FOLIC ACID AS A THERAPEUTIC AGENT

BY

L. S. P. DAVIDSON, B.A., M.D., F.R.C.P.Ed.&Lond., F.R.S.Ed.

Professor of Medicine, University of Edinburgh

AND

R. H. GIRDWOOD, M.B., F.R.C.P.Ed., M.R.C.P.Lond.

Lecturer in Medicine, University of Edinburgh

It has been amply demonstrated in animal experiments by numerous workers that a deficiency of folic acid, however induced, has a profound depressing effect on the production of red cells, white cells, and platelets. The clinical application of this work was immediately recognized by physicians, but therapeutic trials were unsatisfactory until preparations of folic acid derived from natural products of vegetable and animal origin were replaced by *Lactobacillus casei* factor synthesized by Angier *et al.* (1945). Reports of the therapeutic value of this substance in certain types of anaemia and intestinal syndromes have been published in America (Berry and Spies, 1946; Zuelzer and Ogden, 1946; Lopez, Spies, *et al.*, 1946; Doan, 1946) and in Great Britain (Wilkinson, Israëls, and Fletcher, 1946; Davidson and Girdwood, 1946). By courtesy of Messrs. Lederle, Inc., we have been supplied with sufficient synthetic folic acid to treat 48 patients suffering from a variety of disorders of the blood and alimentary tract. This paper comprises a report on the therapeutic results obtained, a discussion of the mechanism underlying the action of folic acid, and a comparison of our findings with those recorded by other workers. The haemoglobinometer used in this investigation gave a reading of 100% = 13.8 g. per 100 ml.

Pernicious Anaemia

Sixteen cases have been treated with folic acid given in various amounts and by different routes of administration. Representative cases are shown in Table I. An effective

haemopoietic response was obtained from the daily oral administration of folic acid in doses of 2.5 mg. in four cases, 5 mg. in two cases, 10 mg. in three cases, and 20 mg. in one case. It is clear that folic acid alone in a dosage of 5 mg. daily can restore the blood level quantitatively and qualitatively to normal (see Case 3). Folic acid in a daily dose of 1 mg. by mouth was given to two patients. In one no change in the blood level occurred, whereas in the other there was an excellent haemopoietic response as shown in Table I (Case 6). In a third case no response was obtained from the daily intravenous administration of 1 mg. for 14 days. A marked fall in the blood level occurred, necessitating a blood transfusion. A subsequent response to 5 mg. of folic acid intravenously resulted.

200 mg. of folic acid intramuscularly and 400 mg. orally in a single dose given to two cases of pernicious anaemia produced no unpleasant side-effects, and there were excellent initial haemopoietic responses, which, however, lasted only for 14 days. Large single doses appear to be a wasteful method of administration, since the same quantity of folic acid given in 5- or 10-mg. doses daily produces a much greater total rise in the red cell count.

Sensitivity to Liver Extract.—Case 1 was sensitive to parenteral liver therapy, as indicated by severe local and general reactions. But no such reactions occurred when synthetic folic acid was given orally, intracutaneously, or intramuscularly to this case and to three others of our cases of pernicious anaemia sensitive to parenteral liver therapy.

Failure to Respond to Folic Acid.—Case 7 was the only one which failed to respond to folic acid, although it was typical of pernicious anaemia in every respect. The patient's erythrocytes reached a level of 5,660,000 per c.mm. on subsequent treatment with "anahaemin." Other points of particular interest in this case were:

1. That severe agranulocytosis developed during treatment with folic acid, the white cell count falling to 800 per c.mm. and the temperature rising to 105° F. (40.6° C.) accompanied by marked prostration.

2. The febrile reaction responded to penicillin therapy and the white cell count started to rise after 48 hours' treatment with 150 mg. of pyridoxine daily by mouth, reaching a peak of 9,000 per c.mm. after 8 days' treatment. Three days after cessation of treatment with pyridoxine the patient developed multiple peripheral neuritis which progressed to a complete paralysis of all four limbs with total loss of reflexes. Eventually she made an excellent recovery. The cause of the peripheral neuritis remains obscure. The

TABLE I.—*Pernicious Anaemia treated with Folic Acid*

Case	Age	Sex	Day	Hb%	R.B.C. (Mills.)	Reticulocyte %		Folic Acid	
						Peak	Day	Daily Dosage	Days
1 {	72	M	1	38	1.25	40.0	9	20 mg. orally	1-20
			21	72	3.31				
			42	80	3.78				
2 {	37	M	1	52	2.05	10.0	10	10 mg. "	1-20
			20	80	2.92				
			70	100	4.19				
3 {	53	M	1	36	1.27	9.0	8	5 mg. "	1-81
			81	104	4.85				
4 {	64	M	1	36	1.20	28.9	8	2.5 mg. "	1-39
			39	90	4.05				
5 {	46	M	1	46	1.55	2.0	8	1 mg. "	1-12
			14	42	1.56				
6 {	68	F	1	30	1.30	25.2	13	1 mg. "	1-37
			37	86	3.57				
7 {	49	F	1	36	1.50	7.2	24	5 mg. "	2-15
			25	33	1.45				

possibility that the metabolic effect of vitamin B₁ was antagonized by the preceding administration of folic acid and pyridoxine, both members of the vitamin B₂ group, was considered, but was rejected in favour of a diagnosis of infective polyneuritis. No satisfactory explanation of the failure of Case 7 to respond to adequate amounts of folic acid is available unless it be postulated that the virus causing the infective polyneuritis inhibited the expected therapeutic response and was also responsible for the development of the agranulocytosis.

Subacute Combined Degeneration of the Cord

Three patients suffering from subacute combined degeneration of the cord were treated with folic acid. In two of these cases no subjective or objective improvement resulted, while in the third case the neurological features deteriorated rapidly coincidentally with a marked improvement in the blood level. The features of this case were as follows:

The patient was a woman aged 30. Her haematological findings were: Hb, 36%; red cells, 1,500,000 per c.mm.; C.I., 1.2. The bone marrow was megaloblastic, and gastric analysis showed a histamine-fast achlorhydria. She gave a history of weakness of several years' duration. For four weeks she had noticed that she was unsteady on her legs, and she had suffered from paraesthesia of the arms. The neurological abnormalities on admission were as follows: Generalized muscular weakness in the legs without any wasting; loss of vibration sense below the level of both knees with loss of position sense; dorsiflexor plantar reflex on the left side with a doubtful reflex on the right side. Both ankle-jerks were absent, and the knee-jerks were impaired. There was ataxia of both legs. During folic acid therapy the patient became completely incapacitated. Both plantar reflexes became dorsiflexor; the incoordination became extreme, and the knee-jerks could not be elicited. Marked improvement in the symptoms and signs referable to the central nervous system resulted from intensive parenteral treatment with anahaemin. The significance of these observations is discussed later.

Refractory Megaloblastic Anaemia

We have previously reported the response of three cases of refractory megaloblastic anaemia to folic acid (Davidson and Girdwood, 1946). Further information is now available about the subsequent course of two of them. Case 8 in our previous report, which had been completely refractory to large doses of anahaemin, showed an initial response to folic acid therapy followed by a further improvement on proteolysed liver, the blood count reaching 50% Hb and 2,780,000 red cells per c.mm. During the next six months he had three courses of folic acid at intervals, which resulted in a slow but steady rise in the red cell count to 4,990,000 per c.mm.

In Case 9 in our previous report the Hb rose to 96% and the erythrocytes to 4,150,000 per c.mm. on folic acid. The macrocytic blood picture, however, persisted. His blood count was restored to complete normality with proteolysed liver ("hepamino"). Two further cases of refractory anaemia are now reported. The blood findings and treatment of one of these are shown in the accompanying graph. The patient was a woman aged 63. She had complained of progressive weakness over a period of two years. A year before admission she developed symptoms of angina pectoris on exertion. She had had loose motions for two years. The stools were watery but never large, bulky, or greasy in appearance. Sometimes her tongue was very sore. On examination she was pale with a yellowish tinge in the skin; the tongue was clean, shiny, and atrophic; no abnormality was found in the central nervous system; she was passing from 2 to 5 stools a day. A fat balance test which was carried out according to the method of

Cooke, Elkes, *et al.* (1946) showed 31.4% total fat and 89.7% absorption. There was therefore no definite evidence of poor absorption of fat. Free hydrochloric acid was present in the test meal after histamine, and the marrow was megaloblastic.

A study of the graph shows that the patient was refractory to parenteral liver therapy, as there was no alteration in the blood level or in the megaloblastic character of the bone marrow despite the fact that after each injection of liver extract an increase of reticulocytes occurred. Folic

Graph of a case of refractory megaloblastic anaemia treated with 20 mg. of folic acid orally per day.

acid produced a third rise in reticulocytes and a gain of 2,330,000 red cells per c.mm. and 40% Hb in 51 days. Since the blood picture still remained slightly macrocytic (C.I., 1.12) and the blood level subnormal after 51 days' treatment with folic acid the haemopoietic response cannot be assessed as entirely satisfactory.

The second case was that of a woman aged 70 whose blood picture and clinical findings were typical of Addisonian pernicious anaemia. She had received parenteral liver therapy for months, including six injections of anahaemin in the six weeks before admission, but her bone marrow was still megaloblastic. After admission she was given a single injection of 4 ml. of anahaemin. This produced a reticulocyte crisis of 14.2% and a slight rise in the blood level, but the bone marrow remained megaloblastic. The haemoglobin was now 44% and the red cell count 1,930,000 per c.mm. Folic acid in a dosage of 2.5 mg. daily by mouth produced a second reticulocyte crisis and a gain of 1,300,000 red cells and 34% haemoglobin in 30 days. The bone marrow was changed to the normoblastic state.

Aplastic and Hypoplastic Anaemia, Leucopenia, and Thrombocytopenia

The results of treatment in aplastic anaemia, leucopenia, and thrombocytopenia are given in Tables II, III, and IV respectively. It will be noted that no therapeutic benefit ensued either in the cases whose causation could not be determined (i.e., idiopathic) or in those arising secondary to some recognizable cause (i.e., symptomatic).

The Sprue Syndrome

Ten cases of the sprue syndrome have been treated with folic acid. They comprise four cases of tropical sprue, three cases of idiopathic steatorrhoea, and three cases of coeliac disease. The character of the anaemia present and the effect of treatment with folic acid, together with details

of the case histories, clinical features, and fat-balance tests before and after treatment, have been recently recorded (Davidson, Girdwood, and Innes, 1947). Accordingly it is only necessary to give a short summary of the results obtained.

TABLE II.—*Aplastic and Hypoplastic Anaemia treated with Folic Acid*

Case	Age	Sex	Diagnosis	Folic Acid (Oral)		Hb%		R.B.C. (Mills.)	
				Dosage	Days	Before	After	Before	After
16	75	F	Idiopathic hypoplastic anaemia	20 mg.	1-21	78	54	3.50	2.97
19	65	M	Idiopathic aplastic anaemia	10 mg.	22-28				
24	14	F	Idiopathic aplastic anaemia	20 mg.	1-8	46	40	2.0	1.63
				20 mg.	1-17	40	38	1.96	2.02
				(2 pints blood on 5th day)					
18	68	M	Hypoplastic anaemia (after sulphonamides)	20 mg.	1-15	50	56	2.07	2.06
17	42	M	Aplastic anaemia (following x-ray therapy for reticulosis)	20 mg.	1-14	64	44	3.11	3.24
				(1 pint blood on 3rd day)					

TABLE III.—*Leucopenia treated with Folic Acid*

Case	Age	Sex	Diagnosis	Folic Acid (Oral)		White Cell Count	
				Daily Dosage	Days	Before	After
7	49	F	Idiopathic agranulocytosis ..	5 mg.	2-15	2,000	800
16	75	F	Idiopathic hypoplastic anaemia	20 mg.	16-25		
				20 mg.	1-21	3,400	3,000
				10 mg.	22-28		
19	65	M	Idiopathic aplastic anaemia ..	20 mg.	1-8	1,600	1,400
24	14	F	Idiopathic aplastic anaemia ..	20 mg.	1-17	2,800	2,400
18	68	M	Hypoplastic anaemia (after sulphonamides)	20 mg.	1-15	1,900	1,400
17	42	M	Aplastic anaemia following x-ray therapy. (Reticulosis)	20 mg.	1-14	2,000	2,000
20	52	M	Leucopenia following x-ray therapy. (Reticulosis)	20 mg.	1-11	2,800	2,200
21	25	F	Leucopenia following x-ray therapy. (Cerebral tumour)	20 mg.	1-13	3,200	2,200
43	38	M	Leucopenia following x-ray therapy. (Spondylitis ankylopoietica)	20 mg.	1-14	2,000	3,100

TABLE IV.—*Thrombocytopenia treated with Folic Acid*

Case	Age	Sex	Diagnosis	Folic Acid (Oral)		Platelets per c.mm.	
				Dosage	Days	Before	After
22	25	F	Idiopathic thrombocytopenic purpura	20 mg.	1-14	40,000	30,000
23	14	F	Idiopathic thrombocytopenic purpura	20 mg.	1-10	20,000	10,000
19	65	M	Idiopathic aplastic anaemia ..	20 mg.	1-8	60,000	35,000
24	14	F	Idiopathic aplastic anaemia ..	20 mg.	1-17	20,000	10,000
18	68	M	Hypoplastic anaemia (after sulphonamides)	20 mg.	1-15	115,000	95,000
17	42	M	Aplastic anaemia following x-ray therapy. (Reticulosis)	20 mg.	1-14	75,000	25,000
20	52	M	Leucopenia following x-ray therapy. (Reticulosis)	20 mg.	1-11	95,000	75,000
21	25	F	Leucopenia following x-ray therapy. (Cerebral tumour)	20 mg.	1-13	190,000	105,000
43	38	M	Leucopenia following x-ray therapy. (Spondylitis ankylopoietica)	20 mg.	1-14	85,000	83,000

1. Haematological Response.—This was considered to be unsatisfactory in nine out of ten cases, since treatment either produced no significant rise in the red cell count or failed to restore the blood level and haematological picture to normality.

2. Fat absorption as estimated by the fat-balance test of Cooke, Elkes, *et al.* (1946) was unaltered in five out of six cases.

3. Dramatic control of the diarrhoea and rapid clinical improvement occurred in the cases of tropical sprue and idiopathic steatorrhoea. In contrast no beneficial effects were noted in the cases of coeliac disease.

We should like to draw attention to one particular point which, so far as we are aware, has not been presented

before—namely, that a most remarkable alteration in intestinal function occurs on or about the fifth day of treatment with folic acid, at a time when no alteration of the blood level or even a rise in the reticulocyte count may have resulted. Moreover, this dramatic clinical change may occur in patients who subsequently show a complete or partial failure in their haematological response to continued folic acid therapy. This finding suggests that folic acid has at least two entirely separate actions—the control of the normal functioning of the haemopoietic and of the alimentary system. Since there may be a coincidental deficiency of other factors that are undoubtedly required for the normal functioning of these systems in addition to folic acid it is understandable why the correction of one deficiency may not result in the expected improvement. Only on such a basis is it possible to explain the findings discussed above and the failure of folic acid alone to restore the blood picture qualitatively and quantitatively to normal in certain patients suffering from the sprue syndrome and from idiopathic refractory megaloblastic anaemia.

Idiopathic Ulcerative Colitis

In view of the remarkable effects claimed by Carruthers (1946) in five cases of severe diarrhoea of unknown aetiology treated with folic acid for a few days we decided to assess its value in idiopathic ulcerative colitis. Five cases were accordingly selected for treatment because of their prolonged history and typical stool and sigmoidoscopic findings. After a carefully controlled observational period folic acid was given in doses up to 60 mg. daily for periods varying from six to eleven days. Neither the clinical state of the patients nor the sigmoidoscopic appearances of their bowel were significantly altered. In fact, two of the cases were definitely worse at the end of treatment.

Discussion

The investigations reported above are in general agreement with those of other workers in this field—namely, that a haematological response to folic acid will be obtained only in patients suffering from a megaloblastic form of anaemia. When leucopenia and thrombocytopenia are part of a nutritional syndrome resulting from a deficiency of folic acid an increase of leucocytes and thrombocytes will result from folic acid therapy. When anaemia is of the normoblastic type, or when leucopenia or thrombocytopenia develops from causes other than a specific nutritional deficiency, folic acid will be found to be ineffective as a therapeutic agent.

Evidence recently accumulated by Welch *et al.* (1946) and by Bethell *et al.* (1947) helps to throw light on these clinical findings and affords a basis for explaining the mechanism by which folic acid functions. There now appears to be little doubt that free folic acid (pteroyl-glutamic acid) is the factor which is essential for the continuation of normoblastic blood formation, and a deficiency causes a reversion of the bone marrow to the megaloblastic state.

Free folic acid is liberated in the body from its conjugated form, which is present in various foodstuffs. A deficiency of free folic acid may arise in various ways—e.g. a failure in intake of conjugated folic acid (nutritional macrocytic anaemia), a failure in absorption of conjugated folic acid (sprue syndrome), or a failure in the liberation of free folic acid from its conjugate form (Addisonian pernicious anaemia). In this last disease it should be noted that the haemopoietic response to folic acid and purified liver extracts given parenterally is identical, although such extracts contain only minute traces of folic acid. This apparently anomalous finding can be explained on the

following basis. When free folic acid (pteroylglutamic acid) is given to patients with pernicious anaemia a haemopoietic response occurs accompanied by a transformation of the megaloblastic bone marrow and a marked increase of excretion of free folic acid in the urine. When conjugated folic acid (pteroylheptaglutamic acid), as contained in natural foods such as yeast, is given in equivalent doses no transformation of the megaloblastic marrow occurs and no increased excretion of free folic acid results. When purified liver extract is given parenterally to a case of pernicious anaemia the classical haemopoietic response occurs together with a marked excretion of free folic acid. Hence it can be assumed that purified liver extracts contain a factor which enables the conversion of conjugated folic acid to free folic acid to take place. This liberating factor, which is the product derived from the interaction of Castle's intrinsic and extrinsic factors in the alimentary tract, is absorbed from the intestine and stored in the liver. It is present in the liver of normal individuals but not in the liver of patients with pernicious anaemia. This liberating factor is hereafter referred to as L.F. The cause of pernicious anaemia therefore does not lie in some inherent abnormality of the bone marrow but in the inability of the body to convert conjugated folic acid to the free form through lack of L.F. The administration of preformed free folic acid to a patient with pernicious anaemia circumvents the need for this conversion and accordingly the expected haemopoietic response occurs.

It is well recognized that patients suffering from nutritional macrocytic anaemia, the sprue syndrome, pernicious anaemia of pregnancy, and idiopathic refractory megaloblastic anaemia may be partially or completely refractory to the injection of potent purified liver extracts despite the presence of a megaloblastic marrow. Such patients will respond to the oral administration of whole liver (Fullerton, 1943), proteolysed liver (Davis and Davidson, 1944), or liver extract (Watson and Castle, 1946). The introduction of folic acid has added another therapeutic weapon effective in this group of diseases. Megaloblastic blood formation in the above conditions is not primarily conditioned, as in Addisonian pernicious anaemia, by a defective production of L.F. but by a deficiency in the body of conjugated folic acid as a result of direct dietary deficiency or a failure in absorption. Hence it is understandable why parenteral liver therapy fails and why free folic acid is effective under these circumstances.

The mechanism by which proteolysed liver and oral liver extracts achieve similar results to those obtained by folic acid is not so simple of explanation. The folic acid content of the effective daily dose of such preparations is stated to be considerably less than 1 mg., a quantity which by itself is unlikely to produce the maximal haemopoietic responses which we regularly obtained. Such oral liver preparations, however, contain, in addition to folic acid, L.F., other members of the vitamin B complex, and amino acids. It may be found in the future that the combination of folic acid and parenteral or oral liver therapy will be effective in doses which, when given individually, are inactive. That substances other than folic acid and L.F. may be required to bring blood formation completely back to the final stage of normoblastic blood formation is suggested by our findings that some cases of the sprue syndrome and idiopathic refractory megaloblastic anaemia continue to have a macrocytic anaemia and a primitive type of normoblastic marrow, despite continued administration of potent parenteral liver extracts and folic acid. In some of these cases, but by no means all, a final and complete transformation to normality was secured by the addition of proteolysed liver (hepamino).

Folic acid is a vitamin, a member of the B₁₂ complex. Hence it is not unreasonable to suppose that the general principles covering the therapeutic administration of vitamins are also applicable to folic acid. These principles may be summarized as follows:

1. A beneficial result will occur only if the body is deficient in the vitamin. Attention is drawn to the dramatic effect of aneurine in beriberi and to its complete failure to influence the course of infective polyneuritis.

2. When an individual has a sufficiency of a vitamin the giving of excessive amounts is valueless and wasteful. It is justifiable during the initial period of treatment of a vitamin deficiency disease to give from 10 to 20 times the amount required for normal maintenance purposes in order to replace the body's depleted stores as rapidly as possible. Thereafter the daily amount prescribed should be reduced to the accepted optimal daily requirements and be given where possible in the form of natural foods.

3. In vitamin deficiency disease replacement therapy produces a therapeutic result rapidly. The beneficial effects will be obvious within a few days and sometimes within a few hours. Failure to achieve therapeutic success within one or two weeks accordingly indicates a mistaken diagnosis, and the continued administration of the vitamin is an expensive and unwarranted procedure.

If these principles are applied to folic acid a rational basis for treatment will be forthcoming. It is believed that the daily requirement of folic acid is in the neighbourhood of 0.5-1 mg., and that normal individuals partaking of an average mixed diet can easily obtain this amount from their food. The same remarks apply to patients with Addisonian pernicious anaemia. Since, however, such patients are unable to obtain free folic acid from the conjugated form in food they require injections of liver extract. Provided they are taking a satisfactory mixed diet the addition of free folic acid will not be required so long as they are receiving adequate parenteral liver therapy.

Since it has been shown by ourselves and by Spies and Stone (1947) that folic acid is unable to prevent or cure subacute combined degeneration of the cord, folic acid cannot be recommended as the sole therapeutic agent for maintenance treatment in pernicious anaemia or when neurological changes are present. It may be used as a temporary measure in the initial treatment of pernicious anaemia and in patients sensitive to liver extracts awaiting desensitization. The suggested dose is 5-10 mg. daily by mouth. Until the factor required for the maintenance of the integrity of the nervous system is isolated and combined with folic acid, parenteral liver therapy must continue to be the accepted routine method of treatment of pernicious anaemia.

Since subacute combined degeneration of the cord very rarely develops in nutritional megaloblastic anaemia, pernicious (megaloblastic) anaemia of pregnancy, idiopathic refractory megaloblastic anaemia, or the sprue syndrome, folic acid can be safely advocated both for initial and for maintenance therapy in doses of 5-10 mg. daily. In the first two diseases the administration of folic acid can be stopped when the blood count is normal provided a satisfactory well-balanced diet is eaten. In the third disease maintenance treatment (suggested dose 5 mg. daily) will be required for life. In the sprue syndrome maintenance requirements will vary in individual cases according to the course of the disease. If the blood level or blood picture in patients with any of the above diseases fails to return quantitatively and qualitatively to normal a supplement of oral liver extract or proteolysed liver (1 oz. daily) should be given. There is sound evidence for the belief that for the treatment of any megaloblastic anaemia quantities of folic acid in excess of 10 mg. daily are unnecessary and

wasteful. Moreover, if haematological and clinical improvement does not occur within two weeks it can be assumed that the disorder is not due to deficiency of folic acid and that continued administration of the vitamin is contraindicated.

Summary

An account is given of the results of treatment with folic acid of (a) 16 cases of pernicious anaemia, (b) 5 cases of refractory megaloblastic anaemia, (c) 10 cases of the sprue syndrome, (d) 3 cases of subacute combined degeneration of the cord, (e) 5 cases of aplastic and hypoplastic anaemia, (f) 9 cases of leucopenia, (g) 9 cases of thrombocytopenia, and (h) 5 cases of ulcerative colitis.

A haemopoietic response was obtained only in the cases in which the bone marrow was megaloblastic—i.e., cases in groups a, b, and c.

No therapeutic changes were obtained in cases of aplastic anaemia, leucopenia, or thrombocytopenia.

In the sprue syndrome folic acid controlled the diarrhoea and produced general clinical improvement in adult patients suffering from tropical sprue and idiopathic steatorrhoea. Folic acid by itself seldom restored the blood level or blood picture to normal. In none of the cases of coeliac disease was any haematological or clinical improvement noted.

The clinical and sigmoidoscopic appearances in 5 cases of idiopathic ulcerative colitis were unaffected by folic acid therapy.

The rationale of the action of folic acid and the principles underlying its therapeutic administration are discussed.

REFERENCES

- Angier, R. B., *et al.* (1945). *Science*, **102**, 227.
 Berry, L. J., and Spies, T. D. (1946). *Blood*, **1**, 271.
 Bethell, F. H., Meyers, M. C., Andrews, G. A., Arbor, A., Swendsen, M. E., Bird, O. D., and Brown, R. A. (1947). *J. Lab. clin. Med.*, **32**, 3.
 Carruthers, L. B. (1946). *Lancet*, **1**, 849.
 Cooke, W. T., Elkes, J. J., Frazer, A. C., Parker, J., Peeney, A. L. P., Sammons, H. G., and Thomas, G. (1946). *Quart. J. Med.*, **15**, 141.
 Davidson, L. S. P., and Girdwood, R. H. (1946). *Lancet*, **2**, 373.
 ——— and Innes, E. M. (1947). *Ibid.*, **1**, 511.
 Davis, L. J., and Davidson, L. S. P. (1944). *Quart. J. Med.*, **13**, 53.
 Doan, C. A. (1946). *Amer. J. med. Sci.*, **212**, 257.
 Fullerton, H. W. (1943). *British Medical Journal*, **1**, 158.
 Lopez, G. G., Spies, T. D., Menendez, J. A., and Toca, R. L. (1946). *J. Amer. med. Ass.*, **132**, 906.
 Spies, T. D., and Stone, R. E. (1947). *Lancet*, **1**, 174.
 Watson, J., and Castle, W. B. (1946). *Amer. J. med. Sci.*, **211**, 513.
 Welch, A. D., Heinle, R. W., Nelson, E. M., and Nelson, H. V. (1946). *J. Biol. Chem.*, **164**, 787.
 Wilkinson, J. F., Isaacs, M. C. G., and Fletcher, F. (1946). *Lancet*, **2**, 156.
 Zuelzer, W. W., and Ogden, F. N. (1946). *Amer. J. Dis. Child.*, **71**, 211.

The New Health Club, in which the late Sir William Arbuthnot Lane was a prominent figure, revived its activities after wartime dormancy on March 19 with a tea-time *causerie* at which Sir Albert Howard, for many years imperial economic botanist to the Government of India, gave an address on "Soil, Food, and Health." Sir Albert Howard has had a large experience of the food habits of primitive peoples which enable them to withstand some of the ills besetting civilization. He admitted that in a community such as ours it was not possible to revert to an entirely primitive dietary; the easiest thing to concentrate upon, he said, was bread. It was possible even in London to obtain properly grown wheat—"properly grown" meaning the cultivation of the soil having regard to its natural properties and without dependence on artificial manures. Such wheat, roughly ground and made into bread or porridge, gave a perfect food quite different from anything ordinarily obtainable in the shops. It was now open for anyone to take out a licence to buy properly grown wheat from the farmer, mill it on his own premises, and make his own bread. A breakfast cup of roughly ground wheat soaked in milk and eaten raw was extraordinarily satisfying, and beginning the day with such a meal he himself could go on happily without troubling about food until evening. It was not quantity that mattered, but absence of sophistication. He hoped to see in England a new type of bakery in which something quite different from ordinary flour was used, the wheat going in at one end and being ground out roughly, with no separation of bran. If the product was put straight into bread the improvement in quality obtained was almost unbelievable.

THE PHYSICAL HEALTH OF CHILDREN ATTENDING DAY NURSERIES

A REPORT TO THE DAY NURSERIES COMMITTEE OF THE MEDICAL WOMEN'S FEDERATION

BY

MARGARET E. McLAUGHLIN, M.B., B.S., D.C.H.

PART I

Aim and Method of Investigation

In 1944-5 an investigation was made under the auspices of the Medical Women's Federation to obtain data concerning the effect of life in wartime day nurseries on the physical health of children under 5 years old. The investigation was made in two parts. In the first part a comparison was made of children attending day nurseries and children attending welfare centres, and the records were based on the results of a single examination of each child by 73 medical officers in different parts of the country in the course of their normal work. The results of this section of the investigation have been published already (*Journal*, Aug. 17, 1946, p. 217).

The present report describes the results of the second part of the investigation, carried out by me; this has been a comparison over a period of twelve months in 1944-5 of a group of children attending Ministry of Health wartime day nurseries in Birmingham with a control group of children living in their own homes. Periodic examinations of the children in both groups were made during the survey.

Selection of Clinical Material

The nursery group of children was composed of the entire population of eight Ministry of Health wartime day nurseries in different parts of the city; thus various social and economic groups were represented. The nurseries were open from 7 a.m. to 7 p.m. for 5½ to 6 days a week, and nearly all the children spent their whole day in the nursery, as their mothers were mostly engaged on full-time war work. Each nursery was under the care of a fully trained nurse with a staff of trained and student nursery nurses and nursery assistants, and a certificated or non-certificated nursery teacher. The approved complement of staff, excluding domestic staff, was one nurse to four children, but owing to the wartime conditions this was not always attained. Each nursery accommodated from 48-60 children aged 0-5 years (one nursery accommodated 80 children). The premises ranged from specially constructed one-story buildings of a semi-permanent character to converted old houses or portions of the premises of infant welfare centres. The children were provided with three full meals or two meals and mid-morning lunch every day. These meals, which were generous and well planned, were provided without the surrender of any of the children's own ration coupons, which were thus still available for their use at home. The rationed food which could be obtained for children attending nurseries was thus nearly double that available to children having all their meals at home—i.e., they could have twice the quantity of meat, butter, bacon, eggs, cheese, etc. An isolation room was provided in each nursery, and all children were examined each morning on arrival by a senior member of the staff, admission being refused to children obviously ill and those with infectious skin diseases. Children with colds could not, however, be excluded as a routine measure. A child-welfare medical officer was available on call for any sick child, and routine medical inspections of all the children were periodically made. A medical certificate of fitness was necessary before admission or readmission to a nursery.

The control group of children was composed of those living at home and attending no nursery school or class for young children. They were classified into eight subgroups, each drawn from the same residential area as one of the eight nurseries chosen for the survey. The children were selected at random from the health visitors' official lists of all those under 5 living