

# Treatment of Neuroblastoma with Vitamin B12

## A Report to the Working Party\* of the Medical Research Council

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**Langman, M. J. S. (1970).** *Archives of Disease in Childhood*, **45**, 385. **Treatment of neuroblastoma with vitamin B12.** A retrospective study of treatment given to 108 children with neuroblastoma failed to confirm that vitamin B12 therapy is beneficial. 43 of 47 children whose treatment did not include vitamin B12 are known to have died, compared with 56 of 61 children who received the vitamin in addition to other treatments. 2 children who received vitamin B12 as their only treatment were alive and well six years later, but this apparently favourable response could well be ascribed to spontaneous remission of the tumour.

In 1960 a Medical Research Council Working Party was set up to examine the suggestion that vitamin B12 might be of value in treating neuroblastoma (Bodian, 1959). It was agreed that a controlled clinical trial could not be started because such a course would have involved the denial to one group of patients of a potentially valuable yet apparently harmless treatment. Data were, therefore, collected retrospectively from various centres in the United Kingdom so that the results of treatment in children with neuroblastoma who had or who had not received vitamin B12 could be compared.

### Method

Questionnaires asking for clinical details of children treated for neuroblastoma were sent to 55 hospitals which agreed to co-operate in the study. The answers to the questionnaires, amplified by later inquiries about follow-up results, form the basis of this report.

### Results

Reports on the clinical course of 134 patients were received but 26 were unsuitable for analysis. In 7 patients a definite diagnosis of neuroblastoma could not be established, in 12 patients information about general treatment was inadequate, and in 3

it was unclear whether vitamin B12 had been given; the remaining 4 died before any medical treatment could be administered.

Sixty-five patients had received treatment with vitamin B12 at some time during their illness and 43 had never been given any such treatment. However, 4 of the treated group had received vitamin B12 only by mouth, and as it has been claimed that to be effective vitamin B12 must be given in large doses (Bodian, 1963), these 4 were transferred to the control group. The 61 remaining treated patients had all received at least 2,000 µg. vitamin B12 by injection during the course of their illness, but at varying intervals after the diagnosis of the tumour. The inclusion in the treated group of individuals who had been given vitamin B12 as a late secondary treatment would clearly have biased the results, and therefore the main comparison was restricted to the 35 whose treatment with vitamin B12 had been started less than one month after the diagnosis had been made and the 47 who received either no vitamin B12 or only oral treatment. In 17 of the remaining 26 the dates of administration of the drug were uncertain, and in 9 it had been given at least one month after diagnosis of the disease.

Table I gives the numbers of children who are known to have died and the number who were still alive when last followed up, and their survival time after the diagnosis of neuroblastoma. Only 9 (8%) of the whole group were still alive at the time of the last inquiry; they included 4 (9%) of the 47 who had not received vitamin B12, and 2 (6%) of those 35 who had received early treatment with

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\*Members of the working party were: Professor W. Gaisford, Professor D. A. G. Galton, Professor Sir Alexander Haddow, Professor Sir Austin Bradford Hill, Professor Sir A. Moncrieff, Dr. Edith Paterson, Professor R. W. Scarff, Professor Sir Brian Windeyer, the late Mr. G. H. Macnab and the late Dr. M. Bodian.

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TABLE I  
*Survival Time and Final Outcome in Patients Treated with or without Vitamin B12*

Treatment Group	Results	Survival Time (mth.)				Survival Time (mth.) in Those Living > 3 years
		0-12	13-24	25-36	37 or more	
No vitamin B12						
Dead	43	30	8	2	3	41, 70, 76
Alive	4	—	—	—	4	72, 76, 120, 120
Early vitamin B12						
Dead	33	27	4	1	1	39
Alive	2	—	—	—	2	51, 120
Late vitamin B12						
Dead	9	5	2	1	1	39
Alive	0	—	—	—	—	—
Vitamin B12 given but dates uncertain						
Dead	14	8	3	3	—	—
Alive	3	—	—	—	3	39, 72, 79
Total	108	70	17	7	14	

vitamin B12. In addition 3 (18%) were still alive of the 17 who had been given vitamin B12 though at uncertain dates. If all in this group had properly been included in the early vitamin treated group, the survival rate in that group would have been raised to 10% but it would still have been immaterially different from that in the group who did not receive vitamin B12.

Tables II and III give details of the comparability of the patients in respect of age, presence or absence of metastases when first seen, and other treatments given. There were no clear differences except that when compared with the group of patients treated early with the vitamin a slightly higher proportion of those who did not receive the vitamin were treated by operation, suggesting that they had localized disease. This difference could not, however, account for the poor general results obtained with vitamin treatment. Of those children living for at least five years 2 received no treat-

TABLE II  
*Comparability in Age and in Presence or Absence of Metastases when First Seen*

Metastases	No Vitamin B12	Early Vitamin B12	Late Vitamin B12	Vitamin B12 Given but Dates Uncertain
Present	33	26	6	12
Absent	12	5	1	2
Not known	2	4	2	3
Total	47	35	9	17
Ages (yr.)				
< 1	4	4	—	2
1-2	11	10	—	3
2-3	5	5	2	4
3-4	4	3	1	—
4 and over	23	13	6	8
Total	47	35	9	17

TABLE III  
*Comparability in Other Treatments Given*

Treatment	No Vitamin B12	Early Vitamin B12	Late Vitamin B12	Vitamin B12 Given but Dates Uncertain
Surgery .. .. .	6 (1)	1	—	3
Radiotherapy .. .. .	15 (1)	10	3	5
Chemotherapy/steroids .. .. .	3	2	—	—
Radiotherapy and excision .. .. .	11 (2)	6	5	3 (1)
Radiotherapy, excision, and chemotherapy/steroids .. .. .	—	—	—	1
Excision and chemotherapy .. .. .	2	—	—	1
Radiotherapy and chemotherapy/steroids .. .. .	1 (1)	5	—	—
None .. .. .	9 (1)	11 (1)	1	4 (1)
Total .. .. .	47 (6)	35 (1)	9	17 (2)

The numbers of individuals surviving at least five years included in each group are given in parentheses.

ment other than vitamin B12, one further patient was given no specific treatment at all and, in general, none of the combinations of treatments appears to have been particularly successful.

### Discussion

The results of this investigation have failed to confirm that vitamin B12 is of value in the treatment of neuroblastoma, and the findings are in agreement with those obtained in a similar retrospective study of American experience (Sawitsky and Deposito, 1965), based on 103 patients with neuroblastoma treated with or without vitamin B12. It was then concluded that the vitamin did not confer any therapeutic benefit, the outcome of treatment being thought to be influenced more by the natural behaviour of the tumour than by the individual remedies prescribed.

Though exact details of vitamin B12 dosage could not always be obtained from the records in this retrospective study, it did not seem likely that inadequate dosage could explain the poor results of vitamin treatment. Most of the treated patients had received frequent injections each of 1 mg. or more of the vitamin, and the intensity of initial treatment did not appear to be related to the length of survival. 2 of the 16 patients given vitamin B12 as their only treatment were still alive five years later, as was 1 of the 9 patients who received no specific treatment, and their survival could be ascribed to slow growth of the tumour or to spontaneous regression which sometimes occurs in the

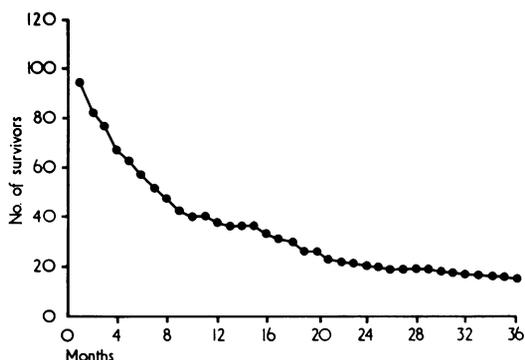


FIG.—Survival curve for the total group of 108 patients initially treated.

absence of specific treatment. The poor general response of patients with neuroblastoma is clearly illustrated by the survival curve shown in the Fig. Half of all the patients were dead within six months and four-fifths within two years.

### REFERENCES

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