PERNICIOUS ANAEMIA IN THE SOUTH AFRICAN BANTU

REPORT OF TEN CASES

J. METZ, M.B., B.CH. (RAND)
Assistant Clinical Pathologist

R. CASSEL, M.B., B.CH. (RAND), D.C.P. (LOND.)
Clinical Pathologist

S. M. LEWIS, B.SC., M.B., CH.B. (CAPE TOWN), D.C.P. (LOND.)
Pathologist

South African Institute for Medical Research, Johannesburg

Addisonian pernicious anaemia is, by definition, a megaloblastic anaemia characterized by achylia gastrica with an associated failure to secrete intrinsic factor, resulting in deficiency of vitamin B12. To prove that a patient is suffering from pernicious anaemia, the following criteria should be established: (1) Presence of a megaloblastic anaemia, (2) deficiency of serum vitamin B12, (3) presence of achylia gastrica, and (4) lack of intrinsic factor.

Intrinsic-factor defect can be demonstrated by noting the absence of a reticulocyte response in a proven case of pernicious anaemia in relapse, when a dose of vitamin B12 is administered orally together with a preparation of gastric juice from the patient under investigation. This rather cumbersome test has been simplified by the use of vitamin B12 labelled with radio-active cobalt in the form of ^{60}Co or ^{58}Co. The absorption of an oral dose of this labelled vitamin B12, and the correction of defective absorption by the addition of intrinsic factor, can be determined by measuring the amount excreted in the stools (Heinle *et al.*, 1952; Bradley *et al.*, 1954), or in the urine (Schilling, 1953). The latter test is not so true a reflection of absorption as the other methods, but it has the advantage of ease of performance, especially under conditions where collection of stools over a period of several days is difficult.

Addisonian pernicious anaemia has long been held not to occur or at least to be very rare in the Bantu. Gelfand (1948) remarks that he has never seen an African suffering from either pernicious anaemia or subacute combined degeneration of the cord. Foy *et al.* (1951) state that no genuine case of pernicious anaemia has been recorded in an African. Megaloblastic anaemia in a Gwana male was described by Trowell (1951) as pernicious anaemia but there is no record of gastric biopsy or vitamin B12 absorption studies. In 1956, Woods and Rymer described megaloblastic anaemia in a Bantu associated with subacute combined degeneration of the cord, and in whom gastric biopsy showed atrophy of the gastric mucosa. Although vitamin-B12 absorption studies were not done in the last-mentioned case, it is acceptable as Addisonian pernicious anaemia, and as such is the first recorded example of the disease in this ethnic group.

The diagnosis of a further 10 cases is presented in this paper. In 9 the diagnosis was established by studies of the absorption of radio-active vitamin B12 and one patient with megaloblastic anaemia who died showed changes in the gastric mucosa consistent with the diagnosis.

Methods

The haematological methods were those described by Dacie (1956). Serum vitamin B12 samples were assayed by Dr. D. L. Mollin (Postgraduate Medical School, London) by the method of Ross (1952) using *Euglena gracilis* as a test organism. Absorption of radio-active vitamin B12 ($^{60}CoB12$) was estimated by a modification of Schilling's test. After an overnight fast the patient was given an oral dose of 0·6 microgram of vitamin B12 (with an activity of 0·15 microcuries of ^{60}Co). The bladder was emptied and the urine discarded. Simultaneously with the administration of the dose, 0·25 mg. of carbachol was administered by subcutaneous injection. The reason for this injection is that in some normal individuals intrinsic factor secretion may be inhibited at the time of the test, but this inhibition is overcome by the carbachol. Two hours after the oral dose of $^{60}CoB12$, 1,000 micrograms of non-radio-active vitamin B12 was administered intramuscularly and all urine was collected for a period of 24 hours. The radio-activity in the urine was determined by measuring the activity in a 1 litre aliquot (or in the total volume if less than one litre had been passed),

in a conical flask placed on top of an enclosed solid sodium-iodide crystal (1 × 1 inch), of a Tracerlab P20A scintillation detector.

The percentage of the original dose excreted in the urine was calculated.

Seven days later the test was repeated with the same oral dose of ^{60}CoB12, together with a potent concentrate of intrinsic factor.

RESULTS

Nine cases were seen during the period January 1955 to June 1957, with anaemia and a classical megaloblastic bone marrow; the relevant haematological features are shown in Table I. All cases had histamine-fast achlorhydria and macrocytic anaemia. Marrow examination performed after the institution of liver therapy showed normoblastic erythropoeisis.

Serum B12 (Table II). This was estimated in cases 1-6, during relapse. The results are uniformly very low, with less than 50 μμg. per ml. in all (normal minimal content is 100 μμg. per ml.).

Schilling Tests (Table II). In cases 1-6, no urinary excretion of ^{60}CoB12 could be detected after the oral dose; when the ^{60}CoB12 was administered together with the intrinsic factor concentrate the urinary excretion was increased to between 7·0 and 19·9% of administered dose. In cases 7-9 there was some urinary excretion (0·8%, 2·9% and 3·7% respectively) after oral ^{60}CoB12, but concomitant administration of intrinsic factor increased this to 10·3%, 27·4% and 18·3% respectively.

Case 5 presented with weakness for 6 months and inability to walk for 1 month before admission. Examination of the nervous system showed absent vibration sense up to the pubis, and absent joint sense in the great toes, knees and ankles. Pin-prick sensation was reasonably good. There was spasticity of the left leg, with extensor plantar reflex. The knee jerks were absent and there was quadriceps wasting, and shuffling gait. The clinical diagnosis was subacute combined degeneration of the cord.

TABLE I. AGE, SEX, AND HAEMATOLOGICAL FINDINGS BEFORE TREATMENT

Case	Approx. Age	Sex	Peripheral Blood: Haemoglobin (g.%)	Reticulocytes (%)	Macrocytosis	Megaloblasts	Leucocytes (thousands c.mm.)	Neutrophils (thousands c.mm.)	Macropolycytes	Platelets (on films)	Marrow: Classical megaloblasts	Giant myeloid cells
1	55	F	6·8	1	—	—	2·0	0·6	+	Scanty	+	+
2	50	F	3·0	2	—	—	3·5	1·4	—	?	+	+
3	40	M	*2·9	?	+	+	7·2	?	+	?	+	+
			5·4	1	—	+	5·2	3·0	—	?	+	+
4	40	F	6·1	2	+	—	3·0	1·3	—	Absent	+	+
5	65	F	4·5	1	+	—	3·5	0·7	+	Scanty	+	+
6	30	M	5·0	3	+	+	3·5	1·2	—	Absent	+	+
7	30	F	2·5	6	—	—	4·7	2·4	—	Scanty	+	+
8	45	M	5·3	4	+	+	7·1	3·2	+	Scanty	+	+
9	40	F	6·3	1	+	—	2·6	0·5	—	?	—†	?
10	70	F	5·8	1	—	+	4·4	1·3	—	Scanty	+	+

* First admission (1952).
† The marrow was examined after institution of liver therapy (1948).

showed no abnormality with barium meals. Complete haematological remission followed the administration of intramuscular vitamin B12; the reticulocyte peaks are shown in Table II. One patient was first seen in 1948 with

TABLE II. SERUM VITAMIN-B12 LEVEL, SCHILLING TEST, AND RETICULOCYTE PEAK FOLLOWING ADMINISTRATION OF INTRAMUSCULAR VITAMIN-B12

Case	Serum B12 in relapse (μμg/ml)	Urinary excretion of oral ^{60}Co B12	Urinary excretion of oral ^{60}Co B12 plus intrinsic factor	Reticulocyte peak on I.M. B12
1	40	0·0%	18·8%	25%
2	<25	0·0%	19·0%	35%
3	25	0·0%	17·8%	31%
4	<25	0·0%	19·9%	30%
5	40	0·0%	7·0%	38%
6	38	0·0%	10·3%	35%
7	—	0·8%	10·3%	*
8	—	2·9%	27·4%	35%
9	—	3·7%	18·3%	†

* Treated initially by blood transfusion. The bone marrow reverted to normal following administration of intramuscular vitamin B12.
† Haematological remission following liver therapy.

Case 10

This patient died shortly after admission, and is reported in detail.

L.M., an elderly Bantu female, was admitted to hospital in September 1956. The only history available was that she had been too weak to move about over the preceding 6 months. Examination showed a very pale, senile female. Her legs were weak and there was bilateral absence of knee and ankle jerks. Blood count showed haemoglobin 5·8 g. per 100 ml., leucocytes 4·4 thousand per c. mm. (with an absolute neutropenia and relative lymphocytosis) and reticulocytes 1·5%, and the smear showed macrocytes, megaloblasts, multilobed neutrophils and scanty platelets. The marrow showed numerous classical megaloblasts, and giant myeloid cells of bizarre morphology.

Blood urea was 104 mg. per 100 ml. The patient became drowsy, failed to respond to a slow transfusion of 500 ml. of blood, and died 3 days after admission.

Autopsy was carried out 48 hours after death, but an attempt was made to prevent autolysis of the gastric mucosa by passing formalin into the stomach, via a stomach tube, shortly after death.

Significant Autopsy Findings. The heart (weight 320 g.) was slightly enlarged, with the myocardium soft, pale and flabby.

There was marked oedema and congestion of the lungs. The tongue was smooth and pale, showing atrophy of the papilli on the dorsum. The stomach showed marked atrophy of the mucosa in the region of the fundus and cardia, the mucosa being pale and smooth, and the wall of the stomach markedly thin. The remainder of the stomach showed no obvious lesion. The sternum and vertebrae showed the presence of red marrow throughout the marrow cavity, and the femur throughout the shaft. The kidneys showed features suggestive of chronic pyelonephritis.

Microscopic Examination. Autolysis unfortunately obscured some detail. The femoral marrow was hypercellular with active erythropoesis. Numerous megaloblasts were present and some of the myeloid cells appeared to be larger than normal. Section of the stomach (Fig. 1) showed marked atrophy of mucosal

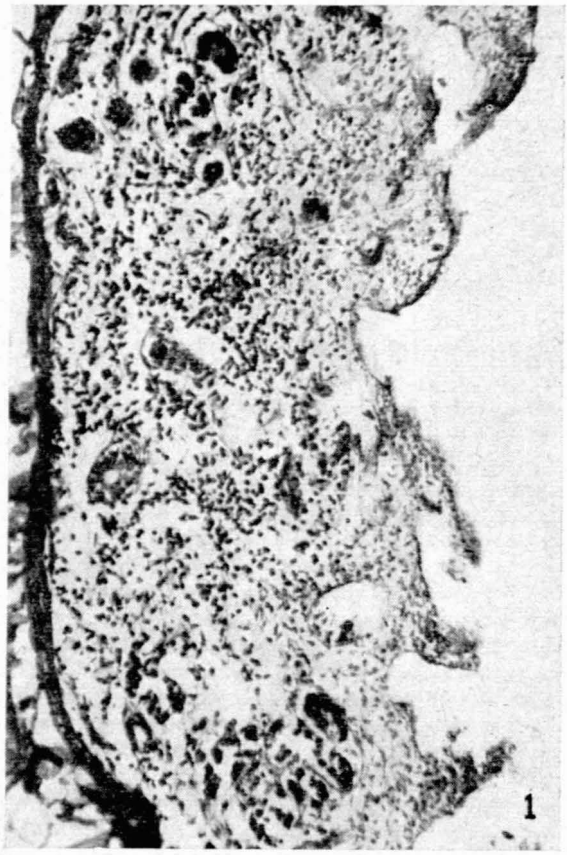

Fig. 1.

glands with complete absence of oxyntic cells. There appeared to be some increased cellularity of the substantia propria, with infiltration by lymphocytes, histiocytes and an occasional plasma cell. There was generalized atrophy of the muscularis. The histological features were those of well-marked gastric atrophy. Section of the tongue showed complete absence of villi with atrophy of the epithelium. The sub-epithelial layers showed increased fibrosis and were diffusely infiltrated by lymphocytes and plasma cells and were moderately congested. The features were those of atrophic glossitis. Sections from the spinal cord showed irregular destruction of myelin, maximal in the posterior columns and to a lesser extent in the lateral columns. The myelin destruction was not accompanied by any significant glial response. The lesions were most conspicuous in the thoracic region. The features were compatible with subacute combined degeneration of the cord. The kidneys showed the features of benign nephrosclerosis.

The Autopsy Diagnosis was:

1. Megaloblastic anaemia with gastric atrophy and atrophy of the tongue consistent with pernicious anaemia.
2. Subacute combined degeneration of the spinal cord.

DISCUSSION

Studies on vitamin B12 have done much to clarify present-day concepts of pernicious anaemia. The disease in relapse shows a low serum vitamin B12, and there is complete haematological response to parenterally administered vitamin B12. With the Schilling test the urinary recovery of ^{60}CoB12 after oral administration is less than 4% of the administered dose, this figure being increased to normal levels (greater than 5%) if a potent intrinsic factor preparation is administered with the ^{60}CoB12.

In the present series, serum vitamin B12 was low in cases in which it was estimated, and apart from the one fatal case, and the patient treated with liver, response to intramuscular vitamin B12 was complete. The mean urinary recovery of ^{60}CoB12 was 0·8%; administration of intrinsic factor with B12 resulted in a urinary recovery ranging between 7·0% and 27·4% (mean 16·5%).

Megaloblastic anaemia is common in the Bantu, the majority of cases being 'nutritional' in type and responding to ward diet, folic acid, and possibly vitamin B12. Megaloblastic anaemias clinically and haematologically indistinguishable from pernicious anaemia are seen from time to time in middle-aged Bantu, as for example the case quoted by Adams and Wilmot (1953). It was the purpose of this study to clearly separate the true pernicious anaemias from the nutritional group. The incidence of pernicious anaemia in the Bantu as compared to the European remains a matter for conjecture. Nine cases here reported all presented at the Baragwanath (1,600 beds) or Coronation (600 beds) Non-European Hospitals, Johannesburg, during a 2½ year period. Any conclusions as to the incidence of the disease in the Bantu must of necessity await further investigation with radioactive vitamin B12 of adult megaloblastic anaemias both in relapse and remission.

SUMMARY

Nine cases of pernicious anaemia in the South African Bantu were diagnosed by study of the absorption of radio-active vitamin B12. A further case of megaloblastic anaemia is described, showing the histological changes in the gastric mucosa consistent with the diagnosis of pernicious anaemia.

We wish to thank the Director, South African Institute for Medical Research, for facilities to perform this study; Dr. D. L. Mollin for carrying out the serum-B12 assays, and for his advice and encouragement in this work; Dr. Lester-Smith, of Glaxo Laboratories, for generous supplies of radio-active vitamin B12; Lederle Laboratories, New York, and Noristan Laboratories, Pretoria, for supplies of intrinsic factor; Glaxo Laboratories, Wadeville, South Africa, for supplies of vitamin B12; the physicians at Baragwanath and Coronation Hospitals, Johannesburg, for their cooperation and permission to study the cases under their care; Drs. B. A. Bradlow and N. S. F. Proctor for the autopsy report; Mr. D. Hart for technical assistance; and Mr. Ulrich for the photograph.

ADDENDUM

Since this paper was submitted for publication, 2 more Bantu patients at Baragwanath Hospital have been diagnosed as suffer-

ing from pernicious anaemia by means of the Schilling test. A further case of pernicious anaemia in an African has also been published—Adams, E. B. (1957): S. Afr. Med. J., **31**, 633.

REFERENCES

Adams, E. B. and Wilmot, A. J. (1953): S. Afr. Med. J., **27**, 1028.

Bradley, J. E., Smith, E. L., Baker, S. J. and Mollin, D. L. (1954): Lancet, **2**, 476.

Dacie, J. V. (1956): *Practical Haematology*. London: Churchill.

Foy, H., Kondi, A. and Hargreaves, A. (1951): Brit. Med. J., **1**, 380.

Gelfand, M. (1948): *The Sick African*, 2nd ed., Cape Town: Stewart.

Heinle, R. W., Welch, A. D., Scharf, V., Meacham, G. C. and Prusoff, W. H. (1952): Trans. Ass. Amer. Phycns., **65**, 214.

Ross, G. I. M. (1952): J. Clin. Path., **5**, 250.

Schilling, R. F. (1953): J. Lab. Clin. Med., **42**, 860.

Trowell, H. C. (1951): Lancet, **2**, 761.

Woods, J. D. and Rymer, J. J. H. (1956): *Ibid.*, **2**, 1274.