PERNICIOUS ANAEMIA IN JAMAICA

BY

**K. L. STUART, M.D., M.R.C.P., M.R.C.P.Ed.
D.T.M.&H.***Senior Lecturer in Medicine*

AND

J. E. MacIVER, M.D.*Senior Lecturer in Haematology**University College of the West Indies, Jamaica*

Megaloblastic anaemias are common in tropical countries and usually have a background of nutritional deficiency. In Jamaica megaloblastic anaemia of infancy is extremely common (MacIver and Back, 1960a, 1960b), and is due to a nutritional deficiency of folic acid. On the other hand, megaloblastic anaemia of pregnancy is rather rare. In Trinidad, Habib (1960) has reported several cases of megaloblastic anaemia in adult males—strict Hindus—apparently due to a primary nutritional deficiency of vitamin B₁₂. Classical Addisonian pernicious anaemia is known to occur in the negro, but there is still some debate on its relative frequency in comparison with other races. It is well known that the incidence of pernicious anaemia varies widely among Caucasian races (Wintrobe, 1956), but it is still usually stated to be very rare in the negro when compared with the Caucasian (Kampmeier and Cameron, 1956; Wintrobe, 1956; Whitby and Britton, 1957). Although the relative frequency in the negro cannot be determined accurately at present, it is becoming increasingly evident that the incidence in this race is probably higher than was formerly thought.

The actual clinical appearance of pernicious anaemia probably depends upon several factors. These include the severity and duration of the gastric atrophic lesion, the dietary intake of vitamin B₁₂ and folic acid, and conditions which may alter the need for the absorption and utilization of these vitamins. It seems likely that these predisposing causes may be encountered more frequently in tropical than in contemporary Western medicine. Further study and increased awareness may indeed show that the incidences of pernicious anaemia in the negro, and some, at any rate, of the Caucasian races, are comparable. The relative incidence in the negro may even be exaggerated by the present trend towards the production of multivitamin preparations by the drug houses and their almost faddist consumption by a sophisticated public in Western communities. This has probably tended to suppress the clinical emergence of classical pernicious anaemia in otherwise predisposed individuals in these areas.

The purpose of this paper is to review the individual data on 10 negro patients with pernicious anaemia admitted to the University College Hospital in Jamaica in the 30 months from January, 1958, to June, 1960, and to indicate the frequency with which this disease is encountered locally. The usually accepted diagnostic criteria were followed. All the patients showed a macrocytic anaemia, a megaloblastic marrow, a histamine-fast achlorhydria, and a satisfactory response to vitamin B₁₂ therapy. In addition, the Schilling test was positive in seven patients. Gastric biopsy showed the characteristic atrophic lesion in the six patients on whom this test was carried out.

Methods

Schilling Test.—The fasting patient was given 0.5 μ c of ⁶⁰Co or ⁵⁸Co-labelled vitamin B₁₂ in 25 ml. of water. Twenty minutes later a light breakfast was given, and two hours later the oral dose of 1 mg. of non-radioactive vitamin B₁₂ was given by parenteral injection. All urine passed in the next 24 hours was collected and the volume measured. A 200-ml. aliquot of the urine was concentrated by evaporation to rather less than 20 ml. and the final volume adjusted to 20 ml. The radioactivity in this concentrate was determined and compared with that of a standard prepared by making a 1 in 50 dilution from the original oral dose. A thallium-activated sodium iodide well crystal and Ecko ratemeter were used. The test was repeated giving 30 mg. of an intrinsic-factor preparation at the same time as the oral dose of radioactive vitamin B₁₂.

Gastric biopsies were carried out using the suction-operated intestinal biopsy capsule described by Crosby and Kugler (1957). Fundal biopsies were taken and correct positioning of the biopsy capsule was ensured by screening.

Clinical and Laboratory Findings

The clinical and laboratory findings are summarized in Tables I and II. The presenting symptoms were in most instances referable to the anaemia and/or the accompanying neurological lesions and did not differ significantly from those of patients described elsewhere. There were, however, a number of points in the history and clinical findings which appear to merit special mention. Anorexia, vomiting, and weight loss of varying severity were particularly common features, and were encountered in 7 of the 10 patients. The duration of these symptoms ranged from a few weeks to several months. Seven of our 10 patients presented neurological symptoms and showed clinical evidence of a peripheral neuritis. Five of these also had central cord involvement (Table II). Hepatomegaly of two fingerbreadths or more was found in eight patients. In Case 7 the liver was hard and irregular and non-tender: liver function was impaired, and the liver biopsy was consistent with a post-necrotic scarring. The liver-function tests in the other patients with hepatomegaly were within normal limits; and the hepatomegaly subsided gradually with treatment. Glossitis was found on examination or as a presenting symptom in five patients. Three cases showed a mild splenomegaly which rapidly subsided with treatment.

In seven patients stools were examined for fat to exclude steatorrhoea as a possible cause for the anaemia. This was normal in all instances except Case 1, in which it was raised slightly. However, the prompt and sustained response to vitamin B₁₂ therapy alone in this patient, as in the others, makes this explanation unlikely. In the seven patients whose stools were examined for parasites the results were negative.

Discussion

In the tropics malnutrition, helminth infestation, and protozoal infections are often the commonest causes of community morbidity and mortality; and not uncommonly they constitute the essential background of a wide variety of disorders. In Jamaica helminth infestation and protozoal infections are becoming less common

and were found in none of our patients. However, an inadequate dietary intake which is low in fats and protein and relatively high in carbohydrate is still far from uncommon. It has been shown in Jamaica to be the common and possibly necessary background to a number of apparently unrelated disorders. These include the vomiting sickness of Jamaica (Stuart *et al.*, 1955), veno-occlusive disease of the liver (Stuart and Bras,

1957), and a number of neuropathies of at present undetermined aetiology (Cruickshank, 1961). More recently folic-acid-deficiency anaemias in malnourished infants have been demonstrated (MacIver and Back, 1960a, 1960b). However, other megaloblastic anaemias, such as those often found with sprue and other forms of malabsorption, with pregnancy, and with malnutrition, are uncommon.

TABLE I.—*Clinical Findings*

Case No.	Age	Sex	Presenting Symptoms	Duration	Weight Loss		Liver (Finger-breadths)	Spleen	Glossitis	Peri-pheral Neuritis	Cord Involvement	Icterus
					lb.	kg.						
1	52	F	Soreness of tongue, nausea, vomiting, weight loss Weakness of legs, paraesthesia Swelling of ankles, exertional dyspnoea	2 years 6 months 2 years	18	8.2	3	+	+	+	+	—
2	53	M	Shortness of breath, palpitations on exertion, generalized weakness Weight loss	3 weeks 2 years	25	11.3	2	+	+	—	—	+
3	45	M	Palpitations, exertional dyspnoea Paraesthesiae	8 months 2 years			3	—	+	+	—	—
4	56	M	Loss of appetite, weight loss, sore tongue, salivation	2 years	15	6.8	2	—	+	—	—	—
5	46	F	Nausea, vomiting, weight loss Palpitations, exertional dyspnoea	2 6 months	40	18.1	2	+	—	+	—	—
6	50	F	Numbness, paraesthesiae Unable to walk Loss of appetite, weight loss	6 3 12 "	+++*		2	—	—	+	+	—
7	46	F	Sore tongue, loss of appetite Drowsiness, disorientation	5 years 3 weeks	30	13.6	3	—	+	+	+	+
8	74	M	Weakness of legs, unsteadiness of gait	2 years	++*		—	—	—	+	+	—
9	45	M	Generalized weakness, paraesthesiae, difficulty in walking, exertional dyspnoea	3 months	+	*	2	—	—	+	+	+
10	38	M	Palpitations, exertional dyspnoea, giddiness	4 weeks	—		—	—	—	—	—	—

* Amount uncertain.

TABLE II.—*Laboratory Investigations*

Case No.	Hb	R.B.C. (mil./c.mm.)	P.C.V. %	M.C.V. (Cubic Microns)	M.C.H.C. (%)	W.B.C. (per c.mm.)	Blood Film	Megalo-blastic Marrow	Reticulocyte Count i. At Onset ii. Maximum Response	Schilling Test % Oral Dose of Radioactive B ₁₂ Excreted in Urine in 24 hr. i. Without Intrinsic Factor ii. After 30 mg. Intrinsic Factor	Histamine-fast Achlorhydria	Atrophic Gastritis on Gastric Biopsy
1	6.3 12.5	1.85 5.26	19 41	100 77	33 30	3,700 7,100	Anisocytosis Macrocytosis Poikilocytosis	+	1 27.1	1.4 6.6	+	Not done
2	4.9		16		30		Hypochromia Anisocytosis Macrocytosis	+	0.8 —	Not done	+	+
3	5.9 14	2.15 5.0	18 45	120 90	32 29	4,400 5,200	Macrocytosis Poikilocytosis Polychromasia	+	7.8 —	" "	+	Not done
4	7.5 13.6	1.82 5.0	19 44	105 31	34 31	3,150 6,750	Macrocytosis Hypochromia Anisocytosis	+	0.4 28	0.2 20	+	+
5	3.2 12.2	1.32 5.26	12 43	92 82	27 29	3,250 7,600	Anisocytosis Poikilocytosis Polychromasia	+	3.0 21.5	0.7 7.1	+	+
6	8.4 14.7	2.2 4.8	27 45	120 100	31 31	2,200 4,850		+		0.53 18.3	+	+
7	5.2 12.9	1.86 4.30	16 42	88 98	32 31	3,750 12,000	Macrocytosis Poikilocytosis Anisocytosis	+	3.5 26.0	Not done	+	+
8	10.3		31		33	3,300 6,150	Anisocytosis Poikilocytosis	+		2.2 16.5	+	Not done
9	3.1 12.3		11		29	10,100	Macrocytosis Poikilocytosis Anisocytosis	+	3 25	0.42 14.9	+	" "
10	4.9 12.0		15		32	3,600	Hypochromia Anisocytosis Poikilocytosis	+	0.1 20	1.75 10.3	+	+

It was tempting at first to assume that our cases were merely clinical variants of the nutritional macrocytic anaemia so commonly found in other tropical areas. It soon became evident, however, that there were no significant differences between the clinical and laboratory findings in our patients and their response to treatment when compared with patients with classical pernicious anaemia. Our findings also confirm those of Watson and Castle (1946), who have summarized and presented the evidence that the basic nutritional deficiency and essential clinical features in cases of nutritional macrocytic anaemia differ from those in Addisonian pernicious anaemia.

Anorexia, vomiting, vague abdominal pains, and sometimes considerable loss of weight were common findings in our patients. Although alimentary symptoms are not uncommon in classical pernicious anaemia it is perhaps unusual to find such marked loss of weight. In his original description Addison stressed this point and emphasized that "to the very last and after a sickness of perhaps several months' duration the bulkiness of the general frame and the amount of obesity often present a most striking contrast to the failure and exhaustion observable in every other respect." The severity of the weight loss in the patients presented here (Table I) was clearly a consequence of the degree and duration of the alimentary symptoms. It is also likely that anorexia would produce an earlier and more marked weight loss in individuals who have lived for a number of years on an inadequate or marginal diet than in better-nourished individuals in temperate climates. Medical advice may be also sought rather later in underdeveloped areas. Hicks and Leavell (1950) thought that the excessive loss of weight found in their negro patients with pernicious anaemia was really explained by the longer duration of the disease and associated anorexia.

Some consideration, however, of the possible role of malnutrition in the genesis of pernicious anaemia in Jamaica is inescapable. That pernicious anaemia is a deficiency disease is certain. The severity and duration of the gastric lesion is clearly the most important single factor that dictates its clinical appearance. It seems reasonable, however, that an inadequate dietary intake of vitamin B₁₂ would tend to enhance the effects of this basic lesion. Infestation with *Diphyllobothrium latum* causes a pernicious type of anaemia presumably by producing a conditioned deficiency of vitamin B₁₂, and probably merely unmasks pernicious anaemia in predisposed individuals. Wokes (1954) studied vitamin B₁₂ deficiency in vegans—that is, persons living on completely vegetarian diets without even milk, butter, cheese, or eggs. One had subacute combined degeneration of the spinal cord, which responded to treatment with vitamin B₁₂ (Badenoch, 1954). The increase in the number of cases of pernicious anaemia seen in Europe during and immediately after the 1914–18 war suggests that economic and, most likely, dietary factors may be of considerable importance (McIntyre *et al.*, 1959). It has also been shown that a large number of new cases of pernicious anaemia appear during the late winter and spring months (Grönberg, 1946), again suggesting the possible effect of dietary factors.

There have been several reports of pernicious anaemia in the negro in his African homeland. Trowell (1951) described a case in a man in Uganda. Adams and Wilmot (1953), in a paper on megaloblastic anaemia of pregnancy, stated that they had seen one African woman in whom the clinical features were indistinguishable

from those of pernicious anaemia. In neither of these cases were there any symptoms referable to the central nervous system. Woods and Rymer (1955) report a case of pernicious anaemia in an African Bantu woman with prominent neurological features. The patient's condition deteriorated during treatment with folic acid and improved markedly when vitamin B₁₂ was administered. Adams (1957) described a case, confirmed by gastric biopsy and estimation of the level of vitamin B₁₂ in the serum, in a Zulu male. Foy and Kondi (1958) also mentioned four cases of proved pernicious anaemia seen by them in East Africa in a four-year period. One of their patients had vague neurological symptoms. Metz *et al.* (1958) reported 10 unequivocal cases in the Bantu, and mentioned two further cases in an addendum. Nine of these patients were seen during a period of two and a half years. One case had subacute combined degeneration of the spinal cord.

It is interesting to note that 7 of our 10 patients presented evidence of peripheral neuritis, and in five of these there was also central cord involvement (Table I). Although slower than the haematological response the degree of improvement in these five patients was surprising and rewarding. Even the most severely incapacitated (Cases 1 and 6) were able to discard their sticks and wheelchairs and return to nearly normal physical activity in spite of some persisting evidence of posterior and lateral column damage. Reports from other tropical areas include that of Zimmermann and Dugger (1948) from Panama; and it is probably of some relevance that 8 of the 10 patients reported by these workers were migrants from the West Indies.

Conclusions on the relative frequency of pernicious anaemia in the negro and white races have been drawn largely from clinical impressions and from analyses of hospital admissions. Friedlander (1934), in analysing 500 cases of pernicious anaemia admitted to hospital, found that only about 0.05% of all negroes admitted had pernicious anaemia, whereas 1.2% of all Scandinavians admitted suffered from the disease. Wintrobe (1956) found 33 cases of pernicious anaemia in negroes out of a total of 329 cases in a hospital where the ratio of white to coloured patients was about three to one. From an analysis in another hospital, where 45% of the patients are coloured, Kampmeier and Cameron (1956) concluded that the disease was about seven times as common in the white as in the negro. Schwartz and Gore (1943) gave a white-to-negro incidence of five to one.

There are a number of factors not considered in these and similar analyses. The first is the relationship to age. A number of studies have shown that the incidence of pernicious anaemia increases strikingly with age (Eason, 1920; Meulengracht, 1925). It is well known that the average age of hospital populations tends to be higher in the more highly developed communities. For this reason alone there may be a false indication of a higher incidence in these communities if reliance is placed solely on hospital statistics. Added to this there is the fact that in many tropical countries survival to the age at which pernicious anaemia is likely to appear may be relatively uncommon. Therefore analyses that do not take into consideration population density in various age-groups and comparative death rates in the populations under study may be incomplete because of the deaths of predisposed individuals from unrelated causes before pernicious anaemia is manifested by clinical symptoms.

Comparison of incidence in biracial communities may also be fallacious if access to hospital and opportunities for full clinical and laboratory assessment are more limited for the negro than for the white on account of local social or economic circumstances. The picture is further complicated by the difficulty of establishing complete racial purity in the modern West Indian or American negro. All of our patients presented essentially negroid characteristics; but it cannot be affirmed with any certainty that there had been no admixture of white, Chinese, or Indian blood. For practical purposes, however, it can be said that they were typical and representative of the negro in the West Indies to-day.

These are aspects of the disease that clearly require careful and detailed analysis and constant awareness of the tendency for preconceptions to persist as misconceptions. For the reasons stated comparison with incidence rates from other hospitals is likely to be unrewarding. In our hospital, however, it is certainly significant that all our patients were diagnosed in the period from January, 1958, to June, 1960, whereas this diagnosis had been made only once in the previous five years (in a white American female). It was during these two and a half years that particular attention was being directed towards the study of two disorders commonly seen in Jamaica, which show some features of pernicious anaemia. These are the megaloblastic anaemia of infancy, which has been shown to be due to a dietary insufficiency of folic acid (MacIver and Back, 1960a, 1960b), and an unusual neuropathy of unknown aetiology, the neurological features of which are very similar to those of subacute combined degeneration of the spinal cord (Cruickshank, 1961). We have thought that it is this detailed study and increased awareness of these and allied disorders that account for the increasing frequency with which the diagnosis is being made locally, and not an increasing incidence.

Summary

Clinical and laboratory details are given on 10 negro patients with pernicious anaemia admitted to the University College Hospital in Jamaica in the 30 months from January, 1958, to June, 1960. All showed the usual clinical and laboratory features of pernicious anaemia; and in the patients on whom these tests were carried out the Schilling test and gastric biopsy findings were characteristic. Anorexia and loss of weight were conspicuous features.

It is thought that the rarity of this disease in the negro has been overemphasized and that hospital statistics may be misleading in this respect.

The literature on pernicious anaemia in other parts of the tropics is briefly reviewed. There is evidence that, in addition to the basic gastric lesion, dietary and economic factors may play a part in the genesis of the disease.

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THE SYMPTOMS OF HYPERPARATHYROIDISM*

BY

W. M. KEYNES,† M.D., F.R.C.S.

Senior Surgical Registrar, St. Bartholomew's Hospital,
London

For practical purposes the presence of a complication is needed to call attention to the diagnosis of primary hyperparathyroidism, but, particularly in recent years, patients have been seen whose initial complaint has not been due to either of the well-known complications of kidney stone and bone disease.

The parathyroid glands were discovered in 1880 by Sandström in Sweden; their relation to the calcium level of the blood was demonstrated by MacCullum and Voegtlin (1908). Von Recklinghausen (1891) described the generalized bone disease of osteitis fibrosa cystica, and Askanazy (1904) found a parathyroid tumour in a patient dead from this disease. Later, enlargement of the parathyroid glands was also noted in rickets and osteomalacia (Erdheim, 1907, 1914), and it was assumed that the parathyroid tumours in von Recklinghausen's disease were secondary to the bone disease. Schlagenhauer (1915), however, suggested that the reverse might be true, though it was not until July 30, 1925, that Mandl, in Vienna, explored a patient's neck, and with removal of a parathyroid tumour the bone condition improved (Mandl, 1926). Hyperparathyroidism was then considered to be synonymous with von Recklinghausen's disease of bone.

Albright *et al.* (1934) pointed out that renal stones were often found in patients with hyperparathyroidism (in 42 of 83 patients reviewed) and that the renal lesions could occur without the classical bone disease. Later it was also noted that osteoporosis might occur without bone cyst formation. Cope (1944) reviewed 78 cases and showed that, in fact, renal disease was more common than bone disease, a finding confirmed by a paper from the Mayo Clinic (Keating and Cook, 1945). Cope (1957) recorded clinical types of primary hyperparathyroidism as shown in Table I. It will be noted that one patient had neither bone disease nor renal stones.

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†Now at the London Hospital, Whitechapel.