ORAL TREATMENT OF PERNICIOUS ANAEMIA WITH A COMBINED VITAMIN B₁₂ AND INTRINSIC FACTOR PREPARATION

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Since the work of Castle and his associates it has been recognized that the deficiency of a gastric secretion is an essential abnormality in the development of pernicious anaemia. More recently it has been demonstrated that the function of this missing intrinsic factor is to aid the absorption of vitamin B₁₂, the extrinsic factor (Castle, 1953). Pernicious anaemia may be satisfactorily treated by parenteral administration of the extrinsic factor, and as this is now available as a pure crystalline substance it is more effective than the older liver preparations of varying composition (Blackburn *et al.*, 1952). Vitamin B₁₂ is only slightly absorbed when given by mouth to patients with pernicious anaemia, but a haematological response may be obtained if relatively large doses are given by this route (Ungley, 1950; Chalmers and Hall, 1954). Smaller doses may be used if the absorption is increased by administering at the same time an intrinsic factor preparation (Glass and Boyd, 1953). The older preparations of hog's stomach used in this way were often effective but were unpleasant to take. Recently the introduction of more highly concentrated and purified preparations from gastric mucosa has made this approach to the treatment of pernicious anaemia more attractive.

Present Investigation

We have studied the efficiency of a preparation ("biopar") which contains in each tablet 6 µg. of crystalline vitamin B₁₂ and 30 mg. of "intrinsic factor." This product has been used in the doses recommended by the manufacturers both for initial and for maintenance treatment of pernicious anaemia, and the results have been compared with those obtained by the parenteral use of vitamin B₁₂.

Methods.—Thirty patients have been included in the trial. In all the initial diagnosis has been confirmed by the examination of the peripheral blood and marrow and by the demonstration of a histamine-fast achlorhydria. Determinations of haemoglobin (M.R.C. grey wedge haemoglobinometer 100% = 14.8 g./100 ml.) and of red-cell counts have been made at least once a month throughout the period of observation. Absorption of ⁵⁷Co labelled vitamin B₁₂ was studied by the method of Callender *et al.* (1954).

Results of Initial Treatment with Intrinsic Factor and Vitamin B₁₂

Five patients with Addisonian pernicious anaemia were treated from the start with five tablets a day. In four patients there was a satisfactory response, shown by a reticulocytosis and a progressive rise in haemoglobin and red-cell count. An example is shown in Fig. 1. In the

fifth patient, however, oral treatment was without effect, though she subsequently responded to parenteral vitamin B₁₂ (Fig. 2). The details of this case are as follows.

A woman aged 68 presented with loss of weight and a severe anaemia (Hb 35%). A clinical diagnosis of gastric carcinoma was made. She was admitted to a surgical ward and given a transfusion of 1,300 ml. of blood. Subsequent investigation of the alimentary tract was negative, but the marrow was megaloblastic and there was a histamine-fast achlorhydria. Of the dose of ⁵⁷Co labelled vitamin B₁₂, 71% was recovered in the faeces. The haematological investigations shown in Fig. 2 were begun 16 days after the transfusion. There was no response during treatment with biopar; during this period radiological and gastroscopic examination of the alimentary tract was repeated, but was again negative. Repeated examination of the faeces for occult blood was negative. The bone marrow remained megaloblastic. The administration of the tablets was checked. They were from the batch used in the other

FIG. 1.—Response to oral treatment of pernicious anaemia in a woman aged 35. R.B.C. ○···○; Hb ●—●.

FIG. 2.—Failure to respond to oral treatment. Satisfactory response to parenteral vitamin B₁₂. R.B.C. ○···○; Hb ●—●.

cases of pernicious anaemia, which had shown a response. A change to parenteral vitamin B₁₂, 30 µg. a day (the same dose as in the tablets), produced a conspicuous reticulocytosis and a subsequent rapid rise in haemoglobin and red-cell count. A balance study showed no abnormality in fat absorption.

Maintenance Therapy

Twelve patients were chosen at random from those with pernicious anaemia who had been attending for maintenance treatment with parenteral vitamin B₁₂ for at least one year and had shown steady blood levels during that period. They were transferred to treatment with one tablet of biopar a day, the recommended maintenance therapy. A further 12 patients, similar in age and clinical state to the first group but otherwise selected at random, were given equally detailed study but were continued on treatment with vitamin B₁₂. The progress of both sets of patients has been reviewed after one year.

The haematological changes in the group transferred to treatment with biopar are shown in Table I. During the

first six months on oral therapy the mean values of haemoglobin and red-cell count showed no significant changes. However, when the mean values during the second six months are examined it is seen that in 10 out of 12 there was a fall in haemoglobin and that in 11 of the 12 there was a fall in red-cell count. In the other instances the mean values were unchanged. There was no doubt that from the haematological point of view their condition was deteriorating. In spite of the declines in haemoglobin and red-cell counts the patients remained symptomatically unchanged and showed no definite alteration in their clinical state. They all preferred tablets to injections. Two patients admitted that they occasionally forgot to take the tablets. The others apparently remembered regularly, and checked by counting the tablets remaining at the end of each week.

To exclude the possibility that the unfavourable blood changes were due either to the ageing of the patients or to a systematic error in the laboratory, the progress of the matched group of 12 patients maintained throughout on vitamin B₁₂ was studied (Table II). No definite trend can be detected.

In one patient, a woman aged 40, not included in the above series, definite clinical features of subacute combined degeneration of the cord developed while on maintenance therapy with one tablet a day. Previously she had received injections of liver extract and of vitamin B₁₂ for eight years without developing any neurological signs. Nine months after being transferred from parenteral vitamin B₁₂ to oral treatment she noticed paraesthesiae in the legs, and these became progressively more severe over the next five weeks. She developed a sore mouth, the calves became tender, and the ankle-jerks disappeared. Some ataxia became apparent. The mean blood values while on parenteral vitamin B₁₂ were: Hb 90%, and R.B.C. 4,700,000 per c.mm., and at the height of these features they were unchanged. The dose

was then increased to five tablets a day. After one week there was some improvement, and this lasted for six weeks, when a further relapse occurred. She was then given injections of vitamin B₁₂, 100 µg. twice a week. Her general condition improved, the paraesthesiae and soreness of the mouth disappeared, and the ankle-jerks were easily elicited.

Discussion

In four out of the five previously untreated patients with uncomplicated pernicious anaemia the administration of 30 µg. of vitamin B₁₂ and 150 mg. of intrinsic factor preparation a day gave a satisfactory response from both the clinical and the haematological point of view. In the fifth patient no response was obtained and no satisfactory explanation has so far been found for this failure. She responded well to the same dose of vitamin B₁₂ given by injection.

Maintenance treatment with 6 µg. of vitamin B₁₂ and 30 mg. of intrinsic factor preparation a day was unsatisfactory when the investigation was continued over a year, and in one patient did not prevent the development of neurological complications. It is important to note that no untoward features were observed during the first six months on oral treatment as in the series reported by Lowther *et al.* (1954). It was only during the second six months that the ill effects became apparent. It is possible that higher maintenance doses might have prevented the fall in blood levels, but the complete failure in one patient treated from the beginning with this preparation suggests that factors other than dose may influence the response to oral treatment in some cases of pernicious anaemia.

Crystalline vitamin B₁₂ is a pure substance of known potency, whereas the activity of intrinsic factor preparations of unknown chemical composition may well be variable. This may in part account for the erratic response to this method of treatment of pernicious anaemia (Vilter, 1955).

TABLE I.—Progress of Patients with Pernicious Anaemia Transferred from Maintenance Treatment with Vitamin B₁₂ to Biopar

Case No.	Age and Sex	Treatment with Vitamin B ₁₂ for 1 Year		Treatment with Biopar for 1 Year							
				First 6 Months				Second 6 Months			
				Mean Hb		Mean R.B.C.		Mean Hb		Mean R.B.C.	
		Mean Hb %	Mean R.B.C. (m./c.mm.)	%	Change	m./c.mm.	Change	%	Change	m./c.mm.	Change
1	66 F	91	4.5	94	-3	4.7	+0.2	91	0	4.2	-0.3
2	71 F	90	4.5	94	+4	4.4	-0.1	89	-1	4.2	-0.3
3	75 M	104	4.8	105	+1	4.8	0	100	-4	4.6	-0.2
4	68 F	85	4.4	89	+4	4.5	+0.1	84	-1	4.1	-0.3
5	71 F	94	4.5	94	0	4.4	-0.1	91	-3	4.5	0
6	77 M	91	4.6	93	+2	4.6	0	90	-1	4.4	-0.2
7	77 M	100	4.9	101	+1	5.0	+0.1	99	-1	4.7	-0.2
8	75 F	98	4.7	99	+1	4.7	0	98	0	4.4	-0.3
9	68 F	100	4.7	99	-1	4.7	0	97	-3	4.5	-0.2
10	47 F	89	4.7	90	+1	4.5	-0.2	88	-1	4.4	-0.3
11	78 F	91	4.5	89	-2	4.4	-0.1	83	-8	4.0	-0.5
12	79 F	92	4.7	89	-3	4.5	-0.2	90	-2	4.4	-0.3
Mean change ± standard error				+0.4 0.67		-0.025 0.18		-2.1 0.64		-0.26 0.035	

TABLE II.—Progress of Similar Group of Patients with Pernicious Anaemia Maintained Throughout on Vitamin B₁₂

Case No.	Age and Sex	Treatment with Vitamin B ₁₂ for 1 Year		Treatment with Vitamin B ₁₂ for 1 Year While Test Group Received Biopar							
				First 6 Months				Second 6 Months			
				Mean Hb		Mean R.B.C.		Mean Hb		Mean R.B.C.	
		Mean Hb (%)	Mean R.B.C. (m./c.mm.)	%	Change	m./c.mm.	Change	%	Change	m./c.mm.	Change
13	64 F	96	4.7	100	+4	4.6	-0.1	96	0	4.6	-0.1
14	75 M	89	4.7	98	+9	4.5	-0.2	99	+10	4.8	+0.1
15	48 F	93	4.5	95	+2	4.6	+0.1	95	+2	4.6	+0.1
16	74 F	90	4.4	94	+4	4.4	0	84	-6	3.9	-0.5
17	71 F	84	4.4	79	-5	4.6	+0.2	84	0	4.2	-0.2
18	68 F	98	4.7	98	0	4.7	0	92	-6	4.6	-0.1
19	75 F	94	4.6	89	-5	4.1	-0.5	93	-1	4.6	0
20	75 F	97	4.6	90	-7	4.6	0	93	-4	4.5	-0.1
21	76 F	86	4.3	94	+8	4.4	+0.1	87	+1	4.0	-0.3
22	72 F	86	4.4	90	+4	4.4	0	88	+2	4.2	-0.2
23	76 F	94	4.8	98	+4	4.6	-0.2	102	+8	4.8	0
24	66 F	89	4.6	90	+1	4.7	+0.1	91	+2	4.6	0
Mean change ± standard error				+1.6 1.52		-0.04 0.055		+0.7 1.46		-0.11 0.052	

Furthermore, the difference in cost between the two treatments is considerable, as maintenance, even on one tablet a day, is nearly nine times as expensive as one injection of 100 μ g. of vitamin B₁₂ once a fortnight. So long as the nature and mode of action of intrinsic factor remain uncertain it is clearly preferable to rely on the parenteral administration of vitamin B₁₂ for the routine treatment of pernicious anaemia. Although the majority of patients prefer taking tablets to receiving injections, more detailed investigation is required before oral treatment can be recommended.

Summary

A clinical trial of oral treatment of pernicious anaemia was carried out with a preparation containing a combination of vitamin B₁₂ and intrinsic factor. In four out of five previously untreated patients there was a satisfactory response; in the fifth the treatment was ineffective, but the patient subsequently responded to parenteral vitamin B₁₂. In 12 patients previously treated with vitamin B₁₂ by injection and transferred to maintenance treatment with the oral preparation the haemoglobin and red-cell count showed over one year a significant fall. In a further patient on oral maintenance therapy, features of subacute combined degeneration developed. It is concluded that at present oral therapy is not as reliable as vitamin B₁₂ by injection.

We wish to thank Dr. Lester Smith, of Glaxo Laboratories Ltd., for the supply of ⁶⁰Co labelled vitamin B₁₂, and Mrs. C. Goldberg for statistical advice.

REFERENCES

- Blackburn, E. K., Burke, J., Roseman, C., and Wayne, E. J. (1952). *British Medical Journal*, 2, 245.
 Callender, S. T., Turnbull, A., and Wakisaka, G. (1954). *Ibid.*, 1, 10.
 Castle, W. B. (1953). *New Engl. J. Med.*, 249, 603.
 Chalmers, J. N. M., and Hall, Z. M. (1954). *British Medical Journal*, 1, 1179.
 Glass, G. B. J., and Boyd, L. J. (1953). *Blood*, 8, 867.
 Lowther, C. P., Alexander, W. D., and Hendry, E. B. (1954). *Lancet*, 1, 495.
 Ungley, C. C. (1950). *British Medical Journal*, 2, 905.
 Vilter, R. W. (1955). *Amer. J. clin. Nutr.*, 3, 72.

DELAYED SPEECH AND DEVELOPMENTAL APHASIA

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We intend in this paper to consider the causes and management of delayed speech. Delay in this important skill, raising as it does disturbing questions of general mental development, is an embarrassment to the child and an anxiety for the parents. Our continuing uncertainty about many of the cerebral processes involved in speech make it also a difficult diagnostic problem for the family doctor and specialist. In 1950 we (Miller and Morley, 1950) suggested the practical need for a simplified classification of speech disorders, and to relate the present observations to our general approach we have with minor modifications reproduced that classification here (Table I). Yet as some of the terms we use are common both to everyday conversation and to the more specialized terminology of speech disorders we must first say what they mean to us in our work and how they are used in this paper.

TABLE I.—A Classification of Speech Disorders in Childhood

- Disorders arising from deafness
1. Congenital nerve deafness:
 - (a) Severe for all frequencies.
 - (b) Partial or high-frequency deafness.
 2. Acquired nerve deafness.
- Aphasia
1. Developmental aphasia:
 - (a) Mainly receptive: (1) auditory imperception; (2) alexia.
 - (b) Mainly expressive.
 2. Acquired aphasia.
 3. Aphasia associated with general mental deficiency.
- Dysarthria
1. Cleft-palate and other anatomical defects of the speech organs.
 2. Dysarthria associated with obvious cerebral palsy or other cerebral disease.
 3. Dysarthria associated with minimal signs of cerebral palsy.
 4. Isolated developmental dysarthria.
- Dyslalia
- Transient defects of consonant omission and substitution.
- Stammering.

Concepts and Definitions

Although mechanistic analysis of such a finely integrated function cannot be pressed too far, it is helpful to think of speech as a triple process: the reception of words by the ear or the eye; their interpretation and synthesis as language within the brain; and, finally, the expression of this language response in further spoken or written words. We regard *speech* as covering the whole of this receptive, formative, and expressive activity.

Words are symbolic sounds which have a consistent range of meaning. In complete or embryonic form they are constructional units of thought and language, and in terms of the movement of speech are heard and understood, arranged and rearranged, and articulated and spoken. *Language* is both the word library of speech and the sum of those meaningful associations of words current in the life and literature of any society.

Aphasia is a breakdown in the comprehension and formulation of words giving rise to a disturbance of thought and a disorder of language. There is therefore both a receptive and an expressive component of aphasia. In some patients either the one or the other predominates, but in many there seems to be an impairment of more than one of the processes concerned and this impairment may be either partial or severe.

Developmental Aphasia

Our present understanding of aphasia is derived from our experience of cerebral injury and disease as they affect adult patients, and in this context the phrase "breakdown in the comprehension and formulation of words" is a proper description of what has taken place. In the children with whom we are mainly concerned in this paper, however, the process is a failure to develop the central processes of speech; a delay in building up a word library and creating a language. In spite of the difference, we propose to use the word aphasia for this disorder of childhood, and, since it becomes apparent during the time that speech is normally developed, to qualify it with the word developmental. For the delayed ability to read, which is often associated with such aphasia but can occur as a specific isolated difficulty, we use the term *alexia*.

Since some aphasic children develop articulatory defects when speech begins we must consider briefly two other conditions. The simpler is *dysarthria*, and implies to us slow and clumsy articulation arising from dysfunction of the muscles used in speech; such dysfunction is evident on physical examination. It does not involve any interference with the internal comprehension and construction of words. A disorder of articulation more commonly in our experience associated with aphasia seems to be an *articulatory apraxia*, and its relationship to aphasia calls for further consideration.