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FOLIC ACID*

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"Folic acid," so named by Mitchell, Snell, and Williams (1941, 1944) because of its isolation as a crystalline substance from spinach and other green leaves and grasses, is a recently identified constituent of the vitamin B group. Since it is necessary for the growth of two organisms—*Lactobacillus casei E* and *Streptococcus faecalis* (*Str. lactis R*)—these have formed the basis of a microbiological method of estimation. It has been shown that a number of substances either similar to or identical with this particular "folic acid" (*L. casei* factor, as it is also termed) can be isolated from many other sources, such as yeast, liver, kidney, milk, mushrooms, grasses, and green leaves.

The isolation, identification, and, later, synthesis of one folic acid was the culmination of a series of different independent investigations which became particularly active after Snell and Peterson (1940) demonstrated the existence of a vitamin-like substance essential for the growth of *L. casei*; several groups of workers (Mitchell *et al.*, 1941, 1944; Hutchings *et al.*, 1941, 1944; Stokstad, 1943) have studied the growth factors for various bacteria and noted that extracts of plants or animal organs are essential for this growth. It soon became clear that there were several different but allied "folic acids," and of these at least four crystalline products have since been prepared and found to have different activities on the growths of *L. casei* and *Str. faecalis*.

The very recent synthesis (Angier *et al.*, 1945, 1946) of one of these "folic acids"—pteroylglutamic acid—and the establishment of its identity with Stokstad's crystalline substance from liver (the liver *L. casei* factor) and with the essential growth factor for both *L. casei* and *Str. faecalis* have led to great advances in its therapeutic applications, especially since the pure substance has become generally available.

Vitamin B_c and Folic Acid

Hogan and Parrott (1940), by feeding a diet containing all the then known essential elements, produced a nutritional macrocytic anaemia in chicks which could be prevented or cured by a fuller's-earth concentrate from liver, yeast, green leaves, etc., containing a factor they termed vitamin B_c (Campbell *et al.*, 1944, 1945; Richardson *et al.*, 1942; O'Dell and Hogan, 1943). Vitamin B_c was also isolated from liver and yeast by Stokstad (1943) and Hutchings *et al.* (1944), the yeast factor being less active than the liver factor for growth of *L. casei* and inactive for *Str. faecalis*. Binkley *et al.* (1944) showed that vitamin B_c from yeast was inactive for *L. casei* until after enzyme digestion, when it became equally active for *L. casei* and *Str. faecalis* (*Str. lactis R*).

The vitamin-B_c-deficiency anaemia of chicks was made worse by the administration of sulphonamide derivatives—presumably through their bacteriostatic action preventing either synthesis of an essential anti-anaemic factor or digestion of the B_c conjugate—much greater quantities of vitamin B_c being required to relieve it. The effects of vitamin B_c now appear to be identical with those of synthetic pteroylglutamic acid.

Pfiffner *et al.* (1943) isolated crystalline chick anti-anaemic factors from liver and yeast; the yeast factor was different from the liver vitamin B_c in that the former did not promote growth of *L casei* or *Str. faecalis* until it had been digested with enzymes. Thus the yeast factor for chick anaemia was considered to be a vitamin-B_c conjugate which after digestion with a conjugase enzyme liberated the vitamin B_c identical with the liver vitamin B_c.

Briggs *et al.* (1943, 1944) also suggested that the so-called liver vitamins B_{10} and B_{11} were responsible for the feather formation and growth, respectively, of chicks—the macrocytic anaemia and leucopenia being cured simultaneously—while Campbell, Brown, and Emmett (1944) produced with a synthetic diet a hypochromic anaemia and leucopenia in chicks which could also be prevented by crystalline vitamin B_c. Later work has shown that synthetic pteroylglutamic acid plus β-pyracin will prevent or cure this deficiency anaemia in chicks better than either separately (Scott *et al.*, 1945, 1946).

Folic Acid and Experimental Leucopenia in Rats

From an entirely different angle it was found that agranulocytosis or leucopenia, aplastic or hypoplastic anaemia, and thrombocytopenia with hypoplasia of the bone marrow could be produced quite readily in rats by the addition to their diets of 1–2% of sulphasuxidine (succinyl-sulphathiazole), sulphaguanidine, or thiourea (Martin, 1942; Daft *et al.*, 1943, 1945; Ransome and Elvehjem, 1943).

Complete haematological remissions were obtained by the use of liver extracts, folic acid concentrates (Axelrod *et al.*, 1943), or synthetic pteroylglutamic acid (Daft and Sebrell, 1943; Endicott, Daft, and Ott, 1945; Petering *et al.*, 1947). Totter and Day (1943) also noticed that xanthopterin relieved the leucopenia in rats fed sulphasuxidine on purified diets, but they and others have since failed to confirm this (Axelrod *et al.*, 1943; Daft and Sebrell, 1943; Wright and Welch, 1943).

Vitamin M and Folic Acid in Monkeys

Wills and her colleagues (1932, 1935), while studying tropical macrocytic anaemia, showed that a macrocytic hyperchromic anaemia with leucopenia and granulocyto-

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penia could be produced in rhesus monkeys fed on a diet similar to that normally taken by many Indians. The features of this condition in the monkey may resemble human tropical macrocytic anaemia or the sprue syndrome (Darby *et al.*, 1945, 1946a, 1946b), including a macrocytic anaemia, a megaloblastic marrow hyperplasia, leucopenia with granulocytopenia, diarrhoea, sore tongue and mouth, and diminution in resistance to infection. Both conditions responded to yeast preparations, such as "marmite," and certain less-purified liver preparations. The unknown factor concerned in relieving this nutritional cytopenia (termed "vitamin M" by Day *et al.*, 1936; Langston *et al.*, 1938) was shown to be different from the anti-pernicious-anaemia liver factor (Wills, Clutterbuck, and Evans, 1937).

Later the good results following the use of yeast, liver, and folic acid on the leucopenia in the macaca monkey were reported by Wilson *et al.* (1942, 1946) and by Waisman and Elvehjem (1943), while it was claimed by Totter *et al.* (1943, 1944) that xanthopterin would relieve the anaemia and leucopenia for a short time, giving a subnormal reticulocytosis (4.5%) but no other permanent improvement.

More recently Day *et al.* (1945) have tried a highly purified *L. casei* factor (active for *Str. faecalis* after enzyme digestion) with complete success in the vitamin-M-deficiency nutritional cytopenia in monkeys. Since synthetic pteroylglutamic acid relieved the condition completely, with a sharp reticulocytosis, rapid improvement in haemoglobin and in the red-cell and white-cell counts, and relief of symptoms, they suggested that vitamin M was probably a vitamin B_c conjugate. Cooperman *et al.* (1945) noticed that fresh liver or lyophilized liver preparations were more active in the treatment of vitamin M deficiency in monkeys than ordinary dried liver powders, which lose some activity from the method of their preparation. They did not find any improvement in the monkeys when fed β-pyracin with folic acid, in contradistinction to their haemotological effects in chick anaemia.

Folic Acid in the Treatment of Pernicious Anaemia

The synthesis of a "folic acid" (pteroylglutamic acid) was soon followed by the early reports of Vilter *et al.* (1945), of Moore *et al.* (1945), and of Spies *et al.* (1945) on its use in the treatment of sprue and pernicious anaemia. Receiving early supplies of this synthetic pteroylglutamic acid for trial, Wilkinson, Israëls, and Fletcher (1946) presented their preliminary results of the treatment of five patients with pernicious anaemia with folic acid when given orally and parenterally. We extended our investigations, and up to date have had some 25 cases of pernicious anaemia under continuous folic-acid therapy for periods up to one and three-quarter years—so that we are able to assess its later effects

My first 20 patients all had the typical features of uncomplicated relapsing pernicious anaemia, and were chosen in conformity with the rigid criteria that I laid down some years ago and have often re-emphasized as being essential in testing the potencies of anti-pernicious-anaemia substances (Wilkinson, 1932)—namely, a patient with pernicious anaemia in relapse, with a megalocytic hyperchromic anaemia, megaloblastic marrow, achylia gastrica, no complications or marked cord involvement, and no effective anti-anaemic treatment to have been given previously.

A satisfactory response to treatment after the preliminary control period without treatment was judged by (1) a good reticulocyte response (inversely proportional to the initial red-cell count) within 5 to 10 days of beginning treatment; (2) transformation of the megaloblastic into a normoblastic marrow; (3) a sustained rise in red cells and haemoglobin with a return to normal levels; and (4) clinical remission of symptoms. The patients were kept on an ordinary hospital diet without liver, other glandular products, or eggs, while no medication was given apart from the "folic acid" under trial.

Pteroylglutamic acid was given (1) orally in the form of 5-mg. tablets as supplied by the manufacturer or (2) parenterally in aqueous solution, which was prepared by dissolving the pure folic acid powder in distilled water or saline with the addition of the minimal amount of disodium hydrogen phosphate or sodium bicarbonate and sterilizing by autoclaving at 10 lb. for 15 minutes or by passage through a Seitz filter. It is tasteless and offers no difficulty in administration, while intravenous or intramuscular injections did not cause any disturbances or ill effects at all. These patients were kept on pteroylglutamic acid only from the beginning, receiving no other therapy, with the exception of those developing subacute combined degeneration of the cord, who were later given liver or stomach extract

Results of Parenteral Therapy

The patients referred to in Table I received folic acid either intravenously or intramuscularly in doses varying from 15 mg. daily to 200 mg. in a single dose.

TABLE I.—*Parenteral Folic Acid in Pernicious Anaemia*

Case	Sex	R.B.C. × 10^6	Hb %	Reticulocytes Max. %	Folic Acid Dosage (mg.) and Duration (Days)
1	F	0·85 3·27 (24) 4·92 (328) 5·20 (468)	18 72 (24) 96 (328) 106 (468)	26 (7)	15 i.m. daily [4] 15 i.m. alternate days (6–12) 15 [456] orally
2	M	0·95 2·50 (24) 5·22 (60) 4·13 (549)	22 54 (24) 96 (60) 88 (549)	45·6 (7)	75 i.v. (1, 2) 15 i.m. (18–28) 1·25–20 orally [521]
3	M	1·42 2·62 (14) 3·19 (33) 4·71 (278)	36 64 (14) 86 (33) 108 (278)	33 (7)	200 i.v. (1) 10–30 mg. daily [260]
4	M	2·20 3·14 (14) 2·54 (34) 4·11 (78)	54 74 (14) 64 (34) 76 (78)	18 (8) 11 (23)	50 i.v. (1, 15 100 i.v. (24) 10 orally from (35)

( ) Day since beginning treatment. [ ] Number of days on treatment.

Case 1.—A married woman aged 63 had had intermittent treatment for pernicious anaemia since 1939. She was referred to my clinic in severe relapse—R.B.C., 1,260,000; Hb, 28%; C.I., 1.12; W.B.C., 4,200 (polymorphs 66.5%, lymphocytes 27%, large monocytes 4%, eosinophils 2.5%, basophils *nil*); anisocytosis and poikilocytosis marked; nucleated red cells *nil*, platelets scanty; pronounced megaloblastic marrow; achylia gastrica. After a preliminary control period (R.B.C., 850,000; Hb, 18%; C.I., 1.06; W.B.C., 4,300) she was given 15 mg. of synthetic pteroylglutamic acid intramuscularly daily for four doses, then a week later 15 mg. on alternate days for four doses.

With a prompt reticulocytosis (26% on seventh day), the sternal marrow became normoblastic, and on the 24th day she had R.B.C., 3,270,000; Hb, 72%; W.B.C., 7,200. After this the dose was gradually reduced from 10 mg. per day orally to 5 mg. on alternate days, on which she continued to July 15, 1947, when she complained of paraesthesia in the hands and fingers (R.B.C., 4,520,000; Hb, 94%); this increased in spite of larger doses of pteroylglutamic acid, and on Oct. 7 she had marked unsteadiness of gait, slight slurring of speech, loss of vibration sense in legs below knees, absent ankle-jerks, and loss of joint sense in the right foot; plantar reflexes were still flexor, knee-jerks brisk; Romberg's sign positive; muscle power poor in limbs; there was no muscular wasting. R.B.C., 5,200,000; Hb, 106%; W.B.C., 5,200. The folic acid was discontinued and she was given parenteral liver extract 2 ml. weekly and "pepsac" 1 oz. (28 g.) daily, with gradual improvement in the neurological condition over the following three months. On Jan 6, 1948, there were still some paraesthesiae

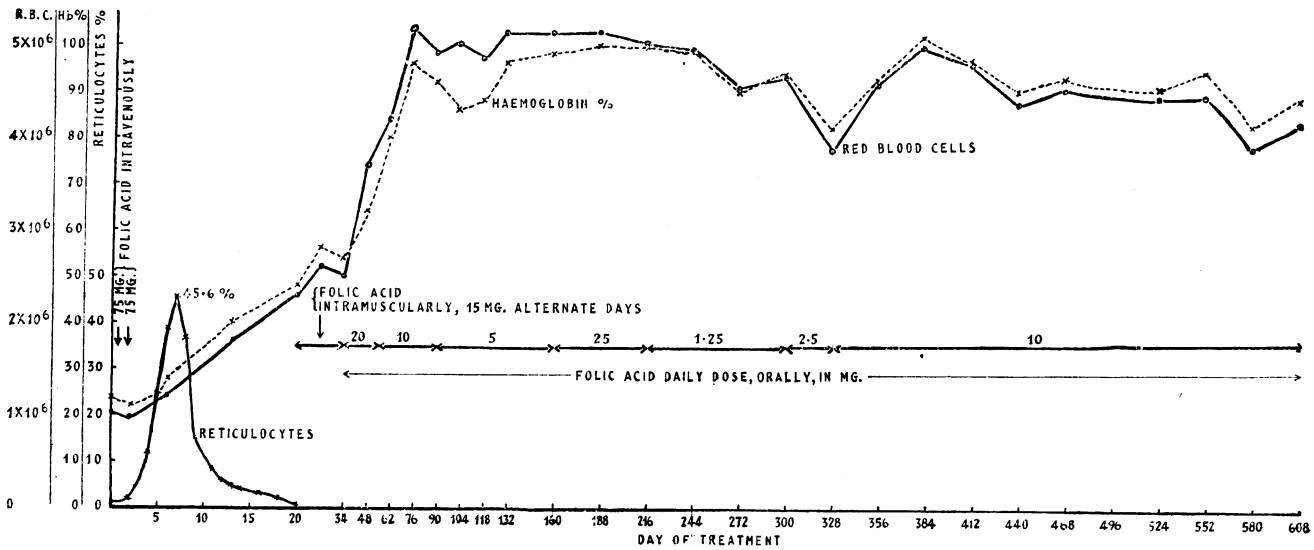

FIG. 1.—Case 2; male aged 58, treated with folic acid parenterally and then orally from 34th day. Preliminary control period omitted from chart. Note change of time scale at 34th day.

of hands and feet; ankle-jerks were negative, Romberg's sign was negative, vibration sense was absent in both legs, plantar reflexes were flexor; R.B.C. 5,320,000, Hb 104%.

Case 2.—A joiner aged 58 had had pernicious anaemia for 18 years, for which he had taken treatment very irregularly. He had relapsed and been referred to me with R.B.C., 1,210,000; Hb, 28%; C.I., 1.16; W.B.C., 2,900 (polymorphs 49%, lymphocytes 45%, monocytes 5%, eosinophils 1%; reticulocytes, 1%; typical megaloblastic marrow hyperplasia; achylia gastrica. He was given 75 mg. of pteroylglutamic acid intravenously on two successive days, the blood rising steadily from R.B.C., 950,000; Hb, 22%; reticulocytes, 1.2% (first day), with a reticulocytosis of 45.6% (seventh day), to R.B.C. 5,220,000 and Hb 96% on Aug. 23, 1946. (See Fig. 1.) On the eighth day the marrow showed a cellular normoblastic hyperplasia. Treatment was continued with 15 mg. intramuscularly on alternate days, and then 20 mg. orally daily. (See Table I and Fig. 1.) On Aug. 23 the dose was gradually reduced to 5 mg. twice weekly, and the blood count, which had remained fairly good until March 4, 1947, began to fall slowly until on April 30 it showed: R.B.C., 3,880,000; Hb, 92%; C.I., 1.05; W.B.C., 4,600; reticulocytes, 2.8% Treatment was then increased to 10 mg. daily, with a good improvement, so that on May 7 his count was: R.B.C., 4,610,000; Hb, 94%; C.I., 1.02; reticulocytes, 3.8%; platelets, 141,000; M.C.V. 84 c.μ, M.C.H.C. 34%, haematocrit 39%. He remained about this level, in good health, on 10 mg. of pteroylglutamic acid daily, and on Jan. 14, 1948, showed R.B.C., 4,130,000; Hb, 88%; C.I., 1.06; W.B.C., 5,800.

Results of Oral Therapy

In Table II are the main details of 17 patients with pernicious anaemia who were treated with pteroylglutamic acid orally in daily doses of 20 mg. initially, with reductions later to 1.25 to 10 mg. daily as the blood counts returned to normal. The following are illustrative cases.

Case 5.—A married woman aged 50 was admitted to hospital with typical features of pernicious anaemia, R.B.C., 950,000; Hb, 24%; C.I., 1.26; W.B.C., 4,400, very active megaloblastic hyperplasia of marrow, and achylia gastrica. She was treated with 20 mg. of synthetic pteroylglutamic acid orally daily, and improved rapidly with reticulocytosis (32.6%) and reversion to a very active normoblastic hyperplasia of marrow on the ninth day—R.B.C. 1,560,000 and Hb 36% on 11th day. (See Table II, Fig. 2.) The dose was reduced to 10 mg.; the blood count reached R.B.C. 3,570,000, Hb 78% (31st day), and then fell on a daily dose of 5 mg. to R.B.C. 3,110,000, Hb 74%. The pteroylglutamic acid was increased, and ultimately was 30 mg. daily before the count could be raised to R.B.C. 4,250,000, Hb 94% on Jan. 27, 1948. She was well clinically.

TABLE II.—*Folic Acid Orally in Pernicious Anaemia*

Case	Sex	R.B.C. × 10^6	Hb %	Reticulocytes Max. %	Folic Acid Dosage (mg.) and Duration (Days)
5	F	0·95 4·51 (57) 4·25 (589)	24 96 (57) 94 (589)	32·6 (9)	20 [18], 10 [38], 5–20 [266] 30 [253]
6	F	1·10 4·00 (82) 2·85 (208)	26 83 (82) 70 (208)	30·6 (10)	5–20 [208]
7	F	1·15 4·22 (68) 4·00 (300)	30 94 (68) 90 (300)	28·4 (8)	15 [17], 10 [22], 5 [28], 1·25 [182], 5 [42], 10 [217]
8	F	1·40 5·30 (115) 4·07 (507)	34 110 (115) 86 (507)	25·2 (7)	20 [17], 10 [56], 1·25–5 [414]
9	M	1·47 5·61 (99) 3·80 (224) 5·37 (476)	36 106 (99) 98 (224) 100 (476)	34·6 (8)	20 [9], 10 [48], 5 [14], 1·25–2·5 [259], 15 [146]
10	M	1·53 5·17 (53) 4·29 (151)	36 86 (53) 86 (151)	30·6 (8)	20 [45], 15 [42], 15 [64]
11	F	1·54 4·82 (201) 5·04 (411)	32 92 (201) 98 (411)	9·8 (7)	20 [36], 10 [164], 10 [210]
12	F	1·82 5·25 (252)	42 106 (252)	28·6 (7)	20 [210]
13	F	2·00 4·30 (34) 4·06 (272)	60 74 (34) 72 (272)	8·9 (9)	30 [20], 20 [63] 30 [189]
14	F	2·08 5·96 (90) 4·60 (377)	40 100 (90) 98 (377)	*13·4 (8)	10 [34], 2·5 [28] 1·25 [56], 2·5 [252]
15	M	2·15 4·35 (40) 4·66 (330)	56 96 (40) 100 (330)	9 (8)	20 [40], 15 [14], 10–20 [276]
16	F	2·45 3·96 (70)	54 58 (70)		20 [56]
17	F	2·46 4·35 (29) 3·81 (197)	80 112 (29) 100 (197)	*4·2 (6)	20 [14], 5 [14], 1·25–20 [168]
18	F	3·28 3·74 (28) 4·13 (63)	86 90 (28) 90 (63)		5 [28] (Liver extract 2 ml. weekly)
19	M	3·76 4·74 (61) 5·82 (117)	94 102 (61) 116 (117)	4·2 (7)	20 [32] Hog's stomach
20	F	3·30 4·12 (7)	90 94 (7)		20 [7]
21	F	3·56 5·30 (56)	96 110 (56)		15 [56]

* Maximum peak probably missed as out-patient.
( ) Day of treatment. [ ] Number of days on treatment.

Case 9.—A male garment-maker aged 47 collapsed at work and was admitted to hospital under my care with pernicious anaemia (R.B.C., 1,470,000; Hb, 36%; very active megaloblastic marrow hyperplasia; achylia gastrica). He was given 20 mg. of pteroylglutamic acid per day orally, and responded very well clinically, with reticulocytosis (34.6% on the eighth day) and an active normoblastic marrow (tenth day); on the 23rd day he had R.B.C. 3,720,000 and Hb 88%. (See Table II.) His treatment was reduced gradually to 5 mg. twice weekly, producing on Sept. 16, 1946, R.B.C., 5,610,000; Hb, 106%; C.I., 0.94; W.B.C., 6,200. Thereafter he gradually fell to R.B.C., 3,800,000; Hb, 98%; C.I., 1.2 on May 6, 1947, and the treatment was increased to 15 mg. daily with improvement in the blood count which has remained at Jan. 12, 1948 (now on 10 mg. daily), R.B.C., 5,370,000; Hb, 100%. Clinically he is very well indeed.

Immediate Results of Treatment

From the results summarized in Tables I and II the following points may be noted:

Rapid haematological responses followed the intravenous or intramuscular administration of pteroylglutamic acid from 15 mg., intramuscularly, to 200 mg. in a single dose, as has been observed with liver extracts when given by the same routes. A daily dosage of 20 mg., orally, was quite adequate to initiate good reticulocytosis and clinical remission in most cases, although the reticulocyte peaks were rather lower than would have been obtained with an active liver or stomach preparation. There was not a striking difference between the rates and the heights of the reticulocyte responses whether the oral or the parenteral route of administration was employed; nor was there more than a very slightly greater rate of red blood cell and haemoglobin formation after parenteral pteroylglutamic acid.

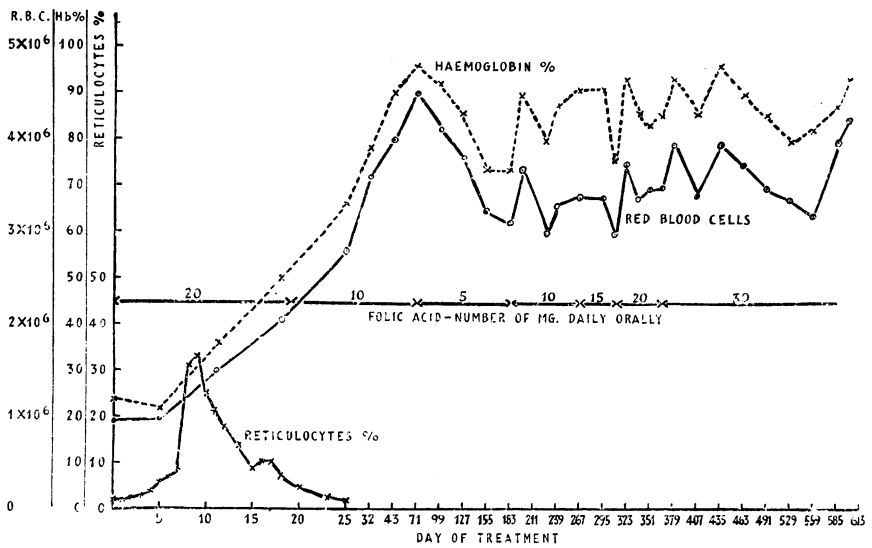

FIG. 2.—Case 5; female aged 50. Preliminary control period omitted from chart. Note change of scale from 25th day.

Not all the patients showed full reticulocytosis in keeping with the initial red cell counts: thus, Case 11 gave only 9.8% (expected 18–26%) on the 7th day, with initial red cell count of 1,540,000; Case 13, 8.9% (expected 14–19%) on the 9th day, with red cell count of 2,000,000; and Case 15, 9% (expected 10–18%) on the 8th day, with initial red cell count of 2,150,000, although subsequently there were satisfactory clinical and haematological improvements.

With the rise of the haemoglobin and red cell counts to normal limits it was often possible to reduce the doses of pteroylglutamic acid to 2.5–5 mg. daily for a time. Eventually, however, with most of the patients the daily maintenance dose had to be increased to 10–20 mg. again after varying periods of time on these smaller doses, since the red cell count and haemoglobin percentage tended to fall slowly—e.g., Cases 5, 6, 8, 9, and 16. (See Fig. 2.)

Macrocytosis still persisted in many patients even when the haemoglobin and red cell count were within normal limits. The white blood cells and platelets showed the expected improvements usually seen after liver or stomach therapy, but not more quickly or effectively.

In all these cases the original megaloblastic sternal bone marrows were rapidly converted to normoblastic ones, and these were always complete before the maximal reticulocyte peaks were reached. This result is in keeping with the observations of Levy (1947) and others, who did serial sternal punctures after giving a single oral dose of 50 mg. of pteroylglutamic acid to one case, and resembles the effects of liver extracts under similar conditions.

The *clinical symptoms* in this group showed rapid improvement in most cases, very much in the same way and at about the same speed as noted after standard liver extracts or hog's stomach therapy (Wilkinson, 1931a, 1931b). Occasional patients—e.g., Cases 12, 15, and 17—however, showed slower responses to pteroylglutamic acid in these doses. The patient usually begins to feel better even before the maximum reticulocyte peak is reached, and this is followed by a rapid improvement in general symptoms; flatulent dyspepsia and diarrhoea clear up, soreness of the tongue disappears, and there is a very rapid improvement in the dyspnoea, palpitation, and lack of energy, the appetite returns, and the whole outlook of the patient becomes more cheerful and normal. Splenomegaly regresses normally as with ordinary standard treatment, but, as would be expected, the achylia gastrica persists. On the other hand I have not seen any improvement in the peripheral neuritis, paraesthesiae, or the more marked symptoms or signs of spinal cord involvement (see below).

Summarizing, the *immediate* effects of treatment with adequate doses of synthetic pteroylglutamic acid, whether administered orally or parenterally, to severe cases of pernicious anaemia were very good, the results being almost but not quite as effective as a potent liver extract or preparation of hog's stomach—there was a sharp reticulocytosis at about the 7th to 9th day, a good increase in red blood cells, haemoglobin percentage, and white cells, and conversion of the megaloblastic to normoblastic marrow, but macrocytosis tended to persist; complete relief of all the clinical symptoms and signs of pernicious anaemia was noted, except those associated with the central nervous system (subacute combined degeneration of the cord and peripheral neuritis). A few patients did show a slightly delayed response even though the reticulocytosis was good. No toxic effects due to the synthetic pteroylglutamic acid, however administered, have been noted in the doses employed.

Later Results of Pteroylglutamic Acid Therapy

Of greater importance are the later effects of continued pteroylglutamic acid therapy. So far, after nearly two years, I have the following additional observations to make. (See Tables I and II.)

No ill effects or reactions due to pteroylglutamic acid itself have followed its continued oral or parenteral use in doses varying from 2.5 to 200 mg. Total dosages in some cases have now reached 10 g. Many of my patients have remained well on doses varying between 2.5 mg. weekly and 20 mg. daily; however, with some it has often been necessary to increase the dose owing to a very definite tendency for the red cells and haemoglobin percentage to fall again in the subsequent months, but in some cases this may probably be due to too small a maintenance dose, which is ordinarily between 5 and 15 mg. daily. A few patients have been slow in regaining normal red cell counts and haemoglobin percentages. Although the red cell counts and haemoglobin percentages were within the normal

ranges, macrocytosis still tended to persist in many patients, the mean corpuscular volume, mean corpuscular haemoglobin concentration, and haematocrit percentage often being outside the normal range. (See Table III.)

TABLE III

Case	Sex	R.B.C.	Hb %	Haematocrit % (M 40–54; F 37–47)	M.C.V. c.μ (82–92)	M.C.H.C. % (32–36)
2	M	4·61	94	39	84	34
9	M	4·92	102	45	90	32
10	M	4·94	104	45	99	28
14	M	4·48	92	42	116	31
1	F	4·62	96	43	94	31
7	F	4·08	90	42	103	32
11	F	4·82	92	45	92	29
13	F	4·19	98	45	107	32
16	F	4·09	108	51	126	29
19	F	4·12	94	42	102	31

Other observers have reported the marked beneficial effects of pteroylglutamic acid on pernicious anaemia (Amill and Wright, 1946; Davidson and Girdwood, 1946; Frommeyer *et al.*, 1946; Goldsmith, 1946; Harrison and White, 1946; Vilter *et al.*, 1947; Wilkinson, Israëls, and Fletcher, 1946); but Kaufmann and Schwager (1946), Meyer (1947), and Vilter *et al.* (1947) do not think that pteroylglutamic acid is as good as a potent liver extract in these patients, and over the longer periods of observation I am inclined to agree, for we have long known that both liver extracts and hog's stomach do produce and maintain complete remissions in pernicious anaemia with an entire return to the normal clinical and haematological state (Wilkinson, 1931a, 1931b).

Subacute Combined Degeneration of the Spinal Cord and Peripheral Neuritis

Perhaps the most important considerations in pteroylglutamic acid therapy are those concerning the neurological system, and the results are disquieting. Eight of my 20 patients had signs and symptoms of central nervous system involvement: one (Case 10) had the symptoms before the beginning of pteroylglutamic acid treatment, which did not lead to any improvement in them; three (Cases 1, 17, and 19) showed definite deterioration in their neurological conditions; while four (Cases 4, 8, 15, and 16), originally free from any neurological involvement, developed within two months acute symptoms and signs of subacute combined degeneration of the cord after receiving pteroylglutamic acid therapy—with peripheral polyneuritis, loss of vibration sense in the lower legs, extensor plantar responses, and poor or absent knee-jerks and ankle-jerks in both legs; nevertheless the haematological conditions improved considerably.

None of these patients showed any improvement on greatly increased doses of pteroylglutamic acid, but some improvement is to be observed since the institution of parenteral liver extracts or desiccated hog's stomach orally (Wilkinson, 1933).

This is a most important point to bear in mind when using "folic acid" preparations, since the development of cord changes is difficult to reverse by any form of therapy, and one of the prime points in the treatment of pernicious anaemia is to give sufficient potent anti-anaemic therapy to prevent the development or progression of neurological symptoms.

These observations parallel those of Spies and Stone (1947) and Vilter *et al.* (1947), who found that during the pteroylglutamic acid treatment of 21 patients with pernicious anaemia four developed neurological signs, while of nine patients with subacute combined degeneration of the cord seven got worse on folic acid. Further, Heinle and Welch (1947) observed, as I have, an acute onset of subacute combined degeneration of the cord in one patient with pernicious anaemia under treatment with pteroylglutamic acid (making a total of three out of their 27 cases). Similar cases are reported by Ross, Belding, and Paegel (1948), Bethell *et al.* (1946), Hall *et al.* (1946, 1947), Davidson and Girdwood (1947), and Heinle *et al.* (1947), who also noted the failure of pteroylglutamic acid to relieve or prevent neurological changes. On the other hand, Doan (1946) and Goldsmith (1946) claimed that the neurological symptoms were relieved by pteroylglutamic acid.

In view of the general experience it is very clear that patients with pernicious anaemia must still have full treatment with potent liver extracts or hog's stomach whether pteroylglutamic acid is given or not. The latter may have a place in initial therapy where quick results are needed, for those sensitive to liver extracts, and perhaps for ill-nourished patients, although highly potent liver extracts are quite adequate. I am fully of the opinion that pteroylglutamic acid is neither the best nor the cheapest form of treatment for pernicious anaemia and must not be given alone to patients with neurological symptoms.

Refractory Macrocytic Anaemias

From time to time cases of macrocytic anaemia are seen with blood pictures resembling pernicious anaemia but usually having normoblastic marrows, although refractory megaloblastic anaemias are also seen. They may have normal gastric acidities or achlorhydria gastrica, and are refractory to ordinary anti-anaemic treatment. Some are said to respond to treatment with proteolysed liver extracts, while others certainly do not.

Four such refractory cases were treated in my clinic with pteroylglutamic acid (three orally, one intravenously) without the slightest haematological or clinical improvement. They all had normoblastic marrows, two had achlorhydria, one a normal gastric acidity, and one hyperacidity. (See Table IV.) None of these patients had any obvious or

TABLE IV.—*Refractory Macrocytic Anaemias*

Case	Sex	Gastric Acidity	R.B.C. Initial	Hb % Initial	W.B.C. Initial	Folic Acid Dosage
W. G.	M	Normal	2·10 2·32 (28)	64 64 (28)	3,200 1,600 (28)	20 mg. orally [28]
R. B.	M	Hyperacidity	1·06	24	3,400	100 mg. i.v.
M. S.	F	Achlorhydria	0·99 (14) 1·72 (1) 1·50 (15) 2·05 (1)	24 (14) 34 (1) 30 (15) 50 (1)	3,600 (14) 3,200 (1) 2,600 (15) 4,200 (1)	20 mg. orally [14] 10 [14], 20 [63]
A. M.	F	,,	2·28 (91) 2·72 2·84 (14) 3·60 (70)	48 (91) 56 62 (14) 64 (70)	3,200 (91) 6,200 8,000 (14)	40 [14] 20 mg. orally [14] Proteolysed liver [56]

All four patients had normoblastic marrows.

detectable nutritional deficiencies and were on perfectly adequate dietary intakes. They do not correspond to the nutritional macrocytic anaemias so commonly quoted in the American literature by Spies and others, in which there were marked nutritional deficiencies.

Davidson and Girdwood (1946, 1947) have noted some response in liver-refractory anaemias, but the blood remained macrocytic until further liver therapy was given, while Watson *et al.* (1945) did not observe any improvement in similar refractory cases after 5 mg. of a folic acid concentrate daily for six days.

Achrestic Anaemia

This is a primary hyperchromic megalocytic anaemia characterized by a megaloblastic hyperplasia of the marrow (identical with that of pernicious anaemia), free hydrochloric acid in the gastric secretion, little or no disturbance of the gastro-intestinal tract, no neurological symptoms or signs, no pyrexia, and no evidence of haemolysis; the

general anatomy resembles pernicious anaemia, and there is a failure in varying degree to respond to specific anti-pernicious-anaemia therapy, the course being sometimes prolonged with the help of blood transfusions (Wilkinson and Israëls, 1935, 1936).

The following is the report of a patient with achrestic anaemia under the care of Dr. Stock.

A housewife aged 26 complained of weakness, lack of energy, dyspnoea, palpitation, and increasing pallor. There were no gastro-intestinal symptoms, glossitis, or involvement of the central nervous system or peripheral nerves. No haemolysis was to be found. Gastric secretion contained normal amounts of hydrochloric acid. Sternal puncture on May 7, 1947, showed an active cellular marrow with 42.5% megaloblasts, while a few days later it contained 8% megaloblasts and 34% normoblasts and was still very active and cellular. A blood count on April 21 showed : R.B.C., 900,000 ; Hb, 25% ; W.B.C., 5,000 ; reticulocytes, 1.6% ; M.C.V., 128 c.μ ; M.C.H.C., 31.3%. On April 30 it was : R.B.C., 1,200,000 ; Hb, 23% ; W.B.C., 3,800 ; platelets, 93,600. She was given synthetic pteroylglutamic acid, 20 mg. per day orally, and a reticulocyte peak of 27.4% was obtained on the 8th day. The bone marrow still showed 8% megaloblasts on the 10th day, and on May 9 the R.B.C. was 1,800,000 ; Hb, 45% ; platelets, 206,000 ; and reticulocytes, 15.2%. The haematological and clinical conditions continued to improve, and on June 4 her blood count was R.B.C., 3,600,000 ; Hb, 75% ; C.I., 1.04 ; W.B.C., 10,000. At this stage she was given liver extract instead of folic acid, and on Dec. 17 reached R.B.C., 4,500,000 ; Hb, 95% ; C.I., 1.05 ; W.B.C., 8,600.

(The conclusion of these lectures, with a list of references, will appear in our next issue.)

ACUTE INTUSSUSCEPTION IN CHILDHOOD

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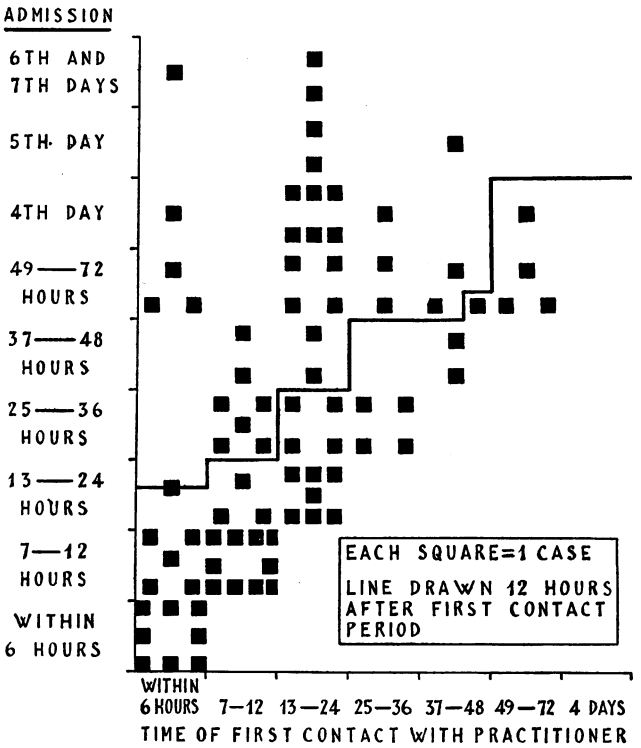
The detailed study of 100 children treated for acute intussusception in this department from 1944 to 1946 has revealed certain facts which we believe will help the family doctor as well as those responsible for treatment. In the past thirty years the reported mortality has fallen from nearly 40% to less than 10%, yet while the figure for children treated in the first 24 hours is below 5% it rises steeply to 20% or more when the disease remains untreated for more than two days.

Time is an important and often a vital element in all disease, and we have paid special attention to the exact duration of the illness and the times when the different symptoms and signs made their appearance, when the doctor was called, and when the child reached hospital.

Of the 100 cases there were 83 in which accurate time-intervals were known, and of these 66 (80%) were seen by the doctor within the first 24 hours, but only 34 (41%) were admitted to hospital within that period. (See Graph.) Of the 80 seen within 48 hours only 53 had reached hospital by the end of the second day, while the admission of the remainder was not completed until the seventh day. This delay is culpable in view of the increasing mortality after the second day. It suggests that the problem of acute intussusception, in this area at least, is primarily not concerned with improving methods of treatment but rather with the ability to suspect this disease in the first 24 hours and ensure prompt admission to hospital.

The accepted description in British textbooks is so dramatic that the failure of the family doctor to recognize it in many cases is unexpected. Further, even the passage of blood from the bowel does not invariably bring the disease to mind ; for of those who passed blood and were seen by the doctor 41 (79%) were admitted within 12 hours and 11 (21%) were not admitted within 12 hours of the event. Of the latter, 6 were not admitted for 48 hours or over. This



Graph showing the relation between contact with the family doctor and admission to hospital in 83 cases.

failure to recognize acute intussusception in its early stages suggests that the traditional description may need modification in the light of local experience.

When faced with a child who may have intussusception the first and most important step is to take a detailed history of the illness from the mother or from someone who has been with the child all the time. This is so essential for diagnosis in an early case, and so valuable in assessing the need for resuscitation and operation in many of the later cases, that we have always considered it worth while to send for the mother if she was not with the child even though many of our patients live up to 50 miles from the hospital.

At the beginning the physical signs alone may not be sufficient to indicate the need for admission to hospital. The diagnosis should not be delayed until the discovery of an abdominal tumour, as its detection may require a level of experience which comes only from frequent and regular contact with the disease in a large hospital.

The description of the disease is similar in most British textbooks. A healthy, well-nourished male child, with no history of recent illness, at 9 months or shortly after weaning is seized by violent abdominal pain, with pallor and collapse. The pain recurs at intervals of about half an hour and the spasms last from a few seconds to a few minutes, the child drawing its knees up and rolling about. Vomiting may occur, although it is not a prominent symptom. Apart from an initial stool, constipation is the rule, though after a variable unspecified interval dark-red blood resembling red-currant jelly is passed per rectum, and the diagnosis then becomes apparent.