Pernicious Anaemia-like Syndromes in the Non-White Population of Natal*

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SUMMARY

In a study of 60 patients with megaloblastic anaemia, drawn from the non-White population of Natal, 15 showed features resembling pernicious anaemia (PA). In only 3 did the disease correspond in every particular to that seen in Europe and America. Among the rest many patients were young. Intestinal malabsorption was a prominent feature. Five patients had intrinsic factor (IF) antibodies, yet at least 3 of them could not have had PA or 'latent PA'. In some cases low acid and IF output were reversed by treatment. Relatively high serum vitamin B\textsubscript{12} levels were the only evidence against PA in some otherwise typical cases. It is concluded that in this population, some as yet unspecified factor or factors cause varying degrees of gastric and intestinal malfunction, thus producing clinical syndromes resembling PA, sometimes even to the extent of the presence of IF antibodies in serum.


It is generally believed that pernicious anaemia (PA) is rare in the Bantu. Over the last 2 decades an increasing number of such cases have appeared in the literature, a fair proportion of them from this Medical School. With further experience and more refined methods of testing, we have had to revise the diagnosis in a number of these cases and are continually finding new ones which pose difficult diagnostic problems.

Out of a series of 60 consecutive cases of megaloblastic anaemia, comprising 51 Bantu and 9 Indian patients in Durban, we have here selected 13 Bantu and 2 Indians for further analysis. Each of these patients had a low gastric acid and intrinsic factor (IF) output, as well as megaloblastic anaemia, and thus bore at least some resemblance to PA.

METHODS

Serum folate levels were assayed by using \textit{Lactobacillus casei} as test organism. In some cases red cell folate was also measured as described by Chanarin. Serum vitamin B\textsubscript{12} levels were assayed by the method of Spray, with \textit{L. leichmannii} as test organism. Seven tests for malabsorption were performed, as follows:

1. Glucose tolerance test—50 g glucose orally.
2. Xylose tolerance test—a loading dose of 25 g and urinary estimation over 5 hours.
3. Vitamin A absorption test.
4. Fat excretion over 72 hours.
5. Schilling test, using 0.5 \( \mu \)g radioactive cyanocobalamin with and without intrinsic factor.

Gastric juice was obtained by continuous aspiration, before and after stimulation with histamine (0.04 mg/kg) or, latterly, with pentagastrin; pH, basal and maximal acid output per hour were determined.

Intrinsic factor was assayed by the method of Gottlieb \textit{et al.} using haemoglobin-coated charcoal as absorbent. IF antibodies in the serum were assayed using the same method in reverse.

Serial reticulocyte and haemoglobin estimations were performed before and after the Schilling test and after treatment with either folate or tetracycline, arranged as a double-blind trial, though consideration for the patients' welfare sometimes interfered with rigid adherence to this scheme.

RESULTS

These are set out in Table I and the results of the absorption tests appear in more detail in Table II.

DISCUSSION

Pernicious Anaemia

The first 3 cases appear to have true PA. One was an Indian, the others were Bantu. Among the latter, one had IF antibodies and also unmistakeable signs of subacute combined degeneration of the cord.

Malabsorption

Of the other 12 patients, 4 had evidence of moderate and 5 of gross intestinal malabsorption, often accompanied by a history of diarrhoea. This led to failure of the vitamin B\textsubscript{12} absorption to rise significantly with IF, except in cases 11 and 15. In these patients, therefore, the Schilling test did not show the typical PA pattern.
In case 5 (at first testing) and in case 7, this was the only evidence against the diagnosis of PA, in others there was other evidence as well.

Malabsorption of substances other than vitamin B₁₂ is not generally a feature of PA. Brummer and Harris found a minimal decrease in vitamin A absorption in this condition and Bezman et al. a slightly lowered urinary xylose excretion in 7 out of 20 patients, which they attributed to poor renal excretion. In the Schilling test, administration of IF often fails to bring absorption to normal levels in PA and this is nowadays attributed to the presence of IF antibodies in the gastro-intestinal tract. This failure to rise with IF, however, is rarely as severe as in the majority of our patients.

Occasional cases of PA with concomitant malabsorption have been described. Mollin et al. found 5 such cases among 66 cases of PA, 2 had intestinal diverticula, 1 a carcinoma of the stomach. The malabsorption was reversed either by vitamin B₁₂ alone, or by this substance together with folate. Ellis et al. described 1 patient who appears to have had gluten enteropathy. Brody et al. found a PA-like syndrome in 4 patients out of 9 presenting with malabsorption. One of these had jejunal diverticula, another a blind loop syndrome. In some of these, malabsorption (even of vitamin B₁₂) decreased on treatment with vitamin B₁₂ or tetracycline. Clark et al. described 2 patients apparently with gluten enteropathy and low immunoglobulin levels. The total number of cases of this combination described in the literature up to now is thus very small, and in only 4 could no cause for the malabsorption be found.

Of our patients, case 6 had had tuberculosis of several joints and a collapsed vertebra several years previously for which he had been adequately treated. Nonetheless his malabsorption could be the end-result of tuberculous enteritis. No diverticula, blind loops or other anatomical changes were found in the other patients. Gluten enteropathy has never been seen in Bantu with the possible exception of 1 case of dermatitis herpetiformis seen by one of us. Of the 5 patients tested for immunoglobulin levels 1 (case 13) had a slightly lowered IgA, with normal IgG and IgM levels. The other 4 were well within the normal range in all three levels. Thus the cause of malabsorption in the majority of our cases remains in doubt. The relation of this syndrome to tropical sprue will be discussed in another article.

### Acid and Intrinsic Factor

In cases 12-15, as well as in case 4 following treatment, IF output was very low, gastric acid output was also reduced, but true histamine-fast achlorhydria as defined in Table I was not present. This is different from the usual sequence in PA. Poliner and Spiro, using the Schilling test as a measure of IF production,
came to the conclusion that in general acid production failed before IF production. With the advent of methods for the direct estimation of IF, exceptions to this rule have been found. Thus Ardeman and Chanarin\textsuperscript{19} found an IF output below 1 000 units in 4 out of 10 patients with folate deficiency, 1 of whom did not have achlorhydria. Our 4 cases may be examples of the same phenomenon, though case 13 had a borderline serum folate level of 5 ng/ml and a red cell folate of 200 ng/ml and was thus doubtfully folate-deficient.

Intrinsic Factor Antibodies

Cases 3 - 7 had IF antibodies in their serum, yet only 1 of them can be regarded unequivocally as suffering from PA. Cases 5, 6 and 7 all had considerable evidence of intestinal malabsorption and hence an atypical Schilling test. The IF output of case 6, though low, was considerably higher than is usually seen in PA. Case 4, a young woman (25 years), appeared to have all the criteria of PA on admission, but after 4 weeks' treatment with folate produced both acid and IF in her gastric juice. She was also iron-deficient. Cases 4, 5 and 7, therefore, and perhaps also case 6, are examples of IF antibodies in the absence of PA.

Such cases are described in the literature, but are rare. The majority are found in thyroid disease,\textsuperscript{21,22} other auto-immune diseases,\textsuperscript{23,24} diabetes,\textsuperscript{25,26} and 'latent PA'.\textsuperscript{27,28} The latter is defined as: atrophic gastritis, achlorhydria and a rise in vitamin B\textsubscript{12} absorption on exhibiting IF in the absence of megaloblastic anaemia. It is assumed that these cases would in time proceed to the full-blown picture of PA. Evidence for this assumption is lacking.\textsuperscript{29}

Our cases differ from all the above. There was a complete lack of a positive family history of PA or auto-immunity, diabetes was excluded by the glucose tolerance test, none of the patients had thyroid disease. The only evidence for auto-immunity was a positive rheumatoid latex fixation test in case 4. She had neither thyroid nor parietal cell antibodies and her gamma globulins were not increased. Nor can our cases be called 'latent PA' as they were all suffering from (vitamin B\textsubscript{12}-deficient) megaloblastic anaemia and did not all have achlorhydria. In view of the now widely held belief that IF antibodies play a key-role in the development of PA, these are very interesting cases. It may be that severe gastric atrophy and/or low IF production can act as stimulus to IF antibody formation, unconnected with a genetic tendency to auto-immunity. These antibodies, once formed, mop up the remaining IF and produce a vitamin B\textsubscript{12}-deficient megaloblastic anaemia.

In true PA the cause of the gastric atrophy may be the presence of parietal cell antibodies on a genetic

### TABLE II. RESULTS OF ABSORPTION TESTS

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GT = glucose tolerance test; maximal rise above fasting in mg/100 ml.
XT = xylose tolerance test; urinary excretion in mg.
Vit. A = vitamin A absorption test: rise above fasting level in units/ml.
Fat = fat excretion in g/24 hours.
Schill. = Schilling test without and with IF.
Ba = barium meal; + = appearance of malabsorption.
Biop. = jejunal biopsy; + = partial villous atrophy.
Diarrh. = diarrhoea; + = positive history obtained.
Rep. = repeat of tests after 4 weeks' treatment with folate or tetracycline.
basis, in our cases another, as yet unidentified, factor may be the cause. Unfortunately parietal cell antibodies were tested for only in case 4.

**Effect of Treatment**

In some cases treatment improved gastric performance. Thus in case 4 acidity reappeared after folate; in case 5, IF reappeared and the IF antibody titre dropped markedly after folate. In cases 13 and 14, IF reappeared and the evidence for malabsorption lessened. It seems that whatever the cause of the gastric dysfunction is in these cases, the lesion is reversible, a phenomenon unknown in PA except after treatment with steroids.25,26

**Serum Vitamin B₁₂ Levels**

Serum vitamin B₁₂ levels were above the PA range in cases 8, 9, 11, 12 and 15. In the first 3 of these this was the only definite evidence against PA.

**Age**

Six of our patients were less than 35 years of age, including 2 with IF antibodies. In a recent survey, only 2.5% of PA patients were under the age of 40 years, so that there is an unusually high proportion of young people in our series.

**CONCLUSION**

It would seem that true PA does occur in the non-White population of Durban, but it is probably rare. Many cases so described may be examples of some other disorder in which an as yet unknown factor or factors produce varying degrees of gastric and intestinal malfunction and may even produce IF antibodies.

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This work comes from the Nutritional Anaemia Group sponsored by the South African Medical Research Council. Part of the work was supported by the Atomic Energy Board of South Africa and part by the Group Chairmen's Funds of the Anglo American Corporation and De Beer's Consolidated Mines Ltd.

We wish to thank Professor E. B. Adams, Head of the Department of Medicine; numerous colleagues for allowing us to investigate their patients; and Dr H. R. J. Wannenburg, Superintendent of King Edward VIII Hospital, for facilities.

**REFERENCES**