group, suggesting that home circumstances were not influencing admission to any great extent.

Breast-feeding certainly does not give complete protection. Work done by Toms *et al*[6] has shown that breast milk varies in its antirespiratory syncytial virus activity; only four of 16 mothers tested had high levels of IgA specific for respiratory syncytial virus and five of 17 had lymphocytes sensitised to respiratory syncytial virus in their milk. This probably relates to recent exposure of the mother to the virus.

It is interesting that infants do not need to be breast-fed at the time of exposure to infection to be protected; there appears to be a lasting effect. This may be due to the fact that lymphocytes in the colostrum or milk that are sensitised to respiratory syncytial virus colonise the infant's nasopharynx, or to stimulation of the infant's own immune response by transfer of sensitised T cells or of antigen on macrophages. Recent work has suggested that the IgE response in the respiratory tract may be important in the pathogenesis of bronchiolitis,[7] and breast milk in rats has been shown to suppress the IgE response.[8]

This demonstration that breast-feeding probably influences respiratory syncytial virus infection in infants suggests three possible approaches to the problem. Firstly, it gives another reason for encouraging mothers to breast-feed their babies. Secondly, it has prompted us to look further at the immune status of mothers and how this is reflected in their milk and in their infants: boosting mothers' immunity might increase the protection they give to their babies. Thirdly, it provides a stimulus to the investigation of the nature of the protective factors in milk, helping to increase our understanding of immunological defences against respiratory syncytial virus infection.

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# The neuropsychiatry of megaloblastic anaemia

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## Summary and conclusions

**The neuropsychiatric states of 50 patients with vitamin $B_{12}$ deficiency and 34 patients with folate deficiency presenting with megaloblastosis in a general hospital were examined and compared. Abnormalities of the nervous system were found in two-thirds of both groups. Peripheral neuropathy was the most common condition associated with vitamin $B_{12}$ deficiency and affective disorder with folate deficiency. The proportions of patients with organic mental change were similar in the two groups. Subacute combined degeneration of the cord was an uncommon complication and occurred only in the patients with vitamin $B_{12}$ deficiency. There was no relation between haematological and neuropsychiatric abnormalities.**

**The neuropsychiatry of megaloblastic anaemia seen in this study of patients presenting to haematologists or general physicians contrasts with that reported previously, before haematological techniques for separating the two deficiencies were introduced.**



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## Introduction

Modern textbook accounts of the neuropsychiatry of megaloblastic anaemia are based on the many clinical reports in the first half of this century before the synthesis of folic acid in 1945 and the isolation of vitamin $B_{12}$ in 1948, and therefore before these two deficiency states could be clearly distinguished.[1 2] No comprehensive study of the neuropsychiatry of vitamin $B_{12}$ deficiency has been carried out since the vitamin $B_{12}$ assay became available in the 1950s, although the effect of vitamin $B_{12}$ deficiency on peripheral nerves,[3] mental symptoms,[4] and the effects of vitamin $B_{12}$ malabsorption after partial gastrectomy[5] have been explored to a limited extent. Furthermore, the neuropsychiatry of vitamin $B_{12}$ deficiency has not been compared with that of folate deficiency despite increasing reports of neuropsychiatric disorders associated with folate deficiency in the past 15 years.[6]

We undertook the present study, therefore, to obtain a more up-to-date perspective of the neuropsychiatric disorders associated with megaloblastic anaemia and to distinguish clearly vitamin $B_{12}$ from folate deficiency with modern haematological techniques. As these deficiency states present more commonly to haematologists and general physicians than to neurologists and psychiatrists we carried out this investigation in a general medical setting.

## Patients and methods

We examined and compared the neurological and psychiatric states of 84 successive patients admitted to Northwick Park Hospital with morphological and biochemical evidence of either vitamin $B_{12}$ or folic

acid deficiency. Only patients referred to consultant haematologists or physicians were included. Neurological or psychiatric admissions were excluded. The criteria for inclusion were a megaloblastic marrow associated with either a serum concentration of vitamin $B_{12}$ (*Lactobacillus leichmanii*) below 150 ng/l (patients deficient in vitamin $B_{12}$) or a serum folate concentration (*Lactobacillus casei*) below 2·5 μg/l together with a red-cell folate concentration below 150 μg/l (folate-deficient group). Patients with evidence of *both* deficiencies were excluded, as were patients with other medical conditions known to produce neurological disease such as diabetes, alcoholism, renal or hepatic failure, and malignant disease.

Disturbances of mental state were classified as organic or affective on the basis of psychiatric interviews by two of us, and according to two self-rating scales—namely, the symptoms rating scale of Kellner and Sheffield, and the Foulds symptoms inventory. Subacute combined degeneration of the cord was diagnosed on the finding of pyramidal signs (weakness, spasticity, clonus, hyperreflexia, or extensor plantar responses) together with impairment of vibration sense or joint position sense, or both, in the legs. The criterion for peripheral neuropathy was distal weakness and wasting, reduced or absent reflexes, or glove and stocking sensory loss to all modalities. Isolated impairment of vibration sense in the legs was also regarded as evidence of peripheral neuropathy; this was confirmed by electrophysiological studies.

Seventy-one of the 84 patients underwent electrophysiological studies of peripheral nerve function. Sural and median sensory action potential and conduction were measured as described elsewhere.[7]

## Results

Table I shows the age, sex, and medical diagnosis of the 50 patients with vitamin $B_{12}$ deficiency and 34 with folic acid deficiency. The sex ratio in the two groups was similar, but the mean age of the group with vitamin $B_{12}$ deficiency was higher, mainly owing to an older subgroup of 32 patients with pernicious anaemia (tables I and II).

*Haematological findings* (table II)—There was no difference in the degree of anaemia or macrocytosis between the two groups. The patients with vitamin $B_{12}$ deficiency who had pernicious anaemia had more pronounced macrocytosis, lower vitamin $B_{12}$ and red-cell folate concentrations, and higher serum folate concentrations than those without pernicious anaemia.

*Neuropsychiatric findings*—Table III shows individual symptoms and signs, and table IV the overall findings. About two-thirds of both groups had some neuropsychiatric abnormality. The most common finding in the patients with vitamin $B_{12}$ deficiency was peripheral neuropathy (in 40%), the main features of which were paraesthesia, absent reflexes, and especially impaired vibration sense in the legs. Only eight patients (16%) had evidence of subacute combined degeneration of the cord. In contrast, evidence of neuropathy was present in only 18% of the patients with folate deficiency, none of whom had subacute combined degeneration of the cord. The most common finding in the folate-deficient group was an affective disturbance (in 56%) compared with 20% in the group with vitamin $B_{12}$ deficiency. In both groups about one-quarter had organic mental changes. Table III shows that among patients with vitamin $B_{12}$ deficiency neuropsychiatric abnormalities are more common in those with pernicious anaemia. Only 19% of the patients with pernicious anaemia were neurologically normal compared with 55% of those without. Neuropsychiatric abnormalities were more common among men (89%) than women (55%) with vitamin $B_{12}$ deficiency. In folate deficiency the opposite trend was observed (men 58% *v* women 68%). The degree of neuropsychiatric disability varied considerably but was severe in one patient with neuropathy, all the patients with subacute combined degeneration of the cord, and many of those with an affective disorder.

*Electrophysiological findings* in 43 patients with vitamin $B_{12}$ deficiency and 28 with folate deficiency are reported elsewhere (unpublished observations),[7] but table V shows that electrical evidence of peripheral nerve disease was present in 28 (65%) of the patients with vitamin $B_{12}$ deficiency, including all those with subacute combined degeneration of the cord. The abnormalities included reduction or absence of sensory action potential in the sural nerve in 24 patients and in the median nerve in 12. Conduction velocity was reduced in the sural nerve in 12 patients and the median nerve in seven. In the group with folate deficiency abnormalities of sensory action potential were found in the sural nerve in six patients and the median nerve in five. Sural conduction velocity was reduced in one and median conduction in two. The combined clinical and electrical evidence suggests that neuropathy is about three times as common in vitamin $B_{12}$ than in folate deficiency. Mental changes without electromyographic abnormalities are, however, more common in folate deficiency in a similar ratio.

TABLE I—*Details of patients and diagnoses*

| | Vitamin $B_{12}$ deficiency (n = 50) | Folate deficiency (n = 34) |
|---|---|---|
| Mean age (range) (years) | 60 (18-87) | 40 (20-77) |
| Sex: | | |
| Male | 19 | 12 |
| Female | 31 | 22 |
| Diagnosis: | | |
| Pernicious anaemia | 32 | |
| Dietary | 8 | 8 |
| Gastrointestinal disease | 7 | |
| Coeliac disease | | 16 |
| Malabsorption | | 8 |
| Unexplained | 3 | 2 |

TABLE II—*Haematological findings (expressed as means ± SD)*

| | Vitamin $B_{12}$ deficiency | | | |
|---|---|---|---|---|
| | Patients with pernicious anaemia | Patients without pernicious anaemia | Total | Folate deficiency |
| No. of patients | 32 | 18 | 50 | 34 |
| Mean age (years) | 70 | 42 | 60 | 40 |
| Haemoglobin (g/dl) | 10·1 ± 3·8 | 10·3 ± 3·0 | 10·2 ± 3·5 | 11·2 ± 2·5 |
| Mean cell volume (mm³) | 107 ± 13·3 | 93 ± 12·4 | 102 ± 14·7 | 97 ± 12·1 |
| Serum $B_{12}$ (ng/l) | 63 ± 40·9 | 91 ± 29·3 | 73 ± 39·3 | 217 ± 91·1 |
| Serum folate (μg/l) | 7·4 ± 3·9 | 5·5 ± 4·4 | 6·6 ± 4·4 | 1·5 ± 0·6 |
| Red blood cell (μg/l) | 178 ± 86 | 196 ± 138 | 184 ± 109 | 87 ± 40·0 |

TABLE III—*Neuropsychiatric symptoms and signs (Figures are numbers (%) of patients)*

| | Vitamin $B_{12}$ deficiency | | | |
|---|---|---|---|---|
| | Patients with pernicious anaemia (n = 32) | Patients without pernicious anaemia (n = 18) | Total | Folate deficiency |
| *Symptoms* | | | | |
| Weakness (legs) | 2 (6) | 1 (6) | 3 (6) | 1 (3) |
| Ataxia (legs) | 4 (13) | | 4 (8) | 1 (3) |
| Parasthesia: | | | | |
| Legs | 8 (26) | 1 (6) | 9 (18) | 2 (6) |
| Legs and arms | 2 (6) | 1 (6) | 3 (6) | 2 (6) |
| *Signs* | | | | |
| Distal weakness | 4 (13) | 1 (6) | 5 (10) | 1 (3) |
| Pyramidal weakness | | | | |
| Ataxia (legs) | 4 (13) | | 4 (8) | 1 (3) |
| Absent ankle jerk | 2 (6) | 1 (6) | 3 (6) | 3 (9) |
| Arreflexia: | | | | |
| Legs | 3 (9) | | 3 (6) | 1 (3) |
| Legs and arms | 1 (3) | | 1 (2) | 1 (3) |
| Extensor plantars | 7 (22) | 1 (6) | 8 (16) | |
| Impaired vibration sense (legs) | 16 (50) | 4 (22) | 20 (40) | 2 (6) |
| Impaired joint position sense | 5 (16) | | 5 (10) | 1 (3) |
| Distal impairment of pain and temperature | 1 (3) | | 1 (2) | 1 (3) |
| Optic atrophy | 1 (3) | | 1 (2) | |
| *Mental state* | | | | |
| Affective change | 6 (19) | 4 (22) | 10 (20) | 19 (56) |
| Organic change | 11 (34) | 2 (11) | 13 (26) | 9 (27) |
| *No neuropsychiatric abnormality* | 6 (19) | 10 (55) | 16 (32) | 12 (35) |

TABLE IV—*Summary of neuropsychiatric findings. (Figures are numbers (%) of patients)*

| | Vitamin $B_{12}$ deficiency (n = 50) | Folic acid deficiency (n = 34) | p* |
|---|---|---|---|
| Normal | 16 (32) | 12 (35) | NS |
| Organic mental change | 13 (26) | 9 (27) | NS |
| Affective disorder | 10 (20) | 19 (56) | <0·001 |
| Subacute combined degeneration of cord | 8 (16) | | <0·05 |
| Peripheral neuropathy | 20 (40) | 6 (18) | <0·1 |
| Optic atrophy | 1 (2) | | NS |

* $\chi^2$ test with Yates's correction.

TABLE V—*Summary of electrophysiological and clinical findings. (Figures are numbers (%) of patients)*

| | Vitamin $B_{12}$ deficiency (n = 43) | Folic acid deficiency (n = 28) | p* |
|---|---|---|---|
| Electrophysiological findings: | | | |
| Normal | 15 (35) | 22 (79) | <0·001 |
| Abnormal | 28 (65) | 6 (21) | |
| Electrophysiological plus clinical findings: | | | |
| Normal | 10 (23) | 11 (39) | <0·1 |
| Electromyographic abnormality only | 3 (7) | | NS |
| Clinical abnormality only | 5 (12) | 11 (39) | <0·02 |
| Electromyographic plus clinical abnormality | 25 (58) | 6 (22) | <0·01 |

* $\chi^2$ test with Yates's correction.

*Relation of neuropsychiatric to haematological findings*—There were no significant differences in the vitamin and haemoglobin concentrations or mean cell volume between those with and without neuropsychiatric abnormalities in either deficiency state. There were no correlations between the haematological or biochemical variables and any particular neuropsychiatric disorder. Among patients with neuropsychiatric disorders haemoglobin concentration was above 12 g/dl in 44% with vitamin $B_{12}$ deficiency and 45% with folate deficiency; and the mean cell volume was below 96 $mm^3$ in 28% with vitamin $B_{12}$ deficiency and 41% with folate deficiency.

## Discussion

The patients in this study were deficient in either vitamin $B_{12}$ or folic acid to a degree sufficient to produce megaloblastic changes in the bone marrow. Interesting similarities and differences arose in the associated neuropsychiatric findings. About one-third of each group had no clinical disturbance referable to the nervous system, and one-quarter had evidence of organic mental change. The most common abnormality in vitamin $B_{12}$ deficiency, however, was peripheral neuropathy (in 40%), indicated by paraesthesia, absent reflexes, and impaired vibration sense mainly in the legs. Electrophysiological evidence of subclinical neuropathy was found in a further 25%, so that, overall, clinical or electrical neuropathy was three times more common in vitamin $B_{12}$ than folate deficiency. Subacute combined degeneration of the cord was present in only 16% of the patients with vitamin $B_{12}$ deficiency and was always accompanied by clinical or electrical evidence of neuropathy. This is also true of patients presenting primarily to neurologists with subacute combined degeneration of the cord (D Jefferson, personal communication). The condition was not seen with folate deficiency in this series but has only rarely been reported.[8] By contrast, the most common neuropsychiatric abnormality in folate deficiency was an affective disturbance, which occurred in 56% of the patients and was thus almost three times more common than in vitamin $B_{12}$ deficiency. Depression has been a prominent feature of the neuropsychiatric disorders attributed to folic acid deficiency.[6 9]

It cannot be assumed that all the neurological abnormalities in these patients were the result of the deficiencies. Both series inevitably included patients with gastrointestinal disease or dietary problems in whom other deficiencies might reasonably be expected. Even in pernicious anaemia secondary deficiencies may occur owing to megaloblastic change in the gastrointestinal tract, and associated autoimmune diseases might also sometimes play a part; certainly the presence or type of neuropsychiatric abnormality is not obviously related to the vitamin concentrations, or, as we have confirmed, the haematological abnormalities. Nevertheless, a causal role, even a major one, seems probable in many patients, especially in view of the reports of neuropsychiatric improvement with the appropriate vitamin replacement.[6 10]

One possible reason for some of the differences between the two groups is the younger age of the patients with folate deficiency. The age factor might operate in more than one way. The younger nervous system might be less vulnerable to the effects of a deficiency, or in the older patients the deficiency might have been present longer, though this last would be difficult to prove. Vitamin $B_{12}$ deficiency usually takes much longer to develop than folate deficiency owing to the much greater body stores of vitamin $B_{12}$. On the other hand, the vulnerability factor may well be important even in vitamin $B_{12}$ deficiency because the incidence of neuropsychiatric disorders was much higher in the older subgroup with pernicious anaemia.

Although the neuropsychiatric complications of the two deficiencies overlap, one reason for the relatively greater impact of vitamin $B_{12}$ deficiency on the peripheral nerves and spinal cord, and of folate deficiency on cerebral function, may be related to the different functional roles of these vitamins in the nervous system. Although little is known of these functions for either vitamin,[6 9] it is already apparent that folate and its derivatives have potent excitatory properties and may play a part in synaptic events,[11] whereas there is no evidence for this with vitamin $B_{12}$. It is interesting, therefore, that deficiency of a substance with excitatory properties leads most commonly to depression.[1] The neuropsychiatric features in common between the two deficiencies may possibly be related to their role in nucleoprotein metabolism, although this has been little explored with respect to the nervous system.

The neuropsychiatry of megaloblastic anaemia shown by this study contrasts with most textbook accounts, which put much greater emphasis on vitamin $B_{12}$ deficiency and, in particular, its spinal-cord complications. This is the first attempt to examine the neuropsychiatric aspects of this anaemia comprehensively since the introduction of haematological techniques to separate the two deficiencies in the last 30 years. Another reason for the changing picture may be that modern techniques such as the Coulter S counter make it possible to detect these anaemias and deficiencies much earlier so that the older, florid examples of subacute combined degeneration of the cord are now much less common. Finally, we emphasise that the view we have presented is that seen by the haematologist or general physician. It is well known, but often overlooked, that these deficiencies may present less commonly to neurologists or psychiatrists, with little or no haematological abnormality.

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