

Clinical Trial of the Effect of Vitamin B₁₂ in Elderly Subjects with Low Serum B₁₂ Levels

DAFYDD HUGHES,* M.B., B.CH., D.P.M.; P. C. ELWOOD,† M.D., D.P.H., D.C.H.; N. K. SHINTON,‡ M.D., M.R.C.P., M.R.C.PATH.
R. J. WRIGHTON,§ M.B., B.S., M.R.C.P.

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Summary: A clinical trial of the effect of vitamin B₁₂ therapy was conducted in 39 elderly subjects who had been found, in a community screening survey, to have low levels of serum B₁₂ without a macrocytic anaemia or neuropathy. The study produced no evidence which suggests that in such subjects B₁₂ is superior to placebo in effecting an improvement in psychiatric state or general well-being. There was a clear tendency for all the subjects to show an improvement during the trial, but this probably represents the therapeutic effect of involvement in a research exercise of this kind.

Introduction

Pernicious anaemia may be accompanied by psychiatric disturbance and in some instances the presenting illness may be psychiatric in nature, the anaemia coming to light only in the course of investigation (Langdon, 1905; McAlpine, 1929; Holmes, 1956; Smith, 1960). More recently it has been suggested that vitamin B₁₂ deficiency, in the absence of anaemia, may produce psychiatric symptoms, the diagnosis being made on serum B₁₂ levels and therapeutic response following admission to hospital (Smith, 1960; Strachan and Henderson, 1965). Shulman (1967b) suggested that organic confusional states and senile or presenile dementias are the conditions most commonly associated with B₁₂ deficiency, though affective disorders may be equally prevalent. Treatment with vitamin B₁₂ in such patients (uncontrolled observations) has been said to produce a rapid alleviation of the psychiatric disturbance, and this change is thought to be dramatic in some patients.

Estimates of the prevalence of subnormal serum B₁₂ levels in patients admitted to a mental hospital have been made by many workers (Edwin *et al.*, 1965; Hansen *et al.*, 1966; Hutner *et al.*, 1967; Shulman, 1967a; Buxton *et al.*, 1969; Murphy *et al.*, 1969). These estimates vary from 0.02% to the high level of 15.4%, but no valid comparison has been made between subjects admitted to hospital and subjects in the community from which they have come. Furthermore, even if it were shown that there is a raised prevalence of low B₁₂ levels in hospital admissions, it would still have to be shown that an association with psychiatric symptoms is not due to chance alone (Strachan and Henderson, 1965; Hansen *et al.*, 1966; Murphy *et al.*, 1969).

Community surveys have shown a surprisingly high prevalence of pernicious anaemia (Mosbech, 1953; Girdwood *et al.*, 1967). Though the community survey which preceded the trial described in the present report did not confirm these earlier reports of the prevalence of pernicious anaemia, yet a high prevalence of low serum B₁₂ levels without anaemia was found (Elwood *et al.*, 1970) as had been expected (Hansen *et al.*, 1966; Girdwood *et al.*, 1967). It is, however, not known if these low levels have any clinical significance, or how many will go on to develop haematological or psychiatric effects of B₁₂ deficiency. From the studies of mental hospital patients quoted above it might be expected that psychiatric ill-health

would occur among such subjects and that this would show a beneficial response to B₁₂.

An attempt has therefore been made to determine the psychiatric status of a population sample of elderly people with low serum B₁₂ levels, and also the effect thereon of B₁₂ supplements by means of a controlled clinical trial. In addition to psychiatric assessment and assessments of general well-being, particular attention was paid to changes in appetite and fatigue, as these symptoms are believed to be influenced by B₁₂ therapy.

Method

A 3:20 random sample of subjects aged 65 years and over was chosen from the records of all the practices in a town in Wales (population 42,000). Each subject was invited to co-operate in a haematological survey, the results of which will be reported (Elwood *et al.*, 1970). Eighty-five per cent. of the male and 82% of the female subjects agreed to co-operate and a sample of venous blood was taken from each. Serum B₁₂ was estimated, *Euglena gracilis* Z. strain being used (Hutner *et al.*, 1956). Occasional samples were submitted to the laboratory in duplicate, and estimates on these showed that reproducibility was excellent.

The lower limit of the normal range of serum B₁₂ levels in the laboratory where these were estimated is 150 pg./ml. Subjects found to have levels below this were asked to co-operate in a clinical trial of the effect of treatment. None of these subjects had anaemia or evidence of B₁₂ neuropathy and no subject was known to be taking drugs, such as chlorpromazine, which might have interfered with B₁₂ assay, or anti-convulsants, which might reduce the serum B₁₂ level. In a parallel study serum pepsinogen estimations were done and only a very small and unimportant difference (21 ± 33 µg.) was found between subjects with low B₁₂ levels and a representative sample of normal subjects.

Of the subjects with serum B₁₂ below 150 pg./ml., half, chosen at random, were given intramuscular hydroxocobalamin (1,000 µg.), twice in the first week and then at weekly intervals for a further four weeks. The other subjects were given intramuscular injections of a matching solution of phenol red (phenylsulphonphthalein 0.075%), the use of which had been approved by the Dunlop Committee.

Each subject was interviewed to assess psychiatric state and general well-being both before and after treatment had been completed. Both interviews were conducted blind with regard to the treatment given. The second interview was also blind with regard to the results of the first interview, and was therefore a fresh assessment. The interview procedure was as follows. Subjects were given a self-administered questionnaire (Goldberg, 1969) which provides information on 60 predominantly psychiatric questions, each answerable by one of four replies which are scored 0, 1, 2, or 3, according to severity. The total score is used as a "global rating" of psychiatric status. The psychiatrist then perused the completed questionnaire and, taking the pattern of replies into account, gave the subject a short and partly structured psychiatric interview. This elicited information on the subject's current and recent psychiatric state, elaborating on any symptoms shown to be present in the questionnaire and evaluating in particular the subject's state regarding affect, anxiety, sleep, energy/

*Member of Scientific Staff, M.R.C. External Staff, Llandough Hospital, Cardiff.

†Member of Staff, M.R.C. Epidemiology Unit, Cardiff.

‡Pathologist, Coventry Hospital.

§Medical Adviser, Glaxo Laboratories.

fatigue, and appetite. An attempt was made to evaluate the psychiatric state independently of any intellectual deterioration which might have been present in these elderly subjects.

On the basis of this interview subjects were classified into five categories: (0) no detectable psychiatric disorder, (1) subclinical disorder, (2) mild disorder (might require treatment), (3) moderate psychiatric disorder (would probably require treatment), and (4) severe psychiatric disorder (should certainly have treatment). The psychiatric assessment thus obtained was not independent of the questionnaire but was an attempt to utilize, in addition to questionnaire replies, other information communicated verbally and non-verbally in a clinical-type interview. The last question on the questionnaire was "Do you think you are at all ill?" This had five possible graded answers, and was used to obtain an overall self-assessment for each subject.

The interview after treatment was identical except that subjects were also asked whether, since the first interview, there had been any improvement or deterioration in sleeping, energy/fatigue, appetite. The subjects were also asked to illustrate any change, improvement, or deterioration, in general well-being compared with the first interview by choosing a point along a 30-cm. line. The midpoint of this line was explained as representing their state at the first interview, and the distance on one side as representing the degree of any improvement and on the other side deterioration. The midpoint therefore represented no change in general well-being during the trial.

This trial was immediately followed by a long-term morbidity study, and each subject is being seen at frequent intervals to assess further the benefit, if any, of therapy, and to detect the development of a macrocytic anaemia in any subject, should this occur.

Results

The distribution of serum B₁₂ levels in the total population sample is shown in Table I. Sixteen men and 28 women had levels below 150 pg./ml. and these were invited to co-operate in the clinical trial. One man and one woman declined and three further women had to be withdrawn dur-

TABLE I.—Distribution of Serum B₁₂ Levels in the Total Population Sample of Subjects 65 Years of Age and Over

Serum B ₁₂ (pg./ml.)	No. of Subjects	
	Males	Females
Under 100	1	7
100-149	15	21
150-199	12	18
200-249	31	29
250-299	21	20
300-349	4	11
350-399	4	3
400-449	2	12
450-499	—	3
500 and over	3	8
Total	93	132

ing the trial—one had a fall and was admitted to hospital, one had moved out of the area, and one was too deaf to enable valid psychiatric assessments to be made. During the trial there was, on average, a small fall in haemoglobin level, but the difference between the mean changes in those given B₁₂ and those given the placebo was very small and not statistically significant (0.01 ± 0.35 g.).

Assessed by questionnaire, improvement in psychiatric symptoms in those given B₁₂ was no greater than in those given the placebo, and the questionnaire score with the two treatments is similar (Table II). A low mean score occurred in men given the placebo, but this is accounted for by a single subject who produced a very high second questionnaire score suggesting a pronounced "deterioration." This was thought to have been spurious, as it was not in keeping with the other results for this subject nor with a clinical impression. If his score is omitted the male placebo mean questionnaire score is similar to that in the other groups.

The subjects' self-assessment as measured by their answers to the last question on the questionnaire showed no significant difference in the proportion improved with the two treatments (Table II). Similarly, the linear self-assessment (Table III) showed no difference between the groups in the proportion improved. A comparison of the two groups with regard to sleep, energy/fatigue, and appetite is shown in Table IV. A high proportion reported benefit with treatment, but there were no significant differences between the groups.

Fourteen subjects were thought to have some psychiatric abnormality as assessed by the first interview—10 in category 1, 2 in category 2 and 2 in category 3. At the second interview only two subjects were judged to be in category 1 and one in category 2. The changes in each group are set out in Table V. No subject deteriorated, but while a third of the subjects improved, again there was no significant difference in the two treatment groups.

TABLE III.—Linear Self-assessment Scale. Number Improved and Unchanged, and Mean Improvement for All Subjects Expressed in cm. (see Text)

Sex	Given B ₁₂			Given Placebo		
	Improved	No Change	Overall Mean Improvement	Improved	No Change	Overall Mean Improvement
Male	6	2	4.58	5	2	4.25
Female	9	3	3.87	9	3	4.43
Total	15	5	4.3	14	5	4.36

TABLE IV.—Changes in Appetite, Energy/Fatigue, and Sleep

Symptom	Given B ₁₂						Given Placebo					
	Males			Females			Males			Females		
	+	○	+	○	+	○	+	○	+	○	+	○
Appetite	3	5	2	10	5	15	2	5	0	12	2	17
Energy/fatigue	2	6	8	4	10	10	4	3	6	6	10	9
Sleep	2	6	3	9	5	15	2	5	2	10	4	15

+ = Indicates an improvement. ○ = Indicates no change.

TABLE II.—Number of Subjects who Showed an Improvement, No Change, or a Deterioration in Scores with Treatment, Assessed by Questionnaire. Number who Changed on the Self-assessment Question Shown in Parentheses

Sex	Given B ₁₂				Given Placebo			
	Improved	No Change	Deteriorated	Overall Mean Improvement in Score	Improved	No Change	Deteriorated	Overall Mean Improvement in Score
Male	5 (2)	0 (4)	3 (2)	7.4	6 (2)	0 (3)	1 (2)	0.4 7.8*
Female	8 (5)	2 (6)	2 (1)	6.8	10 (3)	2 (7)	0 (2)	6.9
Total	13 (7)	2 (10)	5 (3)	7.1	16 (5)	2 (10)	1 (4)	4.5 7.2*

None of the differences is significant.

*Mean excluding one subject with spuriously high second score.

TABLE V.—Changes in Global Rating Based on Psychiatric Interview (see Text)

Sex	Given B ₁₂		Given Placebo	
	Improved	No Change	Improved	No Change
Male	2	6	0	7
Female	5	7	6	6
Total	7	13	6	13

Overall female improvement exceeds male improvement significantly. P (exact test) \approx 0.039, otherwise no differences are significant.

Most of the subjects showed some improvement at the second evaluation. This is not unexpected, nor was it unexpected that in general no appreciable deterioration was detected during the trial. On the questionnaire assessment 29 subjects improved while only six deteriorated. On the self-assessment question 12 improved and none deteriorated. On the linear self-assessment scale 29 improved and none deteriorated, and in the clinical assessment 13 improved and none deteriorated. None of these tests, however, produced evidence that subjects given B₁₂ improved more than those given the placebo.

Discussion

Vitamin B₁₂ appears to be given not infrequently in conditions other than those associated with B₁₂ deficiency (International Medical Statistics, 1969; Ellis et al., 1970), its use being based on the belief that it has a beneficial effect on such symptoms as appetite, fatigue, and sleep and possibly on certain aspects of mental health. This last may be based in part on the clinical observations quoted above. This study does not show that there is any special beneficial effect from the administration of B₁₂ to subjects with low B₁₂ levels. Previous observations on 828 consecutive admissions to the mental hospital serving the area in which the present trial was conducted disclosed several patients with pernicious anaemia, but these patients provided no evidence of an association between serum B₁₂ and severity of psychiatric illness, E.E.G. changes, or psychometry; nor was there any association between B₁₂ level on admission and the proportion of the 828 patients still in hospital six months later (S. Nam, private communication, 1969).

These observations and the results of the present trial do not, of course, exclude the existence of a psychiatric syndrome resulting from B₁₂ deficiency, though they do perhaps emphasize its rarity. Murphy et al. (1969) doubt that it is even common enough to justify, at present, routine serum B₁₂ assays on mental hospital admissions. During the trial a high proportion of the subjects showed evidence of an improvement with treatment whether B₁₂ or the placebo was given, while in general no appreciable deterioration was detected. As the second interviews were all conducted blind, and as there was a long interval between the first and second tests, probably most subjects did actually improve in psychiatric state and general well-being. In the absence of evidence of an effect of B₁₂ this improvement must simply represent the therapeutic effect of the interest and concern shown by a

team of doctors, nurses, and research workers, who paid repeated visits to the homes and gave a course of injections over several weeks. It is of interest, however, that whereas a third of all the subjects improved there was a significant difference between the sexes; only 2 of the 15 men improved, while 11 of the 24 women did so. This difference may well be related to the fact that 17 of the 24 women were widowed and eight lived alone, while only 2 of the 15 men were widowers and none lived alone.

Another methodological aspect of the trial is the relation between the tests. The correlation between independent measures of the same abnormality can be taken as a measure of their validity. Subjects grouped for the degree of improvement assessed by the clinical interviews, the mean improvement in the questionnaire score, and the mean change in the linear self-assessment measurement are shown in Table IV. There is a concordance between the clinical rating and the questionnaire score, and assuming that the distribution of changes in questionnaire score is gaussian, this concordance is statistically significant. This, however, might be regarded as unremarkable, as it can be argued that the tests as conducted were not independent of each other. Nevertheless, the linear self-assessment and the psychiatric rating, which are independent of each other, also show significant concordance.

TABLE VI.—Concordance Between Tests. Mean Changes in Questionary Score and in Linear Self-assessment in Subjects Grouped by Change in Psychiatric Rating Based on Clinical Interviews

Mean Improvement in:		
Psychiatric Rating	Questionary Score	Linear Self-assessment
Nil	2.9	3.0 cm.
One category	11.6	6.6 cm.
Two categories	27.0	7.7 cm.

*Differ significantly (t test) at P < 0.05.

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