in conjunction with other treatment in a surgical emergency, for the rapid relief of symptoms and in patients not responding to or suffering from some complication of other therapy such as thrombocytopaenia. Five hundred millilitres of blood should be removed on alternate days.

The alternative to phlebotomy is some form of marrow depressant or a haemolytic agent such as phenylhydrazine. The latter drug does nothing to remedy the thrombocytosis and this and its toxicity make it very little used nowadays. The most popular marrow depressant has for many years been the isotope P^{32}. This is easily administered usually intravenously but it can be given orally, has a relatively short half life of 14 days, is a β emitter and irradiates the marrow tissues by being incorporated into the actively dividing marrow cells and then into the bones as calcium phosphate. Radiation sickness does not occur and marrow depression is unusual. If one defines a remission as the disappearance of symptoms and the return of the blood counts to normal for at least six months, 84% of patients have a full remission, 50% requiring one dose only and less than 10% more than two doses (Szur et al 1959). Four per cent, however, fail to remit after three injections and 13% have partial remissions only. The average remission is of the order of two years though the range is considerable.

The main objections to P^{32} are the danger of thrombocytopaenia or pancytopaenia and that it is thought to increase the incidence of acute leukaemia. In experienced hands the former is not a real problem but this does not appear to be so with the latter. The incidence of acute leukaemia was initially reported raised by Lawrence in 1955 and more recently Modan and Lilienfeld (1964) have put it at up at over 11 per cent. It is said, however, that acute leukaemia is merely the natural progression of the disease and becomes more obvious when survival is prolonged (Osgood 1964) and some well authenticated cases of acute leukaemia occurring in non-irradiated subjects have been reported (Szur et al 1959). Nonetheless a recent report of chromosomal abnormalities in potients who received P^{32} is disturbing (Macdiarmid 1965) and though their relevance has been challenged (Millard 1965) they recollect the findings of Court Brown and Abbatt (1955) of chromosomal abnormalities in patients irradiated for ankylosing spondylitis in whom an increased incidence of acute leukaemia is accepted.

The main deficiency until recently has been the lack of a series of patients treated by other than P^{32} but a recent series from Manchester of 127 patients treated with cytotoxic drugs remedies this (Perkins et al 1964). Two points in particular are of interest. Firstly none of these patients developed acute leukaemia, those patients not dying of some complication or intercurrent disease developing either myelofibrosis or a leukaemoid reaction simulating chronic myeloid leukaemia but distinguished from this by the absence of the Philadelphia chromosome and the normal alkaline phosphatase reaction. Secondly the mean survival was the same as for patients treated with P^{32} i.e. about 13 years (Perkins et al 1964; Halnan and Russell 1965).

The drugs used in the main were thiotepa, busulphan and the folic acid antagonist pyrimethamine the last two being considered the drugs of choice. Though a relatively small dose of pyrimethamine was used (25mgs daily) 30% of patients had complications in the form of megaloblastic anaemia and thrombocytopaenia, though anorexia, nausea, buccal ulceration and exfoliative dermatitis could occur. These of course are readily reversible with folic acid but treatment necessitates close supervision. Remissions were of the order of 10-12 months. Susulphan was given in a dose of 2-4mgs daily with a maintenance dose of 2mgs once or twice weekly, i.e. doses tended to be smaller than those used in the treatment

of chronic myeloid leaukaemia. Thrombocytopaenia was a problem and 8 of 18 patients did not respond. Six had remissions of 12-30 months.

On the whole the experience of drug therapy appears to be that it is more difficult to apply, necessitates more supervision and that remissions are shorter. Since the survival of patients on drugs is in general similar to that of those on P^{32} it does not seem to matter what one uses providing one uses something but it is possibly wiser to avoid P^{32} in the younger patient with polycythaemia vera.

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