

Folate Deficiency in Depressive Illness

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INTRODUCTION

Two reports have shown that a substantial proportion of patients suffering from various psychiatric syndromes have low serum folate concentrations (Hunter, Jones Jones and Matthews, 1967; Carney, 1967). The present investigation was concerned to examine further the prevalence of low serum folate in a series of depressive patients on admission to hospital. As folate deficiency contributes to the development of mental symptoms in epileptic patients (Reynolds, 1968), we also examined the relationship of low serum folate concentrations to the severity of the depressive illness, certain personality traits, and the response to anti-depressant treatment. The relationship of low serum folate to variables which could influence it such as diet and drugs was also examined. In a proportion of these patients serum folate measurements were repeated just before the patient's discharge. Serum B₁₂ concentrations were also estimated.

METHODS

Serum folate and B₁₂ estimations were carried out on 41 men and 60 women admitted to a clinical investigation ward with the diagnosis of depression. The mean age of the men was 49·1 years (s.d. 14·5 yrs.) and the mean age of the women 46·7 years (s.d. 11·9 yrs.). The patients were selected on the basis of a history of severe unremitting depression with various accompanying symptoms such as diurnal variation of mood, feelings of guilt and unworthiness, suicidal thoughts, insomnia, and loss of appetite and energy. Patients with physical illness were excluded.

All the patients were assessed by means of a self-rating depression inventory (Beck *et al.*, 1961) which has been shown to agree well with psychiatrists' rating of clinical state (Metcalf and Goldman, 1965). Each patient completed

the inventory for measuring depression on admission and then twice weekly on Monday and Thursday mornings. On admission and discharge each patient completed two personality inventories—the Eysenck Personality Inventory (Eysenck, 1964) and the English version of the Marke-Nyman temperament scale (Coppin, 1966). These two inventories give five personality measures. Neuroticism is defined by Eysenck as the general emotional lability of the subject, his emotional over-responsiveness and liability to neurotic breakdown under stress. Extraversion refers to a subject's outgoing social proclivities. In the Marke-Nyman temperament scale Solidity is a dimension related to maturity, Stability corresponds roughly to Eysenck's extraversion dimension, Validity is a dimension of personality concerned with the degree of psychological energy available; thus the individual with low validity scores is regarded as cautious, easily fatiguable, quiet. Both personality questionnaires, as normally administered, are influenced by a depressive illness (Coppin and Metcalfe, 1965; Coppin, 1966), and it is thought that the scores obtained on discharge reflect more closely the patient's usual personality.

A careful nutritional history was taken from each patient on admission and an attempt was made to assess the amount of weight loss. On the basis of this information the patients were grouped into the categories of poor, moderate, good, or unknown nutrition prior to admission.

Each patient and his informant was also questioned about the drugs he had been taking during the six months prior to admission. The patient's general practitioner was also approached and asked to specify the drugs the patient had been receiving during this time.

Serum was collected at 8 a.m. usually on the first and always by the third day after admission, with the patient in a fasting state. Samples were

collected in the same way just before discharge. Patients were treated by either electroconvulsive therapy or antidepressant drugs and in some cases by tryptophan (Coppen, Shaw, Herzberg and Maggs, 1967). Serum folate activity was assayed microbiologically using *Lactobacillus casei* (Baker *et al.*, 1959). Serum vitamin B₁₂ concentration was assayed microbiologically using *Lactobacillus leichmannii*.

RESULTS

Normal serum folates are usually said to be 5 ng./ml. or above although there is some uncertainty about the significance of values between 2.5 and 5 ng./ml. (Girdwood *et al.*, 1967). The serum folate concentrations were therefore at first divided into three groups; low (0.2-5 ng./ml.); equivocal (2.6-5.0 ng./ml.) and normal (5.1 ng./ml. and over). As there was no significant difference in the other variables studied in this investigation between the equivocal and normal groups, these two were combined and compared with the low serum folate group. Serum vitamin B₁₂ concentrations were divided into low (0-200 pg./ml.) and normal (201 pg./ml. and over). Note that 1 nanogram (ng.) is 10⁻⁹ g., and 1 picogram (pg.) is 10⁻¹² g.

Age, sex, method of treatment. None of these factors appeared to influence either serum folate or vitamin B₁₂.

Diet and drugs. The effects of diet are shown in Table I where it will be seen there is little difference between patients with a poor and a good nutritional history. It was found that nearly all the patients had been receiving drugs prior to admission but low serum folate and vitamin B₁₂ did not appear to be associated with any particular medication. However, in view of the depressant effects of anti-convulsant drugs, including barbiturates (Reynolds, *et al.*, 1966), on serum folate concentration this was examined by comparing groups of patients who had and who had not been taking barbiturates prior to admission. Table II shows that there was no significant difference between these groups.

Depression inventory scores and serum values

Table III shows that 22 out of 91 patients (24 per cent) had low serum folate concentrations. Patients in this group had significantly higher depression inventory scores on admission and also on discharge than did those patients with equivocal or normal serum folates. There were 13 out of 90 patients (14 per cent) with low serum vitamin B₁₂ concentrations (<200

TABLE I
Diet and serum folate and vitamin B₁₂ concentration

| Diet | Serum folate (ng./ml.) | | | Serum B ₁₂ (pg./ml.) | | |
|-----------|------------------------|------|------|---------------------------------|------|------|
| | n | mean | S.E. | n | mean | S.E. |
| Poor | 30 | 4.6 | 0.6 | 29 | 316 | 23 |
| Moderate | 18 | 5.5 | 1.0 | 18 | 370 | 34 |
| Good | 31 | 4.9 | 0.6 | 30 | 313 | 21 |
| Not known | 16 | 4.8 | 0.7 | 16 | 306 | 19 |

TABLE II
The effect of barbiturates on serum folate and vitamin B₁₂ concentration

| On admission | Barbiturates | | | Non-Barbiturates | | |
|---------------------------------|--------------|------|------|------------------|------|------|
| | n | mean | S.E. | n | mean | S.E. |
| Serum folate (ng./ml.) | 27 | 5.8 | 0.8 | 45 | 4.8 | 0.5 |
| Serum B ₁₂ (pg./ml.) | 27 | 333 | 26 | 43 | 331 | 16 |

TABLE III
Depression inventory scores and serum folate and vitamin B₁₂ concentrations

| Serum folate and vitamin B ₁₂ concentrations on admission | Depression inventory scores | | | | | |
|--|-----------------------------|-------------------|------|-----------|-------------------|------|
| | Admission | | | Discharge | | |
| | n | mean | S.E. | n | mean | S.E. |
| Serum folate 0-2.5 ng./ml. .. | 22 | 22.1 ^A | 2.1 | 22 | 9.4 ^D | 1.6 |
| Serum folate 2.6-5.0 ng./ml. .. | 41 | 17.1 ^B | 1.6 | 38 | 5.7 ^E | 1.2 |
| Serum folate 5.1 + ng./ml. .. | 28 | 15.8 ^C | 2.0 | 24 | 4.2 ^F | 1.3 |
| Serum B ₁₂ 0-200 pg./ml. .. | 13 | 21.3 | 2.9 | 13 | 10.8 ^G | 2.9 |
| Serum B ₁₂ 201 + pg./ml. .. | 77 | 17.2 | 1.2 | 70 | 5.5 ^H | 0.8 |
| Folate 0-2.5 and B ₁₂ 0-200 .. | 5 | 21.2 | 3.9 | 5 | 15.4 | 3.5 |
| Folate 2.6 + and B ₁₂ 0-200 .. | 8 | 21.4 | 4.2 | 8 | 7.9 | 3.9 |

A vs B+C p<0.03.

D vs E+F p<0.025.

G vs H p<0.025.

pg./ml.) and 2 patients with concentrations less than 150 pg./ml. These patients had somewhat higher admission depression inventory scores than did those patients with normal vitamin B₁₂. The discharge depression inventory scores of the low serum vitamin B₁₂ group were significantly higher than those of the normal level group. These high discharge scores appear to be associated with low folate rather than low vitamin B₁₂, as patients with normal folate and low B₁₂ had low depression inventory scores on discharge. It should be emphasized, however, that these groups are very small and the differences are not statistically different.

The patients were divided on the basis of their admission depression inventory scores into 3 grades of depression: mild (depression inventory score less than 19), moderate (score 20-29) and severe (score 30 and over). The average serum folate and B₁₂ concentrations for each group were found to be very similar (Table IV). The patients were divided into two groups according to their depression inventory on discharge; (a) those with relatively high scores of 8 and over (mean 12.8) had mean serum folate concentration at discharge of 6.9 ng./ml.; (b) those with relatively low depression scores of below 8 (mean 2.1) had a mean serum folate concentration at discharge of 4.6 ng./ml.

Personality in relation to serum values

Two dimensions of personality showed significant associations with low serum folate. (Table

V.) Validity scores were significantly lower in the low serum folate group both on admission and discharge and were lower in the patients with low serum B₁₂ as well as folate but not with low serum B₁₂ and normal folate. The discharge neuroticism scores were significantly higher in the patients with low serum folate concentrations. The 4 patients with low serum B₁₂ and folate also had significantly higher discharge neuroticism scores.

The serum estimations were repeated on 33 patients on discharge. Table VI shows how these changed. The six patients who initially had a low serum folate concentration showed a significant increase towards normal levels. The patients with moderate folate showed no significant change, but the patients with high serum folate concentration on admission showed a significant decrease.

DISCUSSION

This investigation confirms the report of Carney (1967) that a substantial proportion (24 per cent) of patients admitted to hospital with depression have low serum folate concentrations. Some of these patients with low values were retested before discharge and a significant increase towards normal levels was found. Patients with high serum folate concentrations on admission showed a significant decline when retested before discharge, while those with intermediate values showed no change.

Those with low serum folate concentrations on admission had significantly higher depression

TABLE IV
Severity of depression and serum folate and vitamin B₁₂ concentration

| Depression inventory score on admission | Serum folate (ng./ml.) | | Serum B ₁₂ (pg./ml.) | |
|---|------------------------|------|---------------------------------|------|
| | n | mean | n | mean |
| 0-19 (mild depression) | 46 | 4.6 | 46 | 333 |
| 20-29 (moderate depression) | 32 | 4.7 | 32 | 324 |
| 30+ (severe depression) | 12 | 5.1 | 12 | 281 |

TABLE V
Personality and serum folate and vitamin B₁₂ concentration

| Serum folate and vitamin B ₁₂ concentration on admission | Marke-Nyman validity score | | | | | | N. score—EPI | | | | | |
|---|----------------------------|------------------|------|-----------|-------------------|------|--------------|------|------|-----------|-------------------|------|
| | Admission | | | Discharge | | | Admission | | | Discharge | | |
| | n | mean | S.E. | n | mean | S.E. | n | mean | S.E. | n | mean | S.E. |
| Serum folate 0-2.5 ng./ml. | 21 | 4.7 ^A | 0.7 | 19 | 6.8 ^D | 1.0 | 21 | 15.5 | 1.2 | 19 | 13.6 ^G | 1.2 |
| Serum folate 2.6-5.0 ng./ml. | 39 | 7.0 ^B | 0.5 | 36 | 9.6 ^E | 0.9 | 39 | 14.5 | 0.8 | 36 | 10.9 ^H | 1.0 |
| Serum folate 5.1+ ng./ml. | 26 | 6.7 ^C | 0.8 | 24 | 10.5 ^F | 1.0 | 26 | 12.9 | 1.0 | 24 | 9.5 ^I | 1.3 |
| Serum B ₁₂ 0-200 pg./ml. | 12 | 6.0 | 1.5 | 11 | 8.0 | 1.6 | 12 | 15.2 | 1.8 | 11 | 11.6 | 4.3 |
| Serum B ₁₂ 201+ pg./ml. | 72 | 6.3 | 0.4 | 66 | 9.3 | 0.6 | 72 | 14.1 | 0.6 | 66 | 11.1 | 1.6 |
| Folate 0-2.5 and B ₁₂ 0-200 | 4 | 3.8 | 1.8 | 4 | 3.5 ^J | 2.0 | 4 | 16.8 | 3.7 | 4 | 11.5 ^K | 2.2 |
| Folate 2.6+ and B ₁₂ 0-200 | 8 | 7.1 | 2.0 | 7 | 10.6 ^L | 1.5 | 8 | 14.4 | 2.1 | 7 | 8.3 ^M | 2.6 |

A vs B+C p<0.05 J vs K p<0.025
D vs E+F p<0.025 L vs M p<0.05
G vs H+I p<0.05

TABLE VI
Changes of serum folate concentration between admission and discharge

| Serum folate on admission | Mean folate concentration (ng./ml) | | |
|-----------------------------|------------------------------------|-----------|------------------|
| | n | Admission | Discharge |
| 0-2.5 ng./ml. | 6 | 2.0 | 4.5 [†] |
| 2.6-5.0 ng./ml. | 15 | 3.9 | 4.9 |
| 5.1 ng./ml. and above | 12 | 8.5 | 5.8* |

Difference between admission and discharge. *p<0.05
†p<0.02

scores on admission and also on discharge. Their personality inventory scores showed them to have lower validity scores on admission and discharge, while their neuroticism scores were higher on discharge only. Validity is a dimension of personality related to psychic energy and drive.

If the patients were divided according to severity of depression then there did not appear to be any association of severity with low serum folate concentrations. There was no difference in serum concentration between patients with relatively high and relatively low discharge depression scores.

Our observation of two patients with vitamin B₁₂ levels below 150 pg./ml. is in accordance with previous reports of the incidence of this

finding in psychiatric patients which has varied between 0.88 per cent (Henderson, Strachan, Beck, Dawson and Daniel, 1966) and 5 per cent (Edwin, Holten, Norum, Schrumph and Skaug 1965). However, a total of 13 patients had serum B₁₂ values below 200 pg./ml. When this group was compared with the larger group of depressed patients with values above 200 pg./ml. clinical differences were found between them similar to those noted between high and low folate groups. The five patients with both low folate and low serum vitamin B₁₂ values were the most abnormal on both depressive and validity scores.

There are at least two possible explanations for these findings. There are certain patients,

quite severely depressed and with low validity scores, who tend to have a poor diet when ill. As there is a correlation between admission depression scores and discharge depression scores (Coppén, unpublished) this could account for their relatively high discharge scores. The increase in serum folate in some patients during hospitalization would be consistent with the view that the low serum folate is of dietary origin. The dietary history however did not provide any evidence for this hypothesis although admittedly it is hard to acquire reliable data about the nutritional state of the patient.

A second possibility is that the low serum folate concentrations influence the clinical picture, and that the severity of the depression and the relatively high discharge scores are, in part at least, caused by folate deficiency. Reynolds (1967a) reported an improvement in the mental state in 22 out of 26 folate-deficient epileptic patients treated in an open uncontrolled trial with folic acid. The most notable change was in 'drive' and in some patients there was an elevation of mood.

A causal relationship between folate deficiency and depression of mood would be consistent with the biogenic theory of the affective disorders (Schildkraut, 1965; Coppén, 1968) as a pteridine cofactor is necessary in the hydroxylation of tyrosine (Udenfriend, 1966) and tryptophan (Lovenberg *et al.*, 1968). A deficiency of folic acid could interfere with this rate-limiting step (hydroxylation) in the synthesis of the catecholamines or 5-hydroxytryptamine.

These two possible interpretations of the present findings are not mutually exclusive and could interact as a vicious circle (Reynolds 1967b). The relationship of folic acid deficiency to depression is not yet clear and its elucidation must await further work. In particular the question whether patients with low serum folate concentrations would show a better therapeutic response to anti-depressant therapy if given folic acid supplements requires a controlled trial.

SUMMARY

Serum folate and vitamin B₁₂ levels have been measured in 101 patients with depressive illness.

Subnormal folate levels (2.5 ng./ml. or less) were found in 24 per cent and subnormal vitamin B₁₂ levels (150 pg./ml. or less) in 2.2 per cent of patients. Thirteen patients (14.4 per cent) had low vitamin B₁₂ levels (200 pg./ml. or less). Patients with subnormal folate levels were found to have significantly higher depressive scores, and significantly lower validity scores on the Marke-Nyman Temperament Scale, both on admission and on discharge. Subnormal folate levels could be a consequence of dietary deficiency or could possibly be causal of depression through interference with tyrosine or tryptophan hydroxylation.

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