Polycythemia Rubra Vera With Pernicious Anemia
Some Observations on Vitamin B12 Metabolism

By ROBERT E. SAGE

PERSISTENT rather than relative and transient polycythemia was first described in 1892 by Vaquez. Polycythemia rubra vera is now regarded as one of the myeloproliferative disorders. A slowly progressive neoplasm of unknown etiology involving all cell series of the bone marrow, it is inevitably fatal after a varying period of time. The first clinical description of pernicious anemia was that of Addison in 1855. Auto-immune phenomena are now recognized as common occurrences in this disorder, which may be under genetic control. The inability to absorb Vitamin B12 is accompanied by achlorhydria and leads to anemia and neurologic disturbances. Whether it is primarily an auto-immune disorder has yet to be resolved.

Megaloblastoid changes in the red cell series of the bone marrow occasionally develop in the course of polycythemia rubra vera but true megaloblastic anemia and polycythemia rubra vera in the same patient have been rarely reported. The development of some manifestations suggestive of polycythemia rubra vera after the institution of therapy for pernicious anemia or anemia due to folic acid deficiency has been occasionally reported. Most of these cases were described before the development of the accurate diagnostic radioisotope technics and in these, as in most cases studied since, there is doubt as to the diagnosis of the polycythemia rubra vera or the pernicious anemia. In the following case the pernicious anemia was manifest only after the polycythemia rubra vera was treated, a sequence which has not previously been satisfactorily documented. Strict criteria for both conditions make the diagnoses unequivocal and the results of the first autoantibody studies in this combination are presented. The adequate control of both disorders by adjustment of the parenteral Vitamin B12 dosage is described. The coexistence of these two rare diseases in the same patient is discussed in relationship to coincidence, and to possible etiologic factors. An apparent unavailability of Vitamin B12 for normal tissue metabolism and hemopoiesis is discussed with respect to the high serum levels seen in some of the myeloproliferative disorders. It is suggested that the high levels of Vitamin B12 binding proteins described in these disorders with an added intrinsic qualitative abnormality are inhibiting the release of the vitamin at tissue receptor sites.

CASE REPORT

T.B., a 76 year old man of English stock, was admitted to The Queen Elizabeth Hospital in October 1963 for the first time. The following history was obtained of previous laboratory examination and treatment.

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POLYCYTHEMIA RUBRA VERA WITH PERNICIOUS ANEMIA

Past History

Hematologic data are given in Table 1. In 1953 he had a routine medical examination. Epistaxes began in 1956 and increased in severity requiring admission to another hospital for transfusion in 1959, 1960 and 1961. Hemoglobin in 1960 was 16.9 g./100 ml but by his admission in 1961 the red cells showed microcytosis, hypochronia and poikilocytosis and oral iron therapy was instituted. Severe wound bleeding following cholecystectomy in 1962 resulted in Hb. 13.5 g./100 ml. following transfusion with five units of blood.

First Admission, The Queen Elizabeth Hospital

He was admitted in October 1963 with severe epistaxes, occipital headaches, episodic vertigo, weight loss and recent bright blood loss per rectum. Examination revealed a plethoric thin man with a firm liver and spleen palpable 3 cm. below the costal margins. There was no lymphadenopathy, and the tongue was normally furred.

Investigations performed are listed in Table 1. Other data included: E.S.R. less than 1 mm. in first hour; reticulocytes 1.8 per cent; red cell morphology of iron deficiency; bone marrow with extreme hyperplasia of all elements, especially megakaryocytes, normal cell morphology and absent iron stores. Bleeding and clotting studies showed no circulating factor deficiency but complete lysis of clot by tube incubation in 24 hours.

A diagnosis of long-standing polycythemia rubra vera with control by repeated epistaxes and melena associated with a fibrinolytic state was made.

Confirmation of Polycythemia Rubra Vera

Total blood volume by 51Cr method following initial venesections with P.C.V. 47 per cent: Total blood volume 6320 ml. (101.05 ml./Kg.), red cell volume 2990 ml. (47.8 ml./Kg.) and plasma volume 3330 ml. (53.25 ml./Kg.). Normal ranges are 58-77 ml./Kg., 28-38 ml./Kg. and 36.5-49.5 ml./Kg. respectively. Neutrophil alkaline phosphatase score was 240 (Normal 0-30); serum uric acid 7.1 mg./100 ml.; chest x-ray, arterial gas analysis and intravenous pyelography were normal.

Following discharge the hemoglobin was maintained at 12.5 to 13.5 g./100 ml. by venesection but the epistaxes continued with thrombocytosis. In November 1963, 6 millicuries 32P were given and the epistaxes subsided after six months. He left overseas and was temporarily lost to follow up.

Second Admission

In May 1966 he presented with symptoms of severe anemia and an atrophic glossitis which had developed two months previously. The liver and spleen were palpable 4 cm. below the costal margins but there was no lymphadenopathy. Investigations were as in Table 1, with E.S.R. now 42 mm. in first hour; reticulocytes 1.0 per cent and red cells showing marked anisocytosis, macrocytosis and poikilocytosis with neutrophil hypersegmentation. Bone marrow was hyperplastic with gross megaloblastic change evident in all cell series and normal iron stores; serum iron 63 µg./100 ml. with 22 per cent saturation of total iron binding capacity.

Confirmation of Pernicious Anemia

Serum Vitamin B12 level by Euglena gracilis assay using a modification of Hutner et al. was 160 pg./ml. (Normal 200-1000 pg./ml.); serum folic acid by Lactobacillus casei method of Herbert with modifications was 3.8 ng./ml. (Normal 2.0-20 ng./ml.); achlorhydria on augmented histamine test meal; normal gastric cytology; some fundal "ballooning" on barium meal; normal 3 day fecal fat and d-xylose excretion. 57Co Vitamin B12 plasma absorption test showed 0.064 per cent per liter absorbed (Normal 0.67 per cent-2.9 per cent, pernicious anemia 0.02 per cent-0.42 per cent) and after 50 mg. intrinsic factor preparation 0.65 per cent per liter absorbed. The range for pernicious anemia corrected with intrinsic factor is 0.59 per cent-2.00 per cent. Autoantibody studies were performed by Dr. Robert Odgers of The Department of Medicine using the albumin coated charcoal technic.
Table 1.—Progressive Laboratory Data

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<td>Hb g./100 ml.</td>
<td>16.4</td>
<td>11.8</td>
<td>16.6</td>
<td>5.5</td>
<td>13.3</td>
<td>17.1</td>
<td>12.4</td>
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<tr>
<td>P.C.V. %</td>
<td>49</td>
<td>43.5</td>
<td>54.5</td>
<td>15</td>
<td>46</td>
<td>56.5</td>
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<td>6,500,000</td>
<td>6,400,000</td>
<td>1,200,000</td>
<td>5,000,000</td>
<td>7,300,000</td>
<td>—</td>
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<td>M.C.V. μ³</td>
<td>89</td>
<td>75</td>
<td>82</td>
<td>124</td>
<td>94</td>
<td>82</td>
<td>—</td>
<td>86</td>
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<tr>
<td>W.C.C./mm³</td>
<td>17,000</td>
<td>17,800</td>
<td>19,000</td>
<td>1,600</td>
<td>18,000</td>
<td>5,500</td>
<td>3,300</td>
<td>7,000</td>
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<tr>
<td>Platelets/mm³</td>
<td>—</td>
<td>950,000</td>
<td>880,000</td>
<td>130,000</td>
<td>1,200,000</td>
<td>200,000</td>
<td>85,000</td>
<td>180,000</td>
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<tr>
<td>Serum B₁₂ pg./ml.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>95</td>
<td>850</td>
<td>960</td>
<td>720</td>
<td>1,500</td>
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for the blocking intrinsic factor antibody and indirect immunofluorescence technics\textsuperscript{31} for other tissue antibodies. Parietal cell and blocking intrinsic factor autoantibodies were detected, while those against thyroid, muscle, cytoplasm and nuclei were not. One milliliter of patient serum blocked the binding of 27 ng. of Vitamin B\textsubscript{12} by intrinsic factor and parietal cell autoantibody reaction was strongly positive.

Rapid response followed parenteral Vitamin B\textsubscript{12} injections with a peak reticulocyte count of 25 per cent on the sixth day. A total of 2000 \( \mu \)g. of Vitamin B\textsubscript{12} were given in the first four weeks with haemoglobin rising to 12.7 g./100 ml. in that period.

**PROGRESS**

The entire progress has been summarized in Figure 1. With regular parenteral Vitamin B\textsubscript{12} the hemoglobin rose steadily for four months. By September 1966 the epistaxes had returned with increasing severity and red cell morphology indicated iron deficiency (Table 1). The bone marrow was extremely hyperplastic with all elements involved, especially megakaryocytes, normoblastic erythropoiesis and absent iron stores. The serum folic acid was 4.2 ng./ml.; E.S.R. 2 mm. in first hour; serum iron 40 \( \mu \)g./100 ml. with 15 per cent saturation of total iron binding capacity; neutrophil alkaline phosphatase score 260; bleeding and clotting studies were normal.

On oral iron and parenteral Vitamin B\textsubscript{12} the epistaxes persisted despite cautery. The rising thrombocytosis (Fig. 1) appeared the main contributing factor and Myleran 6 mg. per day was started in November 1966. The dose was reduced to 2 mg. per day over six weeks as platelet and white cell counts fell to normal levels. Epistaxes ceased when platelet count fell below 600,000 mm\textsuperscript{3}. By February 1967 the hemoglobin began to rise despite continued Myleran therapy. In May 1967 with Hb 17.1 g./100 ml. the headaches and vertigo returned with plethora. The bone marrow was now 960 pg./ml. (Table 1). Vitamin B\textsubscript{12} requirements had increased following commencement of Myleran therapy with 100 \( \mu \)g. weekly now needed to maintain hemoglobin, platelet and white cell levels and a sense of well being. Parenteral Vitamin B\textsubscript{12} was withheld in order to induce a fall in hemoglobin level. A dramatic fall in hemoglobin from 16.9 g./100 ml. to 12.4 g./100 ml. occurred in eight weeks with hematocrit falling from 56.5 per cent to 38 per cent (Fig. 1). The platelet count fell from 275,000 mm\textsuperscript{3} to 85,000 mm\textsuperscript{3} and white cell count from 5,500 mm\textsuperscript{3} to 3,300 mm\textsuperscript{3}. Myleran was stopped as it was potentiating the developing leucopenia and thrombocytopenia. Serum Vitamin B\textsubscript{12} level despite the fall in blood parameters remained at 720 pg./ml. (Table 1). Vitamin B\textsubscript{12} was reinstituted on alternate weeks in July 1967.

In January and June 1968, 750 ml. venesections were necessary to relieve symptoms of headache and vertigo when hemoglobin reached 15.0 g./100 ml. and 16.5 g./100 ml. respectively. He otherwise remained in reasonable health until July 1968 when he left overseas. The liver and spleen remain enlarged 4 cm. below the costal margin. For the last six months adjustments of parenteral Vitamin B\textsubscript{12} 100 \( \mu \)g. from one- to three-week intervals has allowed control of the blood picture (Fig. 1). The requirements are much higher than normally necessary but are needed to hold the blood parameters.

He was fully reinvestigated in June 1968 with the following results: Barium
Fig. 1.—Progressive blood parameters and therapy for entire course. M. represents the time of bone marrow estimations. The rise in white blood cell and platelet counts following B₁₂ therapy and subsequent fall with Myleran are easily seen. Severity of epistaxes parallel platelet counts.

meal, progress in appearances of atrophic gastritis with "balding," serum folic acid 3.4 ng./ml.; serum iron 95 µg./100 ml. with 27 per cent saturation of total iron binding capacity; total serum proteins 7.8 g./100 ml.; serum albumin 4.1 g./100 ml.; serum globulins 3.7 g./100 ml.; serum electrophoretic pattern normal; serum uric acid 5.1 mg./100 ml.; serum electrolytes, glucose, bilirubin, alkaline and acid phosphatase normal; protein bound iodine 4.0 µg./100 ml.; T₃ resin uptake 97 per cent. There is no evidence of significant liver disease.

The serum Vitamin B₁₂ level was 1500 pg./ml. Plasma Vitamin B₁₂ binding proteins were investigated by Dr. R.W. Beal using technics previously described. The total B₁₂ binding protein was 2680 pg./ml. with a binding globulin 2490 pg./ml. and β binding globulin 190 pg./ml. The unsaturated B₁₂ binding capacity was 1180 pg./ml. Ratio of a to β globulin in total B₁₂ binding protein is 13.1 to 1, and in the unsaturated B₁₂ binding protein, 5.2 to 1.

Current hematological status (Table 1): bleeding and clotting studies normal apart from a bulky fragile clot; neutrophil alkaline phosphatase score 150; E.S.R. 2 mm. in first hour; reticulocytes 1.2 per cent. Red cell morphology for past 12 months has shown moderate anisocytosis, some macrocytes and hypochromic cells, poikilocytosis and, in some specimens, Howell-Jolly bodies.
POLYCYTHEMIA RUBRA VERA WITH PERNICIOUS ANEMIA

COMMENTS

The occurrence of polycythemia and megaloblastic anemia in the same patient has occasionally been reported since Minot and Murphy originally observed that the red cell count sometimes rose above normal levels when pernicious anemia patients were given liver therapy. Polycythemia rubra vera has developed usually within three years of therapy for the anemia which has preceded it. Most cases have been pernicious anemia, but folic acid deficient anemia has been reported and recent cases include associated polyneuropathy and terminal acute myeloblastic leukemia. Folic acid deficiency may develop in the course of polycythemia rubra vera but the unmasking of proven pernicious anemia in a treated case has not been satisfactorily documented. Early reports include probable myelofibrosis or iron deficiency rather than pernicious anemia. The only recent report lacks radioactive studies and the diagnosis of pernicious anemia was not proven. Diagnostic criteria have not been satisfied for these cases and in the majority of those cases reported where the anemia has preceded the polycythemia. These criteria have been satisfied in the present study.

Ten years before the patient's first admission to this hospital routine blood examination showed a high hemoglobin with thrombocytosis and leucocytosis. In 1960 despite a prolonged period of severe epistaxes his hemoglobin was still 16.9 g./100 ml. and a year later the red cell, platelet and white cell counts were all markedly elevated even in the presence of severe iron deficiency. It is probable that by 1963 the polycythemia rubra vera had been present for at least seven years with the patient bleeding himself by the epistaxes and more recently added blood loss from the gastrointestinal tract to maintain near normal hemoglobin levels.

Polycythemia rubra vera is characterized by plethora, commonly a bleeding tendency, splenomegaly, an elevated hemoglobin level, high red cell count, thrombocytosis, leucocytosis, low E.S.R., high neutrophil alkaline phosphatase score and hyperplasia of the bone marrow involving all cell series, especially the megakaryocytes. Confirmation of diagnosis must include the demonstration of an increased red cell volume with or without an elevated plasma volume, by radioactive or nonisotopic technics and the absence of causes of secondary polycythemia. Renal disease, hepatic lesions and chronic hypoxia have been excluded and all criteria satisfied in this case. Iron deficiency may mask the polycythemic state which is indicated by a high red cell count, thrombocytosis and leucocytosis but only manifest after correction of the iron deficiency. The hemoglobin and red cell count never reached the usual extremes due to iron deficiency from severe epistaxes. The hemoglobin and hematocrit levels do not reflect the true red cell volume which was greatly elevated when these values were in the high normal range. The neutrophil alkaline phosphatase is usually high and does not change with treatment. The recent fall from very high levels with disappearance of the bleeding tendency may indicate a change in the underlying myeloproliferative disorder towards terminal myelofibrosis or leukemia. The spleen size is static but larger than is usual in uncomplicated polycythemia rubra vera. In
patients with combined pernicious anemia and polycythemia rubra vera the spleen may be large but few specific changes have been found. Terminal acute myeloblastic leukemia and doubtful myeloid metaplasia have been described but not myelofibrosis.

A diagnosis of pernicious anemia requires the demonstration of achlorhydria, atrophic gastritis, correction of defective $^{57}$Co Vitamin B$_{12}$ absorption by intrinsic factor and response to parenteral Vitamin B$_{12}$ in the absence of malabsorption. In recent years autoantibodies to intrinsic factor, parietal cells and other tissues, especially thyroid, have been found in pernicious anemia. Intrinsic factor autoantibodies have been occasionally described in other disorders but have an incidence of 60 per cent in pernicious anemia and were found with parietal cell autoantibodies in this patient. All of the above criteria have been satisfied to make a diagnosis of pernicious anemia although autoantibodies against the thyroid, evidence of Hashimoto’s disease and hypothyroidism are absent. The serum Vitamin B$_{12}$ level was not as low as is usually seen despite moderate reduction of all blood parameters. Increased demands by the hyperplastic polycythemic bone marrow may have unmasked the latent pernicious anemia. The requirements for Vitamin B$_{12}$ have been excessive and the extreme marrow sensitivity to withholding the Vitamin for periods has been shown in the presence of a normal serum Vitamin B$_{12}$ level. Recently 100 µg. has been necessary every one to three weeks despite a serum level above normal.

This failure of the serum level to reflect metabolic requirements suggests that the Vitamin may not be available readily for the body’s demands. Serum folic acid levels have been normal throughout the course of the patient’s illness. High serum Vitamin B$_{12}$ levels are well-recognized in chronic myeloid leukemia and have been reported in polycythemia rubra vera. Vitamin B$_{12}$ is normally bound principally to $\alpha$ and $\beta$ globulins with the former predominantly binding native B$_{12}$ and the latter acting as a temporary carrier to tissue sites. The elevations in serum Vitamin B$_{12}$ levels seen particularly in chronic myeloid leukemia and polycythemia rubra vera are due to an increase in the $\alpha$ globulin B$_{12}$-binding protein which is physiologically abnormal and unable to release the Vitamin at tissue receptor sites. This increase may be of diagnostic value in the differentiation of myeloproliferative syndromes and between primary and secondary polycythemia, and in assessment of therapeutic response. This patient has an elevated serum Vitamin B$_{12}$ level, a marked increase in $\alpha$ B$_{12}$-binding globulin with reduced $\beta$ B$_{12}$-binding globulin compared with normal. The ratio of $\alpha$ to $\beta$ binding globulins in normal, pernicious anemia and uncontrolled polycythemia rubra vera are 1 to 1.55, 1 to 2.2 and 1 to 1.33 respectively. In “spent” polycythemia rubra vera and untreated chronic myeloid leukemia these ratios reverse to 1.95 to 1 and 6.55 to 1 respectively as mean values. The ratio in this patient is 13.1 to 1. The $\alpha$ B$_{12}$ binding protein level is much greater than that found in uncomplicated pernicious anemia patients and is in the range of those found in “spent” polycythemia rubra vera. These values would indicate that the patient is approaching terminal myeloid metaplasia or chronic myeloid leukemia. The falling neutrophil alkaline phosphatase level
and rising serum Vitamin B\(_{12}\) levels would support this.\(^{24,54}\) The lack of correlation of the white cell count with the elevation in serum Vitamin B\(_{12}\) levels seen in this case which has been previously reported\(^{56}\) may indicate that the binding protein levels reflect cell turnover rather than peripheral white blood cell counts.

In normal serum the \(\alpha\) B\(_{12}\)-binding globulin is almost wholly saturated with endogenous B\(_{12}\),\(^{57,58}\) but in uncomplicated pernicious anemia the amount which is unsaturated is increased.\(^{54,55}\) The persistent abnormal red cell morphology, extreme marrow sensitivity to withholding parenteral Vitamin B\(_{12}\) and excessive dosages necessary for control in this case with an elevated \(\alpha\) globulin binding protein and serum Vitamin B\(_{12}\) level might be expected. The \(\alpha\) globulin is probably physiologically abnormal, it is preferentially\(^{26}\) binding injected Vitamin B\(_{12}\) tenaciously\(^{59}\) and rendering it unavailable for normal cell metabolism.\(^{25,54}\) The \(\alpha\) B\(_{12}\) binding globulin is only 60 per cent saturated and capable of taking up any further parenterally administered Vitamin. The report of the development of pernicious anemia in a patient with chronic myeloid leukemia when the serum Vitamin B\(_{12}\) level was normal\(^{100}\) illustrates why the blood parameters fell in this case in the presence of normal serum levels.

Early workers suggested that polycythemia rubra vera is the antithesis to pernicious anemia, being the result of excessive production of gastric hemopoietic factor.\(^{61}\) The occurrence of the two conditions in the same patient renders this concept untenable and although the serum Vitamin B\(_{12}\) may be high in polycythemia rubra vera\(^{22,52,53}\) repeated administration of large doses of the Vitamin to normal controls does not result in an elevated red cell mass.\(^{62}\) Erythropoietin levels are elevated in anemias but have been variably reported as high\(^{63-65}\) and normal\(^{66,67}\) in polycythemia rubra vera. The role of erythropoietin as an etiologic agent in polycythemia rubra vera is not generally accepted and the pathogenesis and etiology remain unknown.\(^2\) The occurrence of both these conditions in the same patient must represent a pure chance phenomenon.

We have followed this patient for five years, but the polycythemia rubra vera has probably been present for more than twelve years. The prognosis is unknown but he is reaching the average expected survival time for uncomplicated polycythemia rubra vera.\(^{68}\) His spleen size remains static and it is possible that the chance association with pernicious anemia may, by allowing control of blood parameters without frequent venesections or further radioactive phosphorus or Myleran, prolong his survival well beyond the expected time.

**Summary**

A patient with polycythemia rubra vera developed symptoms and signs of pernicious anemia three years after institution of therapy for the polycythemia. This is the first satisfactorily documented report of this sequence. Strict criteria utilized make both diagnoses unequivocal. Autoantibody studies, the first performed in such a patient, show the presence of parietal cell and intrinsic factor autoantibodies but no antibodies to other tissues. Vitamin B\(_{12}\)
requirements have been excessive despite high or high normal serum levels and extreme marrow sensitivity to withdrawal of the Vitamin is evident in the presence of these high serum levels. Studies on Vitamin B₁₂ binding proteins showed an elevation in α binding globulin with reversal of the α to β ratio. It is suggested that this protein is physiologically abnormal. The literature is briefly reviewed regarding the pathogenesis of the two disorders with the conclusion that their appearance in the one patient represents purely a chance phenomenon.

SUMMARIO IN INTERLINGUA

Un patiente con ver polycythemia rubre disveloppava symptomas e signos de anemia perniciose tres annos post le institution de therapia pro le polycythemia. Isto es le prime satisfactorimente documentate reporto de un tal sequentia. Stricte criterios tisate rende le duo diagnoses inequivoc. Studios de autoanticorpore—le prime unquam effectuate in un tal patiente—monstra le presentia de cellulas parietal e de autoanticorpore anti factor intrensec sed nullo anticorpore anti altere typos de tissu. Le requirimentos de vitamina B₁₂ esseva excessive in despecto de anormalmente or quasi anormalmente alte nivellos seral, e un extreme sensibilitate medullari pro le suspension del administraciones de vitamina B₁₂ es evidente in le presentia de tal alte nivellos seral. Studios del proteinas ligante vitamina B₂ monstrava on elevation in globulina α-ligatori con un reversion del proportion α a β. Es suggestionate que iste proteina es physiologicamente anormal. Es presentate un breve revista del litteratura concernite con le pathogenese del duo disordines, con le conclusion que le occurrientia de ambes in le mesme patiente representa tn phenomeno purmente accidental.

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