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ORAL TREATMENT OF PERNICIOUS ANAEMIA WITH VITAMIN B₁₂ AND DESICCATED HOG DUODENAL EXTRACT

BY

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Oral administration of a substance with intrinsic factor activity is a rational approach to the treatment of pernicious anaemia. However, treatment by adequate parenteral vitamin B₁₂ is so consistently effective in maintaining a normal state of the blood and bone marrow, and in safeguarding against the development of neurological complications, that any other form of therapy must be shown to be as effective before it can supplant injections of vitamin B₁₂ in the routine management of the disease. Oral therapy has an obvious attraction, and Wilkinson (1949) has shown that excellent results may be obtained by the use of a relatively crude preparation of desiccated hog's stomach. In recent years preparations have been used in the treatment of pernicious anaemia containing, in tablet form, a small amount (5–15 µg.) of vitamin B₁₂ and an extract of desiccated hog duodenal or pyloric mucosa. Evidence has been accumulating that this form of therapy usually results in a good initial response, but

with continued treatment haematological remission and normal levels of vitamin B₁₂ in the serum are not maintained (Bastrup-Madsen, 1957; Kristensen *et al.*, 1957; Lowenstein *et al.*, 1957; Killander, 1958). It has been shown that many patients treated with such oral preparations ultimately have reduced intestinal absorption of vitamin B₁₂ when hog pyloric mucosa is supplied as intrinsic factor (Lowenstein *et al.*, 1957; Schwartz *et al.*, 1957; Stokes and Pitney, 1958). This leads ultimately to deficiency of vitamin B₁₂ and clinical relapse.

The present report describes the results of treatment of pernicious anaemia patients with "biopar" tablets over a period of five years, and is an extension of a previous report on treatment with biopar for one year (Blackburn *et al.*, 1955). The changes in the peripheral blood, the bone marrow, and the levels of vitamin B₁₂ in the serum have been followed during this period of treatment. In addition, tests were made for skin sensitivity to hog intrinsic factor prepared by the same method as used in biopar tablets.

Patients Studied and Details of Treatment

The results of oral treatment with tablets containing crystalline vitamin B₁₂ and a desiccated extract of hog duodenal mucosa (biopar and biopar forte) have been studied in 22 patients with Addisonian pernicious anaemia. In all cases the diagnostic criteria included megalocytic anaemia, megaloblastic erythropoiesis in the bone marrow, histamine-fast gastric achlorhydria, and the absence of evidence of steatorrhoea or other recognized cause of megaloblastic anaemia. Each tablet of biopar contained 6 µg. of vitamin B₁₂ and 30 mg. of the intrinsic factor preparation; each tablet of biopar forte contained 15 µg. of vitamin B₁₂ and 35 mg. of the intrinsic factor preparation.

Thirteen patients (Cases 1–13) who had previously been treated with parenteral vitamin B₁₂, and in whom steady and normal levels of haemoglobin and red-cell count had been maintained during at least one year, were transferred to treatment with biopar in November, 1953. From then until June, 1955, these patients received one tablet of biopar daily. The dose was then increased to two tablets daily until October, 1956. In 1956 the production of biopar tablets was stopped, and they were replaced by biopar forte. From October, 1956, until March, 1959, treatment was given with biopar forte, two tablets daily.

Nine patients with previously untreated pernicious anaemia who had shown a satisfactory initial response to oral treatment were included in the study. Four of these patients (Cases 14–17) were given initially five tablets of biopar daily. This was continued for two to nine months, until June, 1955, when they were transferred to the above scheme of dosage. Five patients (Cases 18–22) received biopar forte, five tablets daily for six months, and then continued treatment with two tablets daily.

The results during the first year of treatment with biopar in 10 of these patients have already been published (Blackburn *et al.*, 1955). Of the 22 patients included in the present study, five did not complete the trial for reasons detailed below.

Methods of Investigation

In all cases determinations of haemoglobin level (M.R.C. grey wedge photometer; oxyhaemoglobin—

100% = 14.8 g./100 ml.) and standard red-cell count were made every four to eight weeks.

Biopsy of iliac bone marrow was performed in 13 patients after treatment with biopar for 3½ years, and in nine patients further marrow examination was made at the end of five years of oral therapy.

The concentration of vitamin B₁₂ in the serum was estimated after treatment with biopar for 2½, 3½, and 5 years. In five patients this estimation was carried out before starting therapy and again after treatment with biopar for six to 13 months. The amount of vitamin B₁₂ in samples of serum was estimated by microbiological assay, using *Lactobacillus leichmannii* as the test organism (Spray, 1955).

Skin-testing was carried out with an extract of hog pyloric mucosa, as contained in biopar tablets. In each test, 0.02 ml. of a 1/100 dilution of the extract in normal saline was injected intradermally on the front of the right forearm. A control injection of 0.02 ml. of normal saline was also given on the left forearm.

Results

The levels of haemoglobin and red-cell count during the first year of treatment with biopar in 12 patients formed the subject of a previous publication (Blackburn *et al.*, 1955). Of these 12 patients, two were not included in the subsequent study. One died of pneumonia soon after the end of the first year; peripheral blood examination had been within normal limits a few weeks before death. The other patient developed persistent paraesthesiae in the hands at the end of the first year, without objective signs of neurological abnormality and without abnormality of the blood. Nevertheless, treatment with biopar was stopped and injections of vitamin B₁₂ were recommenced. There was little symptomatic change after parenteral vitamin B₁₂ therapy, and it now seems unlikely that any neurological changes due to vitamin-B₁₂ deficiency had been present. Two other patients died during the subsequent study: one (Case 13) died of coronary thrombosis after three years, and the other (Case 6) died of carcinoma of the prostate after four years of treatment with biopar. In each of these cases the last haemoglobin estimation, red-cell count, and blood film, made within a few weeks of death, were normal.

Haematological relapse occurred in three patients out of a total of 17 after treatment with biopar for 2½ to 5 years. These patients were believed to be reliable, and they stated that they had taken the prescribed tablets regularly.

Case 1.—This patient, who had previously received parenteral therapy with liver extract and later vitamin B₁₂ for a total of seven years, showed a persistent fall in red-cell count to about 3,600,000/c.mm., associated with macrocytosis in the peripheral blood film after treatment with biopar for five years. The level of vitamin B₁₂ in the serum at this time was 65 µg./ml. and the bone marrow showed the typical appearances of vitamin-B₁₂ deficiency in the red-cell and white-cell precursors. There was a prompt return of the blood to normal after the resumption of parenteral vitamin-B₁₂ therapy.

Case 3.—Previous treatment with liver extract and later vitamin B₁₂ had been given for a total of six years. After treatment with biopar for 3½ years the red-cell count, which had previously been maintained above 4,500,000/c.mm., showed a persistent fall, reaching 2,500,000/c.mm., and the peripheral blood film contained many macrocytes. The bone marrow showed megaloblastic erythropoiesis. The concentration of vitamin B₁₂ in the serum at this time

was 30 µg./ml. Parenteral therapy with vitamin B₁₂ was followed by an increase in the red-cell count to 5,300,000/c.mm. in one month.

Case 14.—This patient, with previously untreated pernicious anaemia, had initially shown an adequate haematological response to biopar. However, after treatment with biopar for 21 months the level of vitamin B₁₂ in the serum was 56 µg./ml., and seven months later it was 10 µg./ml. At this time the red-cell count began to fall and reached 2,900,000/c.mm., the bone marrow showing megaloblastic erythropoiesis. After parenteral therapy with vitamin B₁₂ the red-cell count returned to normal.

Two other patients (Cases 2 and 4) showed a fall in haemoglobin level and in red-cell count while on biopar therapy. In both cases the appearances of the peripheral blood film suggested concomitant iron deficiency, and the blood returned to normal when oral treatment with iron was given in addition to biopar.

In the remaining 12 patients in this series the levels of haemoglobin and red-cell count have remained within the normal range during the period of biopar treatment. Statistical analysis of all the red-cell counts made during the entire period of treatment in these cases has not revealed any significant trend. In no case did neurological signs develop during biopar treatment.

Examination of the bone marrow was made after treatment with biopar for 2½ to 3½ years in 13 patients (Table I); typical megaloblasts were present in two

TABLE I.—Levels of Vitamin B₁₂ in Serum and the Appearance of Bone Marrow During Treatment with Biopar in 17 Patients With Pernicious Anaemia

Case No.	Age and Sex	Serum Level of Vitamin B ₁₂ (µg./ml.) after Treatment with Biopar for			Evidence of Vitamin-B ₁₂ Deficiency in Bone Marrow	
		2½ Yrs.	3½ Yrs.	5 Yrs.	3½ Yrs.	5 Yrs.
1	69 F	160	35	65	+	++
2	74 F	280	240	250	0	+
3	78 M	140	76	30 (4yr.)	++	—
4	73 F	270	90	65	+	++
5	75 F	190	110	100	0	—
6	82 M	180	120	—	—	—
7	82 M	78	19	35	+	++
8	70 F	210	75	140	+	—
9	50 F	220	120	170	0	0
10	89 F	110	84	72	+	—
11	52 M	—	32	40	0	0
12	53 F	590	430	290	—	—
13	65 M	110	—	—	—	—
14	78 F	10	—	—	++ (2½ yr.)	—
15	58 F	130	69	100	+	0
16	42 F	220	—	170	+	++
17	41 M	460	340	830	0	0

The results of marrow biopsy are classified in three categories: no evidence of vitamin-B₁₂ deficiency, (0); slight abnormalities consistent with but not diagnostic of vitamin-B₁₂ deficiency, (+); evidence of vitamin-B₁₂ deficiency, (++)

(Cases 3 and 14), who therefore were treated subsequently with parenteral vitamin B₁₂. In six there were minor abnormalities suggestive but not diagnostic of vitamin-B₁₂ deficiency, and in the remaining five the marrow appeared normal. Bone-marrow examination after treatment with biopar for five years showed megaloblasts typical of vitamin-B₁₂ deficiency in four of nine cases. Thus within five years megaloblasts were present in at least 6 out of 17 cases.

The results of estimations of vitamin B₁₂ in the serum are shown in Table I. By the method used the normal range is 150–1,000 µg./ml. (Spray and Witts, 1958). After treatment with biopar for 2½ years the level of vitamin B₁₂ in the serum was less than 150 µg./ml. in 6 out of 16 cases, and after treatment for 3½ years the level was abnormally low in 11 cases. It is noteworthy that, in the patients in whom the concentration of vitamin B₁₂ in the serum was normal after treatment

with biopar for 3½ years, the level was still within the normal range after treatment for five years.

In the nine cases (Nos. 14–22) of hitherto untreated pernicious anaemia, treatment with biopar resulted in a satisfactory initial response. The increase in red cells in 14 days was very similar to the “average response” to potent liver extract (Della Vida and Dyke, 1942),

TABLE II.—*Levels of Vitamin B₁₂ in Serum in Five Patients With Pernicious Anaemia Before Starting Treatment, and After Treatment with Biopar Tablets for 6 to 13 Months*

Case No.	Age and Sex	Serum Level of Vitamin B ₁₂ (μg./ml.)		Duration of Treatment with Biopar (Months)
		Before Treatment	After Treatment with Biopar	
18	60 F	20	200	13
19	63 F	22	250	9
20	76 F	25	88	6
21	70 F	52	52	8
22	62 F	30	92	9

except in one case, in which there was evidence of concomitant iron deficiency; a reticulocyte response of 32% (dry method) followed the start of biopar therapy, but the increase in red cells was at first slow. When iron by mouth was added the red-cell count rapidly increased to normal. However, when the level of vitamin B₁₂ in the serum was estimated in five of these patients after treatment with biopar for 6 to 13 months, it was within the normal range in only two (Table II).

Skin tests by intradermal injection of a 1/100 dilution of an extract of hog pyloric mucosa were carried out in 13 patients after treatment with biopar for four to five years. For comparison, skin tests were performed, using the same technique and preparation of hog pyloric mucosa, in 16 patients with pernicious anaemia who had been treated for 2 to 20 years with liver or vitamin-B₁₂ injections, and who had never received biopar tablets or other oral preparation for the treatment of pernicious anaemia. A slight positive reaction was observed in three of the biopar patients; in two of these the level of vitamin B₁₂ in the serum was abnormally low (Cases 11 and 21), and in one it was normal (Case 12). The reaction consisted of an area of erythema about 1 cm. in diameter, observed 15 to 30 minutes after injection, with no reaction to the control injection. In no patient was there any weal formation or pruritus. A similar slight positive reaction was observed in 2 of the 16 patients with pernicious anaemia who had never received biopar.

Discussion

The results of this study show that neither biopar nor biopar forte is reliable in the treatment of pernicious anaemia. In the group of patients who had been well maintained previously by parenteral vitamin B₁₂ the levels of vitamin B₁₂ in the serum became abnormally low in 11 out of 14, after treatment with biopar for 3½ years. In two of these patients there was a reduction in red-cell count with clinical relapse after 3½ to 5 years of biopar therapy. The patients with previously untreated pernicious anaemia showed a satisfactory clinical and haematological response at first to biopar treatment, but in several cases the level of vitamin B₁₂ in the serum was abnormally low after six to nine months, and in one patient there was haematological relapse after 2½ years. One case has previously been reported in which there was a failure of initial response to biopar but subsequent good response to parenteral vitamin B₁₂ (Blackburn *et al.*, 1955). These results with biopar are

very similar to the published results with other oral preparations containing a small amount of vitamin B₁₂ along with an extract of hog pyloric mucosa—“bifactor” (Mollin and Ross, 1954; Killander, 1958), “bendogen” (Berlin *et al.*, 1958), and “cycoplex” (Kristensen *et al.*, 1957; Lowenstein *et al.*, 1957). As with these other oral preparations, increasing the dose of biopar did not prevent relapse.

The haemoglobin concentration and red-cell count remained normal for up to at least two years after the level of vitamin B₁₂ in the serum had been found to be abnormally low; a similar time lag in haematological relapse was reported by Killander (1958), and it is clear that satisfactory levels of haemoglobin and red-cell count over a period of years in a patient with pernicious anaemia is not proof that the treatment given is adequate in preventing vitamin-B₁₂ deficiency.

The failure of oral preparations containing vitamin B₁₂ and hog pyloric mucosa to maintain remission in pernicious anaemia after an initial good response appears to result from a late development of a block in the intestinal absorption of vitamin B₁₂. When refractoriness to these oral preparations develops, labelled vitamin B₁₂ is not absorbed when given orally along with hog pyloric mucosa, but is well absorbed when given with normal human gastric juice (Killander, 1957; Lowenstein *et al.*, 1957; Schwartz *et al.*, 1957; Berlin *et al.*, 1958; and Stokes and Pitney, 1958). Taylor and Morton (1958) have produced specific rabbit antisera which can neutralize human or pig intrinsic factor activity, and Schwartz (1958) has shown that the serum of some patients treated with oral preparations of vitamin B₁₂ and hog pyloric mucosa has the property of inhibiting intrinsic factor. This cannot explain all the observed phenomena in pernicious anaemia treated by oral preparations, as the inhibitory activity was observed against human intrinsic factor as well as hog pyloric mucosa.

The skin tests performed with the extract of hog duodenal mucosa failed to demonstrate any relationship between skin sensitivity to the extract and relapse of pernicious anaemia during treatment with biopar. Although two patients who had low levels of vitamin B₁₂ in the serum after treatment with biopar showed a slight positive reaction, a similar response was obtained in one biopar patient who had a normal level of vitamin B₁₂ in the serum and in two patients with pernicious anaemia who had never received biopar.

Small daily oral doses of vitamin B₁₂ without added intrinsic factor may produce haematological response in some patients with pernicious anaemia (Estren and Wasserman, 1956; Chalmers and Shinton, 1958), and it is possible that the initial response to biopar reported above in previously untreated cases of pernicious anaemia may have resulted entirely from the vitamin-B₁₂ content of the tablets. The patients with previously untreated pernicious anaemia in the series now reported received, in the biopar tablets, 30–75 μg. of vitamin B₁₂ daily for up to nine months. Chalmers and Shinton (1958) have shown that 50 μg. of vitamin B₁₂ daily, given orally, produced haematological response, but did not maintain normal levels of vitamin B₁₂ in the serum, whereas 100 μg. of vitamin B₁₂ daily by mouth resulted in normal levels of vitamin B₁₂ in the serum.

Summary

Oral treatment of pernicious anaemia with “biopar,” a preparation containing vitamin B₁₂ and an extract of

hog duodenal mucosa, has been studied in 22 patients. Thirteen patients who had previously been treated satisfactorily with parenteral vitamin B₁₂ for at least one year, received biopar therapy for up to five years. After 3½ years the level of vitamin B₁₂ in the serum was abnormally low in most patients, and haematological relapse occurred in two patients after four to five years.

Nine patients with previously untreated pernicious anaemia showed a satisfactory initial response to biopar therapy, but one relapsed after 2½ years and in four others the vitamin B₁₂ in the serum did not reach a satisfactory level. The level of vitamin B₁₂ in the serum reached the normal range in the remaining four, in two of whom normal values were still found after treatment for five years.

Skin tests performed with an extract of hog duodenal mucosa did not show any relationship between skin sensitivity to the extract and refractoriness to biopar treatment.

The results of the investigation show that this oral treatment is not reliable for maintenance of patients with pernicious anaemia.

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The polio vaccination campaign among young people is being intensified in two of the L.C.C.'s health divisions in north London. Dr. J. A. SCOTT, the L.C.C.'s Medical Officer of Health, has written to nearly 10,000 firms, coffee bars, dance halls, hairdressers, gramophone record shops, and others in Finsbury, Hackney, Holborn, Islington, Shoreditch, and Stoke Newington, to ask for their help. In Finsbury, Holborn, and Islington the council will use a mobile clinic to take "the jab to the job," parking in or near the factories and offices where the young people work. Up to September this year there have been 84 confirmed cases of polio in these six north London boroughs, six of them fatal. But Dr. Scott points out that quite three-quarters of young Londoners between the ages of 15 and 26 have not yet sought protection: this despite the fact that the chances of being attacked by polio are about five times greater for the unvaccinated than for the vaccinated.

PLACENTAL IMPLANTATION FOR PERIPHERAL VASCULAR DISEASE

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Since Filatov (1935) reported the use of various tissue implants as an aid in corneal grafting, numerous papers have been published from the continent of Europe advocating placental tissue or placental extract in the treatment of many diseases. Sneepe (1955) from Holland, and Piccoli (1954) and Cordaro (1957) from Italy, have recommended this therapy for advancing the healing of wounds and ulcers, while in the German literature several reports have appeared on the use of placental extract in the disturbances of the climacteric (Branger and Krattiger-Müller, 1957). The extract has also been used in skin wounds by Bromilski (1956), of Poland, and in intestinal fistula by Junod (1954), of France. In this country Troensegaard-Hansen (1956) has used amnion both as an implant and as a surface application for ulcers.

In 1956 D. Le Grand (personal communication) stated that implantation of the cotyledon surface of the placenta gave spectacular results in persistent intermittent claudication, and the present paper is a favourable preliminary report of a clinical trial of this method of treatment.

Method

Selection of Patients.—Every patient reporting to the clinic on account of severe intermittent claudication was admitted for investigation and included in the first part of this trial. Later, the method was attempted on an out-patient basis. These patients had previously had Buerger's exercises, and in many cases had received vasodilator drugs. A few had had a previous sympathectomy. Each patient was warned that two implants might be required, so that a control series could be arranged. If the control method of treatment failed, the patient received an implant of placenta.

Assessment of the Patients.—A full history and medical examination revealed the general state of the patient. Examination of the cardiovascular system was supplemented in most cases by an electrocardiogram and ophthalmoscopy. The peripheral circulation was assessed by inspection of the skin, palpation of the pulses, estimation of venous filling time, and exercise tolerance. The actual lesion was identified by arteriography, which also gave an indication of the collateral circulation and general state of the vessels. The capacity of the arteries to dilate was assessed by a reflex heating test and the blood flow in the limbs by oscillometry. This assessment enabled the patient to be placed in one of three groups suitable for: (1) conservative treatment, (2) sympathectomy, or (3) arterial graft. Patients in all three groups received placental implants as the first method of treatment.

Preparation of Placenta.—A placenta was delivered straight from the maternity unit in a sterile container. The blood group of mother and placenta was