

Serum B₁₂ and Folate Concentrations in Mental Patients

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In a leading article on mental symptoms in vitamin B₁₂ deficiency (*Lancet*, 1965), it was pointed out that "though mental illness due to vitamin B₁₂ deficiency is uncommon, it is readily treated, and, as in general paralysis of the insane, its protean manifestations and uncertain physical signs call for an easily applied screening test comparable to the Wassermann reaction". In the correspondence which followed it was suggested that in psychiatric practice today mental symptoms were likely to be found more frequently in association with vitamin B₁₂ deficiency than with a positive serological test for syphilis (owing in part to the increasing number of patients with deficiency syndromes following gastro-intestinal surgery); and that estimation of serum B₁₂ concentration should be performed much more readily without waiting for clear-cut haematological evidence or neurological complications of megaloblastic anaemia (Hunter and Matthews, 1965). This was emphasized by the evidence of Strachan and Henderson (1965) who described three patients with psychiatric syndromes attributed to vitamin B₁₂ deficiency in whom not only peripheral blood but also bone marrow was normal; and the report from a mental hospital in Norway by Edwin *et al.* (1965) that of 396 patients over the age of thirty years admitted over a twelve months period, 23 (5.8 per cent.) had serum B₁₂ concentrations below the critical level of 100 µµg. per ml. as estimated by *Euglena gracilis* assay. This finding was challenged by Herbert *et al.* (1965), who suggested that drugs of the phenothiazine group administered to the patients might have suppressed the growth of the organism, but this was disputed by Edwin *et al.* (1966).

Here we report the results of serum B₁₂ estimations performed in 150 patients admitted to a mental hospital unit in a four-month period. In 75 patients serum folate, lactate

dehydrogenase (LDH) and hydroxybutyrate dehydrogenase (HBD) were also estimated. In all patients, routine haematological investigations were carried out (haemoglobin, mean corpuscular haemoglobin concentration, leucocyte count, erythrocyte sedimentation rate); but results are only given where abnormal or relevant.

Material

Of the 150 patients 69 were men and 81 women. Their ages ranged from 17 to 86 years; 47 were under 30, 53 between 31 and 50, 34 between 51 and 70, and 16 over 71.

Methods

Serum B₁₂ was estimated by a modification of the method of Hutner *et al.* (1956) (*Euglena gracilis*, z strain)—normal range 150-1,000 µµg. per ml.; serum folate with *Lactobacillus casei* by the method of Waters and Mollin (1961)—normal range 5.9-21 mµg. per ml.; random serum iron by the method of Ramsay (Varley, 1962)—normal range for men 80-180 µg. per 100 ml., for women 60-160 µg. per 100 ml.; LDH and HBD by a spectrophotometric method—normal range 70-240 i.u. per litre and 53-140 i.u. per litre (Wilkinson, 1962).

RESULTS

Serum B₁₂

Five patients had serum B₁₂ concentrations below 200 µµg. per ml. Of these, two patients had levels below 100 µµg. per ml. (in the pernicious anaemia range) and their case histories are given in detail below.

Three patients with values in the borderline low range between 100-200 µµg. per ml. had no detectable haematological or biochemical disorder. They were a malnourished widow of 73 living in social isolation—180 µµg. per ml.; a woman of 74 with post-traumatic dementia—120 µµg. per ml.; and a recently delivered

woman of 31–186 μg . per ml. Six months later their serum B₁₂ levels were 260, 680 and 380 μg . per ml.

An unexpected finding was that six patients, one man and five women, with a variety of psychiatric disturbances, had unusually high serum B₁₂ concentrations above 1,000 μg . per ml. with values of 1,020; 1,460; 1,130; 1,180; 1,210; and 2,440 μg . per ml.

None of these showed evidence of any of the recognized causes of high serum B₁₂ levels such as liver disease, myeloproliferative disorder, or chronic renal disease (Spray, 1962; Matthews and Beckett, 1962). The last four values were obtained from West Indians who had been in this country for 2–8 years.

The remaining patients had serum B₁₂ concentrations within the normal range. Excluding patients with B₁₂ concentrations of less than 100 μg . or more than 1,000 μg . per ml., the mean value was 465 μg . per ml.

The case histories of the two patients with B₁₂ concentrations below 100 μg . per ml. were as follows:

CASE I. Retired clerk aged 68 admitted as emergency with six months history of increasing depression, agitation, irritability, difficulty in concentrating, dizziness, weakness, feelings of unreality, constipation, numbness and tingling of extremities, with attacks of panic, parosmia, occasional falls, culminating in urge to kill his wife and himself.

Previous history: 1920 perforated duodenal ulcer; 1929 laparotomy for adhesions; 1949 partial gastrectomy, followed by bouts of dyspepsia with vomiting diagnosed as anastomotic ulcer.

Family history: non-contributory.

On examination: thin, pigmented, apathetic and easily agitated white-haired man looking older than his years, with evidence of recent intellectual deterioration. Positive physical findings were: blood pressure 100/50 mm. Hg, mild pitting oedema up to mid-calf; distended abdomen; slight generalized muscular weakness with symmetrical diminution of deep reflexes, mild inco-ordination, with hypaesthesia and hypalgesia and diminished vibration sense below the knees. Psychological testing confirmed mild intellectual deterioration.

Investigations: X-ray skull normal; X-ray chest showed old right lower zone fibrosis; barium meal showed small stomach remnant with dilatation of jejunum beyond it; barium enema showed atrophic colon. EEG normal. EMG: slight reduction of motor conduction velocity in ulnar and lateral popliteal nerves and abnormally low muscle action potentials, compatible with mild peripheral nerve disease.

Haemoglobin 14.0 g. per ml.; M.C.H.C. 32 per cent.; W.B.C. 2,500 per c.mm.; film normal; E.S.R. 18 mm. in 1 hr.

Serum B₁₂ 50 μg . per ml.; serum folate 9.5 μg . per ml.; serum iron 90 μg . per 100 ml.; LDH 110 i.u. per litre; HBD 70 i.u. per litre. Sternal marrow showed early megaloblastic changes. Histamine-fast achlorhydria. Schilling test (0.5 μg . dose): part 1, 6.4 per cent. excreted, part 2 (with intrinsic factor) 4.3 per cent. excreted (normal excretion > 15 per cent. of dose). Xylose test (25 g.); 5-hour urine excretion 6.4 g.; 2-hour serum concentration 57 mg. per 100 ml. (normal).

The diagnosis of a postgastrectomy vitamin B₁₂ deficiency state was made. In spite of the results of the Schilling test (subnormal excretion with failure to respond to intrinsic factor), it was thought the deficiency probably resulted from mucosal atrophy of the gastric remnant. A response to intrinsic factor does not invariably occur either in gastrectomized patients or those with pernicious anaemia (Maslow *et al.*, 1957; Brody *et al.*, 1966).

He was treated with intramuscular hydroxocobalamin 1,000 μg . twice weekly for four weeks followed by a monthly maintenance dose. He quickly lost his agitation and depression, oedema disappeared and blood pressure rose to 130/90 mm. Hg, but intellectual function and energy took three months to return to normal. Now, nine months later, he is sign and symptom free, apart from some residual paraesthesiae of the feet.

CASE II. A secretary, aged 57, transferred from another hospital where she had been an in-patient for two months and where the diagnosis of depression in a chronic schizophrenic was made. She had an 18 months history of progressive personality change with depression, hypochondriacal delusions and auditory hallucinations followed by increasing apathy and memory impairment, and culminating in three months vagabondism. Early in the illness she had an acute dystonic reaction to trifluoperazine; and in the two months before admission she developed a persistent face-tongue dyskinesia on chlorpromazine.

Previous history: 1962 radical mastectomy for carcinoma.

Family history: non-contributory.

On examination: thin, white-haired, ill-nourished, confused, amnesic, chain-smoking woman with continuous movements of face, mouth and tongue. No other abnormal physical signs. Psychological testing confirmed generalized intellectual deterioration.

Investigations: X-ray skull and chest normal; EEG showed paroxysmal delta activity in left mid- and anterior-temporal regions against a background of a slow dominant rhythm consistent with a metabolic disorder, or possibly metastasis at site of paroxysmal disturbance. Gamma scan: negative. C.S.F. normal.

Haemoglobin 13.6 g. per 100 ml.; M.C.H.C. 34 per cent.; M.C.V. 89 cu. μ .; W.B.C. 5,200 per c.mm.; film normal; E.S.R. 43 mm. in 1 hour.

Serum B₁₂ 95 μg . per ml.; confirmed by isotope dilution assay (Ekins and Sgherzi, 1965) result 100 μg . per ml.; serum folate 6 μg . per ml.; serum iron 140 μg . per 100 ml.; LDH 160 per litre; HBD 160 i.u. per litre.

Sternal marrow: too few cells obtained for opinion, second attempt refused. Gastric intubation refused. Diagnex blue test: presumptive evidence of achlorhydria. Schilling test unsuccessful owing to loss of urine.

Xylose test (25 g.), 5-hour urine excretion 5.1 g.; 2-hour serum concentration 53 mg. per 100 ml. (normal). Four day faecal fat excretion: 1.8 g. per day.

A diagnosis of a vitamin B₁₂ deficiency state was made, and she was treated with twice weekly injections of hydroxocobalamin 1,000 µg. for four weeks, followed by a monthly maintenance dose. At first there was no significant change in her mental state, although her physical health improved and she gained weight. In the third month she lost her psychotic symptoms and as her memory and concentration improved she took an interest in her surroundings. Four months after starting treatment she was regularly employed in one of the hospital utility departments. Psychological testing, however, showed that a moderate degree of intellectual impairment persisted, and she remained solitary in group activities. Repeat EEG now showed only a minor generalized disturbance. Eight months after admission she started working outside as a shop assistant, as she had not regained the confidence to return to her former shorthand/typing; four weeks later she unexpectedly committed suicide by taking an enormous quantity of aspirin.

Serum folate

The serum folate concentration was estimated in 75 patients. 37 (50 per cent.) had values of 3 mµg. per ml. or less, 13 of whom had levels of 2 mµg. per ml. or less. Many of the patients with low serum folate levels were addicted to barbiturates or alcohol or were on long-term treatment with anti-convulsant drugs. Of the 13 patients with folate levels of 2 mµg. per ml. or less, 6 (46 per cent.) fell into one of these groups and one patient was far advanced in pregnancy. Of the 24 patients with serum folate levels between 2–3 mµg. per ml., 7 (29 per cent.) were addicted to drugs, drink or both. In contrast, of the 38 patients with values above 3 mµg. per ml., only 2 (5 per cent.) had taken large amounts of alcohol or drugs and none was receiving anticonvulsant medication.

Other findings

Of the whole 150 patients 10 (7 per cent.), 4 men and 6 women, were found to have a mild iron deficiency anaemia. Five patients had slight elevations of LDH or HBD or both; of these one (Case II) was B₁₂ deficient, one had recently survived an episode of hypothermia, another suffered from bronchopneumonia, the fourth had a chromophobe adenoma of the pituitary, and in the fifth it was unexplained.

DISCUSSION

In this series of 150 patients admitted to a psychiatric unit, only two showed unequivocal

evidence of vitamin B₁₂ deficiency. Neither had a previous history of psychiatric illness, and both responded to treatment with vitamin B₁₂ although it took some months before they became symptom free. In Case I the diagnosis was suspected because of a previous investigation of B₁₂ deficiency as a cause of psychiatric symptoms in gastrectomized patients (Hunter *et al.*, 1967). In Case II, who had been diagnosed elsewhere as schizophrenic, B₁₂ deficiency was not obvious on clinical grounds; she presented as a presenile dementia and the focal disturbance in her EEG gave rise to the suspicion of cerebral metastases from her previously operated breast cancer. It is noteworthy that neither of these patients was anaemic, or showed any morphological changes in their peripheral blood. Case I had other evidence of B₁₂ deficiency, i.e. megaloblastic bone marrow and poor B₁₂ absorption, and in Case II the B₁₂ estimation was confirmed by isotope dilution assay which should be uninfluenced by drugs or their metabolites. Further, both patients responded satisfactorily to vitamin B₁₂ therapy although improvement in their mental state was initially slow. Their histories indicated that developing vitamin B₁₂ deficiency symptoms had been present for at least six months in Case I and 18 months in Case II. Confirmation of this is found in Case II, who developed an acute dystonic reaction when treated with phenothiazines and later a face/tongue dyskinesia which persisted for six months after the drug was discontinued. Evidence has been previously presented that such reactions are more likely in patients with cerebral impairment (Hunter *et al.*, 1964).

Three further patients, one recently delivered and one obviously malnourished, had "borderline" serum B₁₂ levels between 100–200 µµg. per ml. This proportion is no higher than might be expected in a normal group of this size (Mollin and Ross, 1952; Shinton, 1959; Matthews, 1962). They were not treated with vitamin B₁₂ supplement, and repeat estimations eight months later gave values within the normal range. Low values of serum B₁₂ in these patients are unlikely to have been due to drug treatment since at the time of the investigation they were only on small doses of chloral hydrate.

The present findings do not confirm the high incidence of B₁₂ deficiency in psychiatric patients of 5.8 per cent. reported by Edwin *et al.* (1965). Although they examined more than twice as many patients, all of whom were over 30 years of age, it seems unlikely that the difference can be explained solely on these grounds.

Of the six patients with unusually high serum B₁₂ levels, four were West Indians, in whom such values are not uncommonly found (Mollin and Read, 1966). In two patients the high values were unexplained but in one the value was hardly outside the normal range. The majority of B₁₂ values in our patients were normal with a normal mean, and there was no general tendency to low or high B₁₂ concentrations.

The striking incidence of low folate concentrations in this series is partly accounted for by the large number of patients who took alcohol and/or barbiturates to excess, or were on anticonvulsant drugs for epilepsy; in part it may reflect patients' dietary. An association between low folate concentrations and barbiturate and anticonvulsant medication is now well established (Klipstein, 1964; Reynolds *et al.*, 1966; Malpas *et al.*, 1966), and Herbert (1964) has reported an antifolate effect of alcohol. Only four of these 13 patients were anaemic, and they showed evidence of iron deficiency. However, biochemical and haemopoietic disturbances due to folate deficiency, like those due to B₁₂ deficiency, cannot be excluded by the absence of anaemia or morphological changes in the peripheral blood, since many non-anaemic epileptics on anticonvulsants show megaloblastic changes in bone marrow and there is evidence that folate deficiency or disturbed folate metabolism may lead to mental changes in the absence of anaemia (Reynolds *et al.*, 1966; Reynolds *et al.*, 1967).

Five patients had slight elevations of serum LDH and HBD or both. These estimations were performed because both are usually greatly raised in anaemia due to deficiency of B₁₂ or folic acid (Wilkinson, 1962), and it was thought they might provide confirmatory evidence in doubtful cases. However, it has recently become clear that these enzymes are generally only elevated when there is a substantial degree of anaemia (Emerson, 1965; Reynolds *et al.*, 1966).

SUMMARY

Serum B₁₂ was estimated in 150 patients admitted to a mental hospital unit over a period of four months.

Two patients were found to be suffering from vitamin B₁₂ deficiency syndromes, and their psychiatric illness cleared gradually when this was corrected. Neither was anaemic or exhibited signs of spinal cord involvement though one had evidence of peripheral neuropathy. They had been ill for six and eighteen months respectively before the deficiency was discovered. The patient who had been ill the longer, and who made only a partial recovery, committed suicide nine months later.

In the remaining patients serum B₁₂ concentrations were normal, with the exception of two unexplained high values.

Serum folate estimations in 75 patients showed low levels in 37, 13 of whom (35 per cent.) were consuming large amounts of alcohol and/or barbiturates, or were on an anticonvulsant regime.

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ADDENDUM

Since this paper was prepared for publication Henderson *et al.* (1966) have reported an incidence of B₁₂ deficiency of 0.88 per cent. in 1,012 unselected psychiatric patients in Scotland.

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