PERNICIOUS ANAEMIA AND POLYCYTHAEMIA VERA

A Case Report

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The aetiology of polycythaemia vera remains obscure despite much speculation since the disease was first described by Vacquez in 1892. It was characterized as a 'malignant hyperplasia' by Minot and Buckman (1923), who described three cases terminating in myelogenous leukaemia, but an alternative view, strongly advocated by Morris (1933) and others, and for which Hinzenberger (1936) claimed priority, has been well summarized by Wintrobe (1956): 'It has been suggested that erythraemia is the antithesis of pernicious anaemia, the over-production of cells being due to the excessive production of gastric haemopoietic factor.'

Some considerable but circumstantial evidence was raised to support this view and the occurrence of both diseases in one patient provided the opportunity of reviewing this critically.

Case Report

Mrs. E. B., a housewife aged 70 years, was admitted to Dorking General Hospital under the care of one of us (P.E.) on September 27, 1957, following the onset of auricular fibrillation which her family doctor had partially controlled with digitalis. She complained of breathlessness, palpitations, recent ankle swelling and generalized irritation of the skin after a hot bath. Examination showed that she was of good colour, but not florid, with auricular fibrillation, moderate cardiac enlargement, blood pressure 200/100, but no evidence of cardiac failure. There was slight nodular enlargement of the thyroid and hepato-splenomegaly, both liver and spleen being felt about two fingers' breadth below the costal margins. The left eye showed external strabismus and inactive choroidoretinitis. The right fundus showed grade II retinopathy. There was no abnormality in the

nervous system. The right lower limb had been amputated at mid-thigh.

Investigation showed haemoglobin 122 per cent (Haldane), red blood cells 8 million per cu. mm., white cells 25,300 per cu. mm., with polymorphs 90 per cent., eosinophils 5 per cent., lymphocytes 3 per cent. and monocytes 2 per cent. Platelets were 504,000 per cu. mm. and absolute red cell values showed M.C.V. 70 cu. μ , M.C.Hb.C. 30 per cent. and M.C.Hb. 21 μ g. Fractional test meal showed no free acid after histamine stimulation. Wassermann and Kahn reactions were negative and blood biochemistry showed serum uric acid 7.1 mg. per cent., blood urea 22 mg. per cent., serum cholesterol 138 mg. per cent., serum bilirubin 0.2 mg. per cent., serum alkaline phosphatase 14.6 K.A. units and normal empirical liver function tests. Plasma proteins were albumin 3.8 g. per cent. and globulin 3.7 g. per cent. The electrophoretic strip showed low albumin and raised gamma globulin. Faecal occult blood tests were negative and barium meal showed no abnormality in the stomach or duodenum. Intravenous pyelography showed ptosis of the right kidney.

Digitalization and bed rest led to improvement but upper respiratory and urinary infections and a pulmonary infarct of the posterior basal segment of the right lower lobe occurred before her discharge, at which time the haemoglobin was 103 per cent. and red cells 4.73 million per cu. mm.

The family history revealed the patient's father to have had pernicious anaemia and there was an extensive past history of haematological disorders summarized in Table 1. The patient said she had been anaemic since adolescence, but our first confirmed record is of hypochromic anaemia responding to oral iron at the age of 52. Occult blood tests were negative. She had at this time 'ulcerated

legs' and at the age of 59 she had the right leg amputated for intractable ulceration.

In 1951, when the patient was 64, the blood film showed macrocytosis and gastric achlorhydria was demonstrated. Treatment with anahaemin injections and iron produced slight improvement in the anaemia, but was not regularly maintained and during a relapse in 1954 megaloblasts were found in the bone marrow and the serum vitamin B₁₂ was 20 µg. per ml. At this time she was given daily folic acid, which she continued to take until August 1957, when she was admitted to Leatherhead Hospital with haematemeses, and polycythaemia with packed cell volume 58 per cent. and R.B.C.s 8.6 million per cu. mm. was demonstrated. No abnormality was demonstrated by radiography in the gastro-intestinal tract. Shortly after her discharge she developed auricular fibrillation and entered Dorking General Hospital.

No further haematinics were given before the patient was admitted to Hammersmith Hospital under Professor J. V. Dacie for further investigation on January 29, 1958. She had then relapsed and showed a macrocytic anaemia with R.B.C.s 2.4 million per cu. mm., and the bone marrow was grossly megaloblastic. An augmented fractional test meal showed histamine-fast achlorhydria. Absorption from 1 µg. of oral ⁵⁶Co-labelled vitamin B₁₂ was only 0.2 µg., rising to 0.82 µg. on adding 'intrinsic factor.' Folic acid absorption was normal from a 3-mg. oral dose and vitamin A absorption was normal. Faecal fat estimations on a normal diet showed average daily output of 5.9 g. and 1.9 g. respectively in two three-day collection periods. Intravenous folic acid clearance suggested a deficiency, but a spontaneous reticulocytosis beginning just before vitiated a therapeutic test with folic acid. A second reticulocytosis rising to 9.5 per cent. followed the institution of vitamin B₁₂ therapy and the haemoglobin rose by 4.5 g. per cent. to 12.5 g. per cent. at her discharge on March 5, 1958. Marrow trephine biopsy at this stage showed a hyperplastic marrow with many megakaryocytes and a diffuse increase in reticulin network suggesting incipient myelosclerosis. A splenic infarct occurred during this admission.

Discussion

There is clearly adequate evidence in this patient of iron-deficiency anaemia, succeeded by pernicious anaemia and polycythaemia vera. The abnormal liver function tests and plasma proteins observed at various times may indicate the hepatosplenomegaly to be due to hepatic cirrhosis; this association with polycythaemia vera was first described by Mosse (1914). It does not afford an alternative explanation for the macrocytic anaemia

as a low serum vitamin B₁₂ level is not a feature of the hepatogenous anaemia (Jandl, 1955).

The occurrence of red cell counts above the levels conventionally regarded as 'normal' has been observed in treated cases of pernicious anaemia since therapy was first effective. Thus, Minot and Murphy (1926) described two patients (of 45 treated) who developed red cell counts over 6 million per cu. mm. after four to six months on a liver-rich diet. Koessler and Maurer (1927) and W. B. Castle (quoted by Goldstein, 1942) have apparently seen similar cases. This appears to be essentially a mild non-progressive erythrocytosis without serious sequelae.

Polycythaemia vera has been established as following pernicious anaemia in relatively few cases: those of Galt, Hunter and Hill (1952), Hinz (1957) and Zarafonitis, Overman and Molthan (1957) are well documented and the last of these is the only one yet described as terminating in myeloblastic leukaemia. They are compared with the present case in Table 2. Other cases suggesting the occurrence of both diseases, but not described in such detail, are those of Birnie (1936), Ferrary (1942) and Minot and Castle (1937). Possibly the cases of Emile-Weil et Boic (1932) and Skouby (1952) are further examples.

The main problem raised by the occurrence of the two diseases in one patient is whether the haematinics used were responsible for inducing polycythaemia vera. This is related to the hypothesis that polycythaemia is due to excessive production of 'intrinsic factor' on the presumption that this would act by causing excessive absorption of extrinsic factor. Morris, Schiff, Foulger *et al.* (1932) claimed that intramuscular injections of neutralized gastric juice could cause remission of pernicious anaemia, and this was extended to non-human gastric juice by Morris, Schiff, Burger *et al.* (1932). Morris (1933) suggested that there was the 'theoretical possibility' that erythraemia was the result of excess production of this 'gastric haemopoietic factor.' Barath and Fülöp (1935) treated pernicious anaemia with gastric juice given rectally and found that from polycythaemic subjects to be more effective than normal gastric juice. In addition, they produced a reticulocytosis in rats with subcutaneous neutralized gastric juice, the effect being earlier and more marked when gastric juice from polycythaemic patients was used. Hinzenberger (1936) failed to confirm this, but upheld the theory of the gastrogenous origin of polycythaemia.

Adamson and Storey (1940) also produced a reticulocytosis in rats by subcutaneous injection of neutralized normal human gastric juice, and obtained no response with gastric juice from pernicious anaemia patients. Gastric juice from

TABLE I
SUMMARY OF HISTORY AND INVESTIGATIONS IN PATIENT E.B.

Date	Hb. %	R.B.C.s (M./cu. mm.)	W.B.C.s (No./cu. mm.)	Haematological Investigation	Other Observations
2. 5.39	18	2.44	7,400	Differential count: P57, L40, M3.	Ulcerated legs (? varicose). Responded to iron therapy.
25. 7.39	74	4.7	17,600		No occult blood in stools.
4. 2.42	84	4.2	7,600	P82, L10, M7, E1.	Urine N.A.D. Ulcerated legs.
15. 2.50	68	3.2	27,000	Moderate anisocytosis, many macrocytic and a few hypochromic red cells.	(Patient failed to attend for further investigation).
12. 4.51	65	2.9			
28. 5.51	60	2.4	13,000	R.B.C.s show anisocytosis, marked poikilocytosis and macrocytosis.	F.T.M. showed achlorhydria (31.5.51).
8. 6.51	55				
15. 6.51	65	3.0	23,000		Treated with anahaemin in May-June 1951 and intermittently afterwards. (No iron given at this time).
28. 6.51	67				
25. 7.51	71		28,000		
2. 2.53	47	3.9	31,500	Anisochromasia + Hypochromia ++, anisocytosis and polychromasia + Sternal marrow showed predominantly Fe deficient anaemia and mirrored leucocytosis of blood. L : E ratio 8 : 1. A few giant metamyelocytes present. (3 or 4 injections anahaemin given before this examination).	
5. 2.53					
9. 2.53				Takata Ara—weak +ve. Globulin 3.5 g. %. γ -globulin raised in E.P.S.	
14. 2.53				Occult bloods —ve. Blood transfusions given.	
2. 3.53	90		19,600	Anisocytosis ++, anisochromasia +	Intermittent iron and heparino.
9. 6.54	52	2.1			
17. 6.54				Bone marrow showed megaloblasts and giant metamyelocytes. L : E ratio 6 : 1.	
28. 6.54	53	2.9		Reticulocytes 17%	Serum vit. B ₁₂ = 20 μ g. per ml. Treatment started with folic acid, continuing until 1957.
13. 7.54	84		26,000	" 3%	
3. 8.54	98			Slight anisocytosis and polychromasia.	
21. 6.56	62	5.3	37,000	Hypochromia ++ and anisocytosis ++	
12.12.56	62			Hypochromia and anisocytosis ++. Polymorph leucocytosis and platelets 'very plentiful.'	'Occasional' ferrivenin from then on.
10. 8.57	106	8.6	25,000	Hypochromia. PCV 58%, MCV 67 cu. μ . MCHC 27%. Platelets very plentiful with some bizarre forms.	LFT's—Thymol turbidity 6 Kunkel 10, Popper 5, Alk. Phosph. 20.7, Albumin 4.3 Globulin 3.9. Moderate diffuse γ -globulin rise.
24. 9.57	106	8.7	25,000	PCV 56%. Platelets 650,000/cu. mm.	Folic acid stopped.
2.10.57	122	8.0	25,300	P90, L5, M3, E2. Platelets 504,000/cu. mm.	Admitted D.G.H. (Investigations in text).
5.11.57	105	5.45	21,400	P82, L12, M2, E4.	
26.11.57	103	4.73	16,700	P80, L11, M2, E6.	

TABLE 1—continued

Date	Hb. %	R.B.C.s (%/cu. mm.)	W.B.C.s (No./cu. mm.)	Haematological Investigation	Other Observations
31. 1.58	54	2.4	16,000	P86, L6, M3, E6. Platelets 263,000/cu. mm. PCV. 28%.	Investigated in Hammersmith Hospital (see text). Treated with folic acid and vitamin B ₁₂ .
6. 2.58	61	2.6	29,000	Platelets 320,000/cu. mm.	
10. 2.58	67	2.9	33,000	Reticulocytosis.	
13. 2.58	69	2.9	27,000	Platelets 313,000/cu. mm.	
17. 2.58	75	3.3	31,000	Platelets 436,000/cu. mm.	
21. 2.58	77	3.1	34,000	Platelets 384,000/cu. mm.	
24. 2.58	81	3.8	26,000	Platelets 510,000/cu. mm.	
28. 2.58	84	3.3		Platelets 605,000/cu. mm.	

TABLE 2
SUMMARY OF REPORTED CASES OF PERNICIOUS ANAEMIA AND POLYCYTHAEMIA

	Sex	Age at Diagnosis of P.A.	Treatment of P.A.	W.B.C.s during P.A.	Interval on P.A. Treatment to P.R.V.	Treatment of P.R.V.	Other Conditions	Outcome
Birnie (1936) ..	M.	63	Liver extract. Cooked liver	—	7 months (from relapse)	Phenylhydrazine Liver withdrawn	—	Relapse of P.A. responding to liver extract.
Ferrary (1942) ..	F.	59	Liver extract	—	5 months (from relapse)	Reduction to half liver dosage	Diabetes mellitus	Satisfactory maintenance.
Calt, Hunter and Hill (1952)	F.	75	Liver extract. Vitamin B ₁₂	17,400	2½ months	Venesection. Radioactive P	Hypertension. Nodular thyroid	Remission.
Hinz (1957) ..	M.	55	Liver extract. Vitamin B ₁₂ . Transfusions	8,000— 26,500	6 years	Terminal diagnosis	—	Death (cerebral haemorrhage)
Zarafonitis et al. (1957)	F.	68	Vitamin B ₁₂	6,400	3 years	Venesection. Radioactive P	Hypertension	Death (myelo- blastic leu- kaemia)
Present case ..	F.	63	Liver extract. Folic acid. Vitamin B ₁₂	13,000— 37,000	6 years	Withdrawal of haematinics	Hypochromic anaemia. Cho- roidoretinitis. Hypertension. Nodular goitre	Relapse on withdrawal.

P.A. = Pernicious anaemia. P.R.V. = Polycythaemia vera.

polycythaemic subjects produced a higher and maximal response. However, the identity of the 'reticulocytosis factor' with intrinsic factor was not established and the response was also obtained with histamine. Wilkinson and Klein (1934) found parenteral liver from a case of polycythaemia rubra to be more effective in treating pernicious anaemia than normal liver.

Alleviation of polycythaemia vera was claimed to follow various measures intended to reduce the production or utilization of 'intrinsic factor,' including prolonged, repeated gastric lavage (Oerting and Briggs, 1935; Briggs and Oerting, 1935), gastric resection (Singer, 1935), gastric resection and irradiation (Hinzenberger, 1934), and irradiation of the pyloric region of the stomach (Klapproth, 1940). These provide no evidence that 'intrinsic factor' was produced in excess, however, and the effects might have resulted non-specifically from an induced anaemia.

On the other hand, excessive amounts of liver

extract or vitamin B₁₂ are said to produce no change in red cell counts or haemoglobin in normal persons (Castle, 1956) and Gingold (1939) produced only a slight delayed rise in red cell levels in rabbits given excessive doses of liver extract. Barnard, Kopet and Stahl (1951) claim to have produced red cell counts of 6.7 million per cu. mm. in a patient with Hodgkin's disease, and of 5.85 million per cu. mm. in a case of subacute sub-leukaemic leukoblastosis, by administering crude vitamin B₁₂ preparations.

In our case a leucocytosis of 27,000 W.B.C.s was observed in 1950, 15 months before the first liver therapy, and this has persisted since. Blood platelets were noted 'in excess' even when the anaemia was still uncorrected in 1956. Similarly, in the case of Galt, Hunter and Hill (1952), there was a leucocytosis of 17,400 per cu. mm. prior to treatment. This suggests that the polycythaemic tendency was present before haematinics were given, the associated anaemia preventing the ex-

pression of this in the red cells. A parallel case in which polycythaemia vera was masked by the anaemia of infection is described by Ellman and Fairburn (1953), and Chazan and Exton-Smith (1958) quote a case of myeloproliferative syndrome with anaemia.

It is therefore suggested that the occurrence of pernicious anaemia and polycythaemia in one patient is due to the coincidental appearance of both traits in the same subject and is not related to the treatment given, except in so far as this permits the fuller manifestation of the polycythaemia in the red cells. This situation emphasizes that the term 'polycythaemia vera' is to be preferred to 'primary erythraemia,' as the disease may be present despite suppression of the erythraemic aspect. It follows from this demonstration that the concept of the antithesis of pernicious anaemia and polycythaemia vera can have no significance in the aetiological sense, in that the two diseases can exist simultaneously in one subject with only partial modification of expression.

Conclusions and Summary

1. The case is described of a patient with hypochromic anaemia, pernicious anaemia and polycythaemia vera, the erythraemic aspect of the last being denied expression by the associated anaemia.

2. The hypothesis that polycythaemia vera is the antithesis of pernicious anaemia and results from an excess of 'intrinsic factor' is shown to be untenable in that the polycythaemic tendency may be partially manifested despite the absence of 'intrinsic factor.'

3. The role of administered haematinics is discussed and it is shown that these allowed fuller expression of the polycythaemia, but did not initiate the condition.

4. It is concluded that the occurrence of these conditions in one subject must be coincidental.

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