ADDISONIAN PERNICIOUS ANAEMIA IN YOUNG BANTU FEMALES

BY

J. METZ, M.D.

Pathologist

F. W. RANDALL, M.D.

Physician

AND

C. H. KNIEP, M.B., B.Ch.

Registrar

From the South African Institute for Medical Research and
Department of Medicine, Baragwanath Hospital,
Johannesburg

Addisonian pernicious anaemia occurs predominantly in middle-aged subjects. The disease is rarely seen in young adults; thus 46 (2.8%) of Wilkinson's (1949) 1,600 patients and 4 (1.2%) of Wintrobe's (1946) 329 patients were less than 30 years of age. The disease, although uncommon in negro populations, has been reported in the Bantu (Woods and Rymer, 1955; Adams, 1957; Metz *et al.*, 1958). In the largest Bantu series reported (Metz *et al.*, 1958), a tendency to affect a younger age-group was noted, but the numbers were too small to compare with the large series reported in whites.

Megaloblastic anaemia in Bantu adults occurs predominantly in young females, and is usually associated with pregnancy. In this form the serum vitamin B₁₂ levels are within normal limits, and complete haematological remission can always be induced with folic acid. The clearance from the plasma of injected doses of folic acid is very rapid, but the absorption of an oral dose of the vitamin is normal (Metz *et al.*, 1960a). The condition is apparently due to deficiency of folic acid conditioned by poor diet and precipitated by pregnancy. It has been suggested that the routine administration of folic acid to Bantu subjects during pregnancy would diminish the morbidity and mortality of the condition (Metz, 1958). It could, however, precipitate neurological changes, but in view of the rarity of pernicious anaemia in the Bantu this was not assumed to be of major importance. Recently, however, three young Bantu females suffering from a condition indistinguishable from Addisonian pernicious anaemia have been encountered, and the rarity of this occurrence appears to warrant it being recorded.

Case Reports

The three patients presented at Baragwanath Hospital, Johannesburg, during a period of 18 months. They were aged 23, 28, and 34 years respectively. All three knew their exact date of birth. The first presented to the gynaecology wards with a one-year history of amenorrhoea. The second was admitted in a collapsed state with severe anaemia, but subsequently gave a history of dyspnoea and palpitations for two years. The third patient complained of headache and dizziness for some months. Two were well nourished and the third was obese. Physical examination revealed no abnormality other than anaemia and features attributable to it. The patients did not appear older than their stated ages. No gynaecological abnormality was detected, and the uterus was of normal size. The last pregnancies were 2, 6, and 14 years prior to admission. The second patient had amenorrhoea for four months.

Family Studies.—The difficulties of investigating members of the families of Bantu patients are well recognized. Only in the second patient was any member of the family available: in the study of her mother the absorption of radioactive vitamin B₁₂ was found to be defective (Schilling test, 1%); this defect was corrected by the concomitant administration of intrinsic factor (Schilling test, 11.2%).

Investigations

All three patients had severe macrocytic anaemia, with classical megaloblastic bone-marrow. The findings are detailed in the Table.

The augmented histamine test was carried out according to Kay (1953), and in all three patients there was no significant fall in the pH of the gastric juice after maximum stimulation with histamine.

Serum vitamin B₁₂, assayed with *Euglena gracilis*, was 15, 95, and 25 µg./ml. (normal range 140–900 µg./ml.) in the three patients respectively. The second, in whom the serum vitamin B₁₂ was 95 µg./ml., was admitted in a collapsed state, and the specimen for vitamin B₁₂ assay was drawn after 600 ml. of blood had been administered.

Schilling Test.—The absorption of radioactive vitamin B₁₂ was studied by the Schilling (1953) technique. A test dose of 0.6 µg. of vitamin B₁₂ labelled with 0.5 µc ⁶⁰Co was administered by mouth to the patient in the fasting state, and two hours later a 1-mg. flushing dose of vitamin B₁₂ was administered by intramuscular injection. All urine passed during the ensuing 24 hours was collected and the radioactivity assayed. When the effect of intrinsic factor on the absorption of vitamin B₁₂ was studied a potent source of the factor in the form of 100 mg. of a hog-stomach preparation was administered together with the dose of radioactive vitamin B₁₂. In all three patients the absorption of vitamin B₁₂ was subnormal, and this was corrected by the concomitant administration of the intrinsic-factor preparation (see Table).

Gastric biopsy was carried out with a Woods tube. The specimens showed gastric atrophy in all three patients, with the presence of an intestinal type of epithelium (see Fig.).

Peripheral Blood, Bone-marrow, Serum Vitamin B₁₂, Schilling Test, Fat Balance, and Reticulocyte Peak in
Bantu Women with Addisonian Pernicious Anaemia

Case No.	Peripheral Blood						Marrow		Serum Vitamin B ₁₂ (µg./ml.)	Urinary Excretion of Oral ⁶⁰ Co Vitamin B ₁₂	Urinary Excretion of Oral ⁶⁰ Co Vitamin B ₁₂ Plus Intrinsic Factor	Fat Absorption / Day	Reticulocyte Peak on I.M. Vitamin B ₁₂
	Hb (g./100 ml.)	Macrocytosis	Megaloblasts	Leucocytes (Thousands/c.mm.)	Neutrophils (Thousands/c.mm.)	Platelets (on Films)	Classical Megaloblasts	Giant Myeloid Cells					
1	7.8	+	+	4.4	0.8	Scanty	+	+	15	0.9% 0.5%	7.5% 8.2%	98.6%	19%
2	2.5	+	—	4.7	1.2	„	+	+	95	0.8% 1.0% 0.0%	10.3% 6.2% 7.4%	93.9%	*
3	6.9	+	+	3.2	1.6	Normal	+	+	25	1.5% 1.5%	9% 9%	92.6%	24%

* Treated initially by blood transfusion. The bone-marrow reverted to normal after administration of intramuscular vitamin B₁₂.

Fat-balance studies were made. 50 g. of fat per day was administered for five days in Cases 1 and 2 and for nine days in Case 3, and the fat-excretion in the stools measured. Fat-absorption was normal in all (see Table).

Barium-meal and follow-through examinations did not reveal anything abnormal in any of the three patients.

Gastric mucosa from Case 3, showing atrophy. (H. and E. $\times 120$.) Gastric mucosa obtained from Cases 1 and 2 showed a similar picture.

Response to Vitamin B₁₂ Therapy

Reticulocytosis (see Table), with haematological remission and return of the haemoglobin value to normal, followed the daily administration of 100 μ g. of vitamin B₁₂ by injection. The patients have been maintained in remission by the regular administration of parenteral vitamin B₁₂. In the first patient menstruation began six weeks after the institution of vitamin B₁₂ therapy. The second patient has since become pregnant, and the pregnancy and delivery were uncomplicated.

Discussion

The disease in the three patients does not differ significantly from Addisonian pernicious anaemia in white subjects, and the diagnostic criteria have been satisfied. The occurrence of pernicious anaemia in a younger age-group in Bantu subjects may possibly be a reflection of the age distribution of the population at risk. The significance of these cases lies in the possible confusion of the diagnosis with the much more common megaloblastic anaemia occurring in association with pregnancy—most often after the pregnancy. It is of significance that the second patient has subsequently become pregnant, and it is apparent how easily her pernicious anaemia could be confused with the form associated with pregnancy.

Addisonian pernicious anaemia must be considered in the differential diagnosis of megaloblastic anaemia in young Bantu females. Pernicious anaemia and megaloblastic anaemia occurring after pregnancy can be readily differentiated with the aid of specialized techniques: the serum vitamin B₁₂ is low in pernicious anaemia, while it is normal in post-pregnancy megaloblastic anaemia; the absorption of vitamin B₁₂ is defective in the first group, while normal in the second (Metz *et al.*, 1960b); gastric atrophy is present in pernicious anaemia, but not in the post-pregnancy group (Metz, 1959). These techniques are not available to all, and the most practical method of excluding pernicious anaemia is the augmented histamine test.

Summary

Three young Bantu women were found to be suffering from a condition indistinguishable from true Addisonian pernicious anaemia.

The significance of this finding is discussed with reference to the megaloblastic anaemias found in malnourished populations.

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CIRRHOTIC HEART FAILURE

BY

A. PATON, M.D., M.R.C.P.

AND

JAMES W. THOMPSON, M.D., M.R.C.P.

Consultant Physicians, Dudley Road Hospital,
Birmingham

Some patients with portal cirrhosis have a higher cardiac output than normal (Kowalski and Abelmann, 1953; Murray *et al.*, 1958). Clinically the skin is warm and often dry (because of inability to sweat), the pulse is rapid and full, and the pulse pressure is increased. The cardiac impulse is forceful, with an accentuated mitral first sound, and often there is a systolic ejection murmur maximal internal to the apex; there may even be a short diastolic murmur.

Such a hyperdynamic state can occur in uncomplicated portal cirrhosis and in hepatic failure, the result of both cirrhosis and severe infective hepatitis. It is most frequently observed, however, in patients with extensive portal collateral circulations as a result of liver disease, especially if accompanied by a fall in the serum albumin concentration (Murray *et al.*, 1958).

It is not directly due to the anaemia or vitamin B deficiency, which may complicate portal cirrhosis: It is possible that failure to detoxicate a vasodilator substance (Shorr *et al.*, 1951) may account for the hyperdynamic circulation, or that the increase in cardiac output is secondary to the development of extensive arterio-venous anastomoses as a result of portal hypertension. Portal-systemic communications and spider naevi are well recognized, and there may also be intrahepatic shunts. In addition, anastomoses between the portal