FOLIC ACID IN COELIAC DISEASE

A STUDY OF ITS ADMINISTRATION IN TWENTY-TWO CASES

BY

JOHN DUNCAN HAY, M.A., M.D., M.R.C.P.

Assistant Physician, Royal Liverpool Children's Hospital; Assistant Clinical Lecturer in Paediatrics, University of Liverpool

Introduction

Folic acid, as a component of the vitamin B complex, has been recognized for many years as an essential food factor. Crude preparations of it were shown to have a haemopoietic effect in some animals. Deficiency of it was followed by depression of the formation of red cells, white cells, and platelets. In 1945 Angier et al. (1945) synthesized pure folic acid. Spies (1945) and his co-workers were the first to report the haemopoietic properties of folic acid in man. Clinical trials by Berry and Spies (1946), Zuelzer and Ogden (1946), Lopez et al. (1946), Doan (1946), Wilkinson et al. (1946), and Davidson and Girdwood (1946, 1947 a, b) followed. These proved that the administrations of synthetic folic acid was followed by a haemopoietic response similar to that produced by adequate liver therapy in some types of megaloblastic anaemia, including pernicious anaemia and the anaemias associated with sprue, pellagra, pregnancy, infancy, and malnutrition, but that there was no such response in cases of iron-deficiency anaemia, hypoplastic and aplastic anaemia, or leukaemia.

In cases of sprue, folic acid administration was shown by Spies et al. (1946) and by Davidson and Girdwood (1947 b) to be followed by improvement in intestinal function as demonstrated by the disappearance both of an abnormal radiological picture and of gastro-intestinal symptoms. Mucosal oedema, intestinal segmentation, spasm, dilatation and hypomotility were no longer present, and control of the diarrhoea and resolution of oral lesions were accompanied by gain in weight. Davidson found that intestinal function was improved after five days' administration of folic acid and before any improvement in the blood picture took place.

In three cases of coeliac disease Davidson et al. (1947 b) observed no beneficial effects following folic acid administration. The anaemia, which was hypochromic in all three cases, did not improve. The

sternal marrow was examined in two of the cases and proved to be normoblastic. Weight did not increase, and diarrhoea was not relieved.

The treatment of a single case of coeliac disease by folic acid was described by Brody and Gore (1946). In their case improvement in the character of the faeces and in the general condition, and increase in weight followed the administration of folic acid. Hypochromic anaemia was present before treatment. No detailed blood findings following treatment were stated.

Dalton et al. (1946) reported the administration of folic acid in doses of 5 mg. daily to two cases of coeliac disease with megaloblastic changes in their sternal marrow. In these cases reticulocyte responses of over 25 per cent. were accompanied by striking clinical improvement.

May (1947) treated five cases of coeliac disease with folic acid intramuscularly in large doses. None of his patients had macrocytic anaemia or megaloblastic arrest in the bone marrow, and none showed any beneficial effect of the folic acid, the stools remaining unchanged, the weight stationary, and the anaemia, which was of microcytic hypochromic type, unaltered.

Investigation

In this series twenty-nine cases of steatorrhoea in infancy and childhood were selected for the exhibition of folic acid. In each case the following investigations were carried out whenever possible:

Detailed clinical history and physical examination on which an attempt was made to assess the severity of the condition.

Faecal fat analysis by a modification of Holt, Courtney, and Fales' method (vide Harrison, 'Chemical Clinical Methods,' p. 490) using a single extraction with ethyl ether.

In all cases 25 to 30 g. of fat were ingested daily for three days, and the faeces passed during this period were 'marked' by charcoal biscuits. In some of the cases the faeces were bulked and weighed and an aliquot portion analysed, an

approximate estimate being so obtained of the percentage of ingested fat excreted during the period and so of the total fat balance. In a greater number of cases bulking was not possible and a sample of faeces during the period was analysed without any attempt being made to estimate the total fat excreted.

Trypsin and lipase content of duodenal juice. In eleven cases trypsin was estimated by the casein digestion method of Gross. In three the gelatin digestion method was used. In many cases three or four attempts to withdraw duodenal juice were unsuccessful. Lipase was estimated by the ethyl butyrate breakdown method.

Fractional test meal, the Boas' gruel meal being used to estimate free and combined acid.

Oral glucose tolerance test, followed the ingestion of 0.7 to 1.5 g. of glucose per kg. of body weight, the blood glucose being estimated by Folin and Wu's method.

Blood plasma protein by Van Slyke's method; serum calcium by Kramer and Tisdell's method; inorganic phosphate by Briggs' method; and alkaline phosphatase by King and Armstrong's method.

Blood haemoglobin by Haldane's method (13.8 g. per 100 ml. = 100 per cent.); red and white cell counts.

Sternal marrow puncture.

Radiography of the alimentary tract following a barium meal; of the skeleton for evidence of osteoporosis, rickets, and delayed ossification, and of the lungs for evidence of fibrosis.

Treatment with a low-fat-high-protein diet, oral and parenteral liver extract, and vitamins was then begun in those cases not already receiving it before investigations, and during a period of one or more months the rate of gain in weight and the naked-eye character of the faeces were observed and, in some cases, further blood haemoglobin estimations were done.

Folic acid in doses of 20 mg. or 10 mg. daily was then added to the treatment for one or two months while similar observations of the weight, faeces, and haemoglobin were made.

It was considered that the rate of gain in weight and the character of the faeces were the most reliable criteria of the progress of the patient, and that a comparison of these in the same patients during periods of folic acid administration and of withholding folic acid would demonstrate any uniform effect of the folic acid better than the use of half the cases as controls.

Of the twenty-nine cases, seven were excluded from the series owing to: failure to confirm the steatorrhoea by chemical analysis of the faeces before the exhibition of folic acid in four; the general condition of the patient being too good at the time of the investigation in one; the general condition being too bad both before and during folic acid administration and death occurring just after its

completion in one; and the presence of calcified abdominal glands in one.

In none of the remaining twenty-two cases was there conclusive evidence of fibrocystic disease of the pancreas. In six, examination of the duodenal juice revealed trypsin in amounts falling within the accepted normal figures—25 to 50 ml. of N/10 sodium hydroxide. In five cases less than 25 ml. were found; in three, trypsin was shown to be present but was not estimated quantitatively; and in the majority of the remainder several attempts to obtain duodenal juice failed. Radiological evidence of pulmonary fibrosis was, however, present in only one case, and in this patient the figure for trypsin was 50 ml. of N/10 sodium hydroxide. For the purposes of this clinical trial, therefore, all the patients were regarded as suffering from coeliac disease.

Summary of Clinical and Laboratory Findings

Age. The average age at the onset of symptoms was 19.8 months, the earliest 3 months, and the latest 5 years.

Sex. There were thirteen girls (59.1 per cent.) and nine boys (40.9 per cent.).

Familial incidence. There was a history of coeliac disease in the families of three of the patients (13.6 per cent.). Two of the cases were brothers, and one had a brother with coeliac disease. Also, one had a younger sister who had had steatorrhoea which had been transient.

Duration of the disease. At the time of the investigation and treatment the duration had varied from one month to six and a half years, the average being 22.5 months.

Severity of the condition. There was a considerable variation from case to case in this also: one mild case, in whom steatorrhoea was unaccompanied by any other definite disability; ten moderate cases, in whom there was also definite wasting, abdominal distension, and anorexia, but who were not seriously ill or grossly dwarfed; and eleven severe cases who manifested marked dehydration, wasting, and diarrhoea sufficient to render them dangerously ill or markedly dwarfed.

Faecal fat analysis. The results of the faecal fat analysis are shown in Table 1.

It will be seen that in the ten cases in which it was estimated the total fat excreted during the fat balance period was calculated as ranging from 14.0 per cent. to 98.0 per cent. These figures were only approximations, and 98.0 per cent. was obviously an excessive approximation. The total fat percentage by weight of dried faeces ranged from 27.3 per cent. to 69.0 per cent., the percentage of this fat which was split ranging from 60.3 per cent. to 92.5 per cent. and unsplit from 7.5 per cent. to 48.0 per cent.

Duodenal juice. Duodenal juice was obtained in only fourteen cases. In all of these trypsin was demonstrated. The amount of trypsin was estimated in eleven and the number of ml. of 0.1 per cent. casein solution completely digested by 1 ml.

TABLE 1
RESULTS OF FAECAL FAT ANALYSIS

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Fat balance (percentage of ingested fat excreted) ..	16.0	38.6	14.0	33.0	15.0								46.6			97.0		14.0		98.0	39.0	
Total fat (percentage of faeces by dried weight) ..	37.0	26.3	56.6	26.0	36.8	50.0	49.6	69.0	27.3	47.3	32.0	27.7	35.4	34.3	41.4	38.9	40.4	27.3	52.8	46.9	39.0	47.6
Percentage of total fat split ..	89.0	77.4	86.4	52.0	86.4	92.5	86.9	90.5	86.2	87.3	85.0	84.0	75.1	84.0	85.4	80.6	76.6	70.2	80.1	60.3	88.4	83.9
Percentage of total fat unsplit ..	11.0	22.6	13.6	48.0	13.6	7.5	13.1	9.5	13.8	12.7	15.0	16.0	24.9	16.0	14.6	19.4	23.4	29.8	19.9	39.7	11.6	16.1
Duodenal Trypsin ml. of 1% casein sol. ..	present			present				50		20	25	200	50	20	20		100	10		50	present	20
Juice Lipase ml. of N/10 sodium hydroxide ..	0.1							0.2		0.2	1.9	0.1	0.2		0.2			0.1		2.0		0.3

of duodenal juice was found to be between 20 and 200 ml. in ten of the cases and to be 10 ml. in the other case. Lipase was estimated in nine cases, and the number of ml. of N/10 sodium hydroxide will be seen to range from 0.1 to 2.0 ml. (normal, 0.2 to 2.0) and to be at, or above, the lower limit of normal in six.

Fractional test meals. Normal acid curves were found in twelve patients (54.6 per cent.), low acid curves in nine (41 per cent.) and absent free and combined acid in one (4.4 per cent.).

Blood sugar estimations. The minimum fasting level obtained was 55 mg. per 100 ml. and the maximum 174 mg. per 100 ml. It lay between 55 mg. and 99 mg. per 100 ml. in seven patients and between 100 mg. and 174 mg. per 100 ml. in fifteen. In the oral glucose tolerance test blood sugar estimations were only possible at half-hourly intervals up to two hours after the ingestion of glucose, and some of the patients were inadvertently given glucose in excess of 1 g. per kg. of body weight. The results obtained in this series are, therefore, of limited significance.

An initial fall of the type described by Emery (1947) was observed in two patients: in one the blood sugar failed to return to the fasting level by two hours after the ingestion of glucose: in the other, it returned to, but not above, the fasting level.

In only eight patients was there a rise of less than 40 mg. per 100 ml. above the fasting level: in seven, of 40 to 69 mg. inclusive: in two, of 70 to 99 mg. and in three of 100 to 150 mg.

Blood plasma protein, etc. The findings for blood plasma protein, serum calcium, inorganic phosphate, and alkaline phosphatase are summarized in table 2. Plasma protein will be seen to have ranged from 5.8 to 9.5 mg. per 100 ml. (normal = 6.0 to 7.3). These high values were accounted for by the copper sulphate solution used in Van Slyke's method being found to be below standard.

The values for serum calcium ranged from 7.1 to 11 mg. per 100 ml. (normal = 9.0 to 11.0); for inorganic phosphate from 1.6 to 3.75 mg. per 100 ml. (normal = 4.0 to 6.0), and for alkaline phosphatase from 5 to 31 units (normal = 3 to 31 units).

The blood haemoglobin will be seen from table 3 to have ranged from 40 per cent. to 85 per cent., being between 50 per cent. and 59 per cent. in four cases, between 60 per cent. and 74 per cent. in seven cases, and over 65 per cent. in eleven cases. The red blood cells numbered from 3.3 to 6.8 million per c.mm. The colour index was less than 1.0 in all cases. The sternal bone marrow showed no

TABLE 2
THE FINDINGS FOR BLOOD PLASMA, PROTEIN, SERUM CALCIUM, INORGANIC PHOSPHATE, AND ALKALINE PHOSPHATASE

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Plasma protein g. per 100 ml	8.9	6.15	8.2	8.9	7.85			8.1	7.1	6.4	9.5	6.15	7.5		8.6	6.8	8.2	7.15		5.8	9.5	
Serum calcium mg. per 100 ml.	10.3	10.5	10.0	9.0	7.1	10.6		10.0	10.8	9.0	11.0		11.0		9.2	8.5	10.8	9.0	10.2	9.0	10.0	7.25
Inorganic phosphate (mg. per 100 ml.)	1.6			3.0	3.75			2.4			3.0		2.3							2.3	2.8	2.0
Alkaline phosphatase (units per 100 ml.)		10	16	8	15	5	7.5	20	14	10	25		31	6	11	18	10	10	15	15	5	5

megaloblastic erythropoiesis in any of the six cases examined.

Radiological appearances. In all cases segmentation of the barium in the small intestine with loss of the normal haustration compatible with a diagnosis of coeliac disease was seen in radiographs of the small intestine following a barium meal. In three cases (13.9 per cent.) these changes were only slight.

Radiographs showed rickets to be present in two cases (9.9 per cent.), osteoporosis in sixteen (72.7 per cent.); no relationship was demonstrable between the presence of osteoporosis and the level of alkaline phosphatase. Delayed ossification in the epiphyses of the wrists was found in nine patients (40.9 per cent.).

Radiological evidence of pulmonary fibrosis was present in one case only (4.5 per cent.).

Results of Treatment

Twelve cases (A1) showed slight increase in weight on preliminary treatment; and of these, eight (A2) showed further slight increase in weight accompanying folic acid administration.

Ten cases (B1) showed no increase in weight on preliminary treatment; and of these, eight (B2) showed slight increase in weight on folic acid.

Twelve cases (C1) (eight of which were included in group A1) showed improvement in faeces on preliminary treatment. Of these nine (C2) maintained this improvement or showed further improvement accompanying folic acid administration.

Ten cases (D1) showed no improvement in faeces on preliminary treatment; and of these seven (D2) showed improvement on folic acid.

Of the twenty-two cases, therefore, sixteen (twelve of group A1 plus four of Group C1 not included in group A1) may be said to have shown slight clinical improvement on preliminary treatment, and twenty-one (eight of group A2, plus five of group C2 not included in group A2, plus five of group B2 not included in groups A2 or C2, plus three of group D2 not included in groups A2, B2 or C2) further clinical improvement, or improvement in those cases where there had been none on preliminary treatment, accompanying folic acid administration: that is, improvement which might be attributed to folic acid.

The actual measurement of this improvement, however, by rate of gain in weight showed it to be

very slight indeed. The average gain for all the cases per month on preliminary treatment alone was only 0.4 lb., and on preliminary treatment plus folic acid 0.5 lb.; and in the cases which improved on preliminary treatment alone the average gain was 0.9 lb., and in those which improved or further improved on folic acid 1.2 lb.

Such small differences in the rates of gain during the periods under comparison do not provide convincing evidence of any beneficial effect of folic acid; especially in view of the fact that the majority of the children were much underweight at the beginning of treatment.

Observation of the haemoglobin during treatment in the six cases where it was possible also revealed no uniform beneficial effect. In five of the cases no rise of haemoglobin occurred during the period of preliminary treatment or of folic acid administration, and in the sixth some increase of haemoglobin was observed during both periods.

Conclusions

This clinical trial of folic acid in twenty-two cases of coeliac disease, in none of which there was a macrocytic anaemia, would appear, therefore, to support May's findings in his five similar cases: namely, that there is no definite evidence of any effect on the progress of the condition.

In the absence of macrocytic anaemia in any of these cases a comparison with Thompson's results with folic acid administration in this type of anaemia complicating coeliac disease is not possible.

Summary

Twenty-two infants and children considered to be suffering from coeliac disease were treated for a period with a low-fat and high-protein diet, liver extract, and vitamins. Folic acid was then added to the treatment for a comparable period. The clinical condition of the children during these periods was compared by observations on rate of gain in weight and on the naked-eye character of the faeces.

No conclusive evidence was obtained of any beneficial effect of the folic acid.

TABLE 3
BLOOD HAEMOGLOBIN, RED CELLS, COLOUR INDEX, AND STERNAL MARROW FINDINGS

Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Haemoglobin (%)	67	85	50	70	50	75	75	75	80	85	56	65	75	80	85	55	85	70	90	60	65	60
Red blood cells (millions per c.mm.)	5.6		3.7	5.0	3.3			3.9		4.5	3.8	4.0	4.9			3.5				3.5	6.8	4.2
Colour index	.58		.67	.7	.8			.96		.9	.72	.8	.77			.78				.85	.48	.71
Sternal marrow normoblastic erythropoiesis		+	+						+								+		+	+		

I wish to thank Profs. Norman B. Capon and Richard W. B. Ellis for advice on the presentation of my findings; Prof. Capon, Dr. R. W. Brookfield, and Dr. Netta Hay for allowing me to investigate and treat cases in their care who form part of this series; Drs. C. A. St. Hill, R. H. Mole, and R. M. Rawcliffe and their technical staffs for undertaking the laboratory investigations; Dr. Nora Walker for the radiological reports; and the registrars, house physicians, and members of the nursing staffs of the Royal Liverpool Children's Hospital, the Royal Liverpool Babies' Hospital, and the Birkenhead and Wirral Children's Hospital for their invaluable assistance in the investigation and treatment of the patients.

REFERENCES

- Angier, R. B. et al. (1945). *Science*, **102**, 227.
 Berry, L. J., and Spies, T. D. (1946). *Blood*, **1**, 271.
 Brody, H. P., and Gore, L. (1946). *Lancet*, **2**, 618.
 Dalton, H. W., Thompson, M. L., and Wilson, V. K. (1946). *Ibid.*, **2**, 652.
 Davidson, L. S. P., and Girdwood, R. H. (1946). *Ibid.*, **2**, 373.
 —, — (1947 a). *Brit. med. J.*, **1**, 587.
 —, —, and Innes, E. M. (1947 b). *Lancet*, **1**, 511.
 Doan, C. A. (1946). *Amer. J. med. Sci.*, **212**, 257.
 Emery, J. L. (1947). *Arch. Dis. Childh.*, **22**, 41.
 Lopez, G. G., Spies, T. D., Menendez, J. A., and Toca, R. L. (1946). *J. Amer. med. Ass.*, **132**, 906.
 May, C. D. (1947). *Amer. J. Dis. Child.*, **73**, 241.
 Spies, T. D. et al. (1945). *South med. J.*, **38**, 707.
 —, — (1946). *J. Amer. med. Ass.*, **132**, 906.
 —, — (1946). *Amer. J. Roentgen.*, **56**, 337.
 —, — (1946). *J. Lab. clin. Med.*, **31**, 227.
 Wilkinson, J. F., Israëls, M. C. G., and Fletcher, F. (1946). *Lancet*, **2**, 156.
 —, — (1948). *Brit. med. J.*, **1**, 822.
 Zuelzer, W. W., and Ogden, F. N. (1946). *Amer. J. Dis. Child.*, **71**, 211.