Stage I: Early Intrinsic (37 patients).—Early lesions were confirmed by removal of the thyroid cartilage in every case. One patient died from the operation, three from cancer (one after 10 years), and sixteen from other causes. Seventeen are still living. Most of the survivors have strong resonant voices. The survival rates are shown in Table IV.

Stage II: Advanced Intrinsic (72 patients).—Usually these were unilateral, extensive, and apparently intrinsic with no enlarged lymph nodes. Twelve were bilateral. Soft tumours, if movable, responded better than the hard nodular ulcerated types. There were five operative deaths from chest infections, which were common when tracheotomies were performed, all of them before the introduction of antibiotics. Forty-two died of cancer, 31 in less than three years, six during the third year, but only five after this critical period. Among these 72 patients 26 survived with their larynges and excellent voices for periods ranging from five to twenty-four years. The survival rates are shown in Table IV.

Stage III: Extrinsic (9 patients).—These patients, who were found to have definite extrinsic lesions without obvious enlargement of cervical nodes, were needled and all of them died within three years. Needling alone has therefore been a failure. But, excepting for two who died of heart failure after operation, seven were temporarily improved for two to three years. Here again, laryngectomies should have been performed while the disease was arrested, and I regret that this was not done.

Summary

Lesions suitable for radium needling are therefore the following :

(1) Early lesions (stage I). Even if the vocal cord is fixed. Lymph nodes are never affected in this group.

(2) Localized lesions in the anterior commissure without involvement of the base of the epiglottis or of the tongue. In this region the dose is always a high one and needling usually succeeds in controlling the disease.

(3) Extensive lesions that appear to be intrinsic (stage II).

(4) Subglottic lesions (really stage III). In a few patients good results have been obtained and there is no risk in trying this treatment first, but laryngectomy should be performed early, in a month or two, if the swelling persists.

(5) Lesions of the false cord and vestibule (stage III). These growths are unusually malignant and difficult to cure. Probably needling plus laryngectomy is the best treatment.

ENVOY

In putting on record the results of 30 years' work with this particular treatment for intrinsic carcinoma of the larynx it would seem to be reasonable to claim that the method has been unduly neglected. I am aware that as good figures have been published claiming that teleradium is superior to interstitial needling for early lesions. I have always maintained that cancer should be treated in special centres by the united efforts of a team of specialists in this disease. Yet there is still a place for simplicity in surgery, and no one can deny that the establishment and maintenance of a teleradium unit is extremely costly. Radiation techniques become increasingly complex and require more and more planning and space and time. The method which we have adopted (and which has been described, possibly a little grudgingly, as "a piece of brilliant empiricism") is relatively cheap and extremely simple in the hands of a competent surgeon. It gives really excellent results if used for the right patient. And it is here, of course, that the clinical experience gained in a long apprenticeship in laryngology counts.

The proof of the pudding is in the eating. I think that this has been a good pudding and that it would be a pity if the recipe were lost.

FOLIC-ACID-EXCRETION STUDIES IN THE INVESTIGATION OF MALIGNANT DISEASE

BY

RONALD H. GIRDWOOD, Ph.D., M.B., Ch.B. F.R.C.P.Ed., M.R.C.P.

Senior Lecturer in Medicine, University of Edinburgh

When a test dose of 5 mg. of folic acid is injected in a normal individual a significant proportion is promptly excreted in the urine. Most of this excretion occurs within a few hours, but for metabolic studies it is advisable to collect the urine for twenty-four hours after the injection. It has been shown that the urinary excretion of folic acid is diminished in many cases of pernicious anaemia (Bethell *et al.*, 1947; Girdwood, 1951, 1953). In a short review of the subject (Girdwood, 1952a) it was suggested that the controls used in the studies of pernicious anaemia patients were unsatisfactory, and that patients with other forms of anaemia should be employed. Accordingly the present investigation was started as a study of folic acid excretion in various types of anaemia. At an early stage it was found (Girdwood, 1952b) that, of eight patients with iron deficiency anaemia, folic-acid excretion was diminished in four. All of these four suffered from carcinoma. It was decided, therefore, to investigate further the urinary folic-acid excretion in patients suffering from malignant disease and from various non-neoplastic conditions. About this time it was reported (Swendseid *et al.*, 1952) that folic-acid excretion was impaired in leukaemia. The patients in the present investigation were all given 5 mg. of folic acid subcutaneously.

Methods and Materials

The estimation of the urinary content of folic acid was carried out microbiologically. Under the conditions of the test the growth of *Streptococcus faecalis* in a suitable medium depends upon the amount of folic acid present in that medium. The growth of the test organism in tubes containing that medium and various dilutions of urine is compared with that in tubes containing the medium and dilutions of a standard solution of folic acid.

Estimations of folic acid were by the method of Teply and Elvehjem (1945), *Str. faecalis R* being used as the test organism. Estimations of citrovorum factor were by a modification of the method of Sauberlich and Baumann (1948) with *Leuconostoc citrovorum* as the test organism. In both instances turbidity readings were carried out in a Spekker photo-electric absorptiometer after incubation at 37° C. for 16 hours. The resting urinary content of folic acid is so small that no correction requires to be made for it in the folic-acid readings. The proportion of folic acid excreted as citrovorum factor is very small, as shown in the accompanying Tables, and the "folic acid" figures include any growth activity due to citrovorum factor. The citrovorum-factor readings have not been corrected for the resting urinary content of citrovorum factor, which on the average is of the order of 1 μg.

The folic acid was given by subcutaneous injection from a tuberculin syringe, and was taken from one or other of two batches of "folvite" that had been tested by us and found to contain 15 mg. of folic acid per ml. Several batches were rejected as they contained more than the stated amount. The volume injected was 0.33 ml.

Twenty-four-hour urine collections were put in brown bottles containing toluene and a phosphate buffer of *p*H 6.8. The greatest possible care was taken to ensure that the urines were total 24-hour specimens. The specimens were kept in a refrigerator at 4° C., and readings were usually

made within three days. All readings were at least in duplicate, usually triplicate. No antibiotics or sulphonamides were given to the patients during the period of the test.

Results

Folic-acid Excretion in Patients Not Suffering from Malignant Disease, Pernicious Anaemia, Intestinal Malabsorption, or Prolonged Infection

The results of the urinary excretion of folic acid in a number of patients with various non-malignant diseases are given in Table I. It will be seen that the only patient in whom the excretion was less than 30% of the dose administered (less than 1.5 mg.) was a man with severe congestive cardiac failure and oedema (Case 43). Two patients, one with a large pleural effusion and the other with massive ascites, are not included; in both instances folic-acid excretion was impaired, but it was possible to show that much of the vitamin was present in the effusion, and that urinary excretion took place over several days. These results suggest that in a patient with normal renal function and without oedema or a large effusion the 24-hour urinary excretion of a 5-mg. dose of folic acid should be greater than 1.5 mg.

It will be seen from Table I that anaemia in itself, even if severe, does not cause an abnormally low folic-acid excretion following a 5-mg. test dose. The same is true of hepatic cirrhosis.

TABLE I.—*Folic-acid Excretion in Patients Without Evidence of Malignant Disease or Prolonged Infection*

Case No.	Sex and Age	Diagnosis	Hb (g.%)	R.B.C. (mil./c.mm.)	Urinary Folic-acid Excretion (mg./24 hrs.)	Urinary C.F. Excretion (µg./24 hrs.)
1	M 35	Normal	15·2	—	3·80	
2	F 34	Agranulocytosis	11·0	5·11	3·75	—
3	M 30	Normal	15·4	—	3·56	—
4	F 34	Erythema nodosum (rheumatic); mitral stenosis	12·3	—	3·55	—
5	M 35	Bleeding duodenal ulcer	13·2	—	3·52	—
6	F 46	Portal cirrhosis; portal hypertension	10·0	3·15	3·41	5·10
7	F 48	Acquired haemolytic anaemia	10·3	3·53	3·32	3·7
8	M 42	Lobar pneumonia	14·8	5·16	3·30	9·6
9	M 77	Neurological features due to vitamin deficiency. Very strict vegetarian	12·3	4·22	3·20	0·83
10	F 32	Brachial neuritis	14·2	—	3·19	—
11	M 49	Bleeding duodenal ulcer	11·6	—	3·19	—
12	F 36	Iron-deficiency anaemia	3·8	2·60	3·16	10·8
13	M 63	Hypertensive cardiac failure	15·4	—	3·16	2·42
14	F 42	Iron-deficiency anaemia	8·1	4·21	3·04	—
15	F 43	" "	7·1	4·98	3·02	4·10
16	F 45	" "	8·6	4·18	2·96	1·55
17	F 49	Portal cirrhosis; portal hypertension	9·0	4·07	2·90	7·4
18	M 51	Gastric ulcer	15·2	—	2·89	—
19	F 34	Peptic ulcer; mitral stenosis	14·0	—	2·89	2·04
20	F 70	Coronary thrombosis; cardiac failure; pulmonary oedema; oesophageal hernia	11·2	5·5	2·80	—
21	F 17	Bronchial asthma	7·3	5·5	2·71	5·4
22	M 57	Polycythaemia	17·3	6·91	2·68	9·0
23	M 52	Gastric ulcer	15·3	—	2·66	—
24	F 66	Iron-deficiency anaemia	7·9	3·65	2·58	—
25	F 16	Thyrotoxicosis	14·8	4·99	2·57	—
26	F 84	Aplastic anaemia	8·0	2·71	2·56	2·0
27	F 72	Portal cirrhosis	13·5	4·40	2·55	3·32
28	M 56	Bleeding duodenal ulcer	9·2	4·72	2·54	1·9
29	F 45	Portal cirrhosis	9·7	3·85	2·50	2·9
30	F 69	Myelosclerosis	8·1	3·15	2·47	3·0
31	F 42	Iron-deficiency anaemia	5·6	4·64	2·42	2·1
32	F 36	Sciatica	11·9	—	2·31	—
33	M 42	Gastric ulcer	14·6	—	2·27	—
34	F 53	Para-oesophageal hernia	8·0	3·13	2·18	6·2
35	F 32	Dyspepsia	13·9	—	2·17	3·1
36	F 18	Bronchial asthma	12·5	—	2·05	—
37	F 48	Gastric neurosis	15·3	5·01	2·02	1·38
38	F 46	Iron-deficiency anaemia	8·1	4·67	1·93	7·36
39	F 42	Sciatica	14·2	—	1·73	—
40	F 66	Chronic alcoholic; bronchopneumonia; malnutrition	15·0	—	1·73	—
41	F 68	Malnutrition	9·3	3·6	1·52	1·47
42	F 84	"	4·0	3·1	1·52	2·8
43	M 66	Hypertensive cardiac failure with oedema	15·2	—	0·79	1·60

C.F.=Citrovorum factor

Folic-acid Excretion in Patients Suffering from Malignant Disease and Allied Conditions

In Table II there are given the urinary folic-acid excretion results in a number of persons suspected of having malignant disease (including leukaemia and the reticuloses) or found as a result of hospital investigation to be so afflicted. The Table is constructed so as to include the provisional diagnosis when the patient was first seen in connexion with the present investigation. Thus in many instances it was not known whether or not malignancy was present, and it will be seen that in some cases it was fortunately possible to show that no neoplastic disease existed. In the cases included in this Table the final diagnosis had been definitely established, in many instances by biopsy or laparotomy. Most of the patients included in Table II had had no therapy, but a few had been treated by *x* rays or other means several months before the present investigation.

It will be seen from Table II that a *normal* folic-acid excretion (1.5 mg. or less after the subcutaneous injection of 5 mg.) is of no help in excluding the presence of malignancy. Fourteen patients with carcinoma, leukaemia, lymphadenoma, or some other form of reticulosis had a normal folic-acid excretion. It is true that in most of these cases the general condition was good and there was little evidence of spread, but this was not so in Cases 53, 64, 66, and 73. Case 63 suffered from weakness and pyrexia, but no abnormality was found on physical examination. The diagnosis of lymphadenoma at the time of the folic-acid test was made only by exclusion and treatment with nitrogen mustard was begun. Despite the satisfactory folic-acid test, the diagnosis of lymphadenoma was confirmed at necropsy only three months later. Case 51 felt so well despite the abnormal blood picture that no treatment was given.

Inspection of the records of cases in Table II who excreted less than 1.5 mg. of folic acid shows that all of them suffered from malignant disease. In some instances the folic-acid-excretion results were available some time before the presence of malignancy was established by *x*-ray films, biopsy, or laparotomy. Obvious weight loss was not invariably present in patients with a positive test. It will be seen, too, that there was no correlation between the sedimentation rate or the degree of anaemia and the result of the folic-acid-excretion test in either malignant or non-malignant cases.

Folic-acid Excretion in Chronic Infection

There are occasions on which it would be helpful to have a test to determine whether a patient suffers from chronic infection or from malignancy. For this reason a separate table (Table III) has been constructed to include untreated patients with chronic infections and collagen diseases. In all the cases of pulmonary tuberculosis the disease was extensive, but except in Cases 106 and 115 the general condition under a sanatorium regime was good.

Case 118 illustrates most clearly that prolonged generalized bacterial infection can give a diminished output of folic acid after a test dose. No treatment had been given for a year.

In Case 115 the possibility that amyloid tissue has an affinity for folic acid would require consideration.

It is possible that the diagnosis in Case 117 was incorrect, as there was an increase in plasma cells in the marrow, and the symptoms and fever did not respond to salicylates.

Case 114 is of interest in that the patient's general condition was good, and the only obvious abnormality was splenic enlargement. Nevertheless the test was positive.

Four patients with pyrexia, the cause of which is not yet certain, are included to show that prolonged fever will not itself necessarily lead to a diminished excretion of folic acid. In this respect Case 99 is of interest in that quite high fever—rising to 103° F. (39.4° C.)—has been present intermittently for 18 months without evidence of general deterioration. The diagnosis of Case 108 is uncertain, but,

although emaciation was severe, folic-acid excretion was normal. Case 116 (lupus erythematosus disseminatus) was also much wasted, and, although cortisone therapy led to marked clinical improvement, the folic-acid excretion remained abnormal in this patient.

Folic-acid Excretion in Megaloblastic Anaemia

This is the subject of other communications (Girdwood, 1951, 1953), and hence the only information required here is a summary of the findings in 20 cases of untreated pernicious anaemia, 2 cases of intestinal malabsorption that had

TABLE II.—*Folic-acid Excretion in Patients Suspected of Having Malignant Disease*

Case No.	Sex and Age	Suspected Malignancy or Diagnosis on Admission	Hb (g.%)	R.B.C. (mil/c.mm.)	E.S.R. (mm./hr.) (Westergren)	Final Diagnosis	Urinary Folic-acid Excretion (mg./24 hrs.)	Urinary C.F. Excretion (µg./24 hrs.)	Remarks
44	M 64	Gastric carcinoma (*x*-ray confirmation)	10·0	3·82	45	Gastric ulcer (non-malignant) at operation	4·05	—	
45	F 48	Carcinomatosis	13·6	—	45	Carcinoma of cervix. No evidence of secondaries	3·7	—	Good general condition
46	F 52	,, ...	14·9	—	3	Brain-stem thrombosis	3·7	1·87	
47	F 50	Gastric carcinoma	12·2	5·26	50	Gastric ulcer (non-malignant) at operation	3·7	—	
48	F 51	Hepatic carcinoma ..	14·0	—	90	Rheumatoid arthritis	3·54	—	
49	M 43	Lymphadenoma ..	16·0	5·31	—	Lymphadenitis	3·50	—	
50	F 43	Plasma-cell tumour of breast (biopsy before admission)	14·2	4·92	3	Plasma-cell tumour of breast	3·48	4·7	Good general condition
51	M 66	Chronic lymphatic leukaemia	14·8	—	—	Chronic lymphatic leukaemia	3·46	10·3	Feels quite fit. No glandular, hepatic, or splenic enlargement. W.B.C. 112,800. No treatment given
52	M 60	Carcinoma of liver ..	14·0	—	38	Carcinoma of gall-bladder	3·33	2·47	
53	F 67	Bronchial carcinoma ..	6·0	4·3	90	Pulmonary tuberculosis; carcinomatous glands in neck; primary uncertain	3·19	5·5	
54	F 68	Carcinomatosis; myxoedema	10·0	2·89	112	Spondylitis; myxoedema	3·16	0·63	
55	F 44	Gastric carcinoma ..	11·5	5·5	8	Hiatus hernia	3·10	—	
56	F 63	Suspected malignancy ..	11·8	4·08	110	Coronary thrombosis	3·06	—	Weakness and raised E.S.R.
57	M 58	,, ,, ..	12·3	4·8	14	Anxiety state	3·02	—	Tiredness and weight loss
58	F 23	Lymphadenoma ..	13·6	—	24	Pulmonary and glandular tuberculosis	2·88	5·1	
59	F 70	Neck swelling; diabetes	15·6	5·62	5	Lymphosarcoma; diabetes	2·72	16·3	Liver and spleen not enlarged; good general condition
60	M 74	Carcinoma of gall-bladder	13·2	—	12	Gastric carcinoma: local spread to liver	2·6	3·1	Good general condition
61	M 45	Lymphadenoma ..	15·2	—	28	Lymphadenitis	2·6	8·47	
62	F 73	Bronchial carcinoma; rheumatoid arthritis	13·0	—	62	Bronchial carcinoma; rheumatoid arthritis	2·50	—	Slowly progressive over years
63	M 51	Lymphadenoma ..	8·7	3·21	127	Lymphadenoma	2·42	—	Pyrexia. No enlargement of glands or organs; died 3 months later
64	F 42	Acute lymphatic leukaemia	13·3	4·98	32	Acute lymphatic leukaemia	2·40	1·58	Enlarged liver, spleen, glands. Died soon after. W.B.C. 26,200
65	F 60	Suspected malignancy	14·1	—	48	No abnormality found	2·35	—	Weight loss; epigastric discomfort
66	M 56	Bronchial carcinoma ..	14·0	—	5	Bronchial carcinoma with metastases	2·27	3·5	
67	F 74	Carcinoma of caecum ..	—	—	—	Carcinoma of caecum (localized)	2·24	—	
68	F 50	Carcinoma of liver ..	12·3	—	—	Infective hepatitis	2·04	3·98	Serum bilirubin 13 mg./100 ml.
69	F 77	Carcinomatosis	8·8	2·47	70	Pelvic abscess	2·0	10·2	
70	F 46	Intestinal reticulosis ..	14·8	4·86	9	Intestinal reticulosis	1·97	4·4	Biopsy diagnosis. No evidence in other organs
71	F 56	Carcinoma small intestine	12·2	—	80	Adhesions	1·95	0·76	
72	M 63	Hepatic carcinoma ..	15·2	4·83	2	No abnormality found	1·90	2·70	
73	M 55	Aleukaemic lymphatic leukaemia	9·8	3·4	65	Aleukaemic lymphatic leukaemia	1·75	2·85	W.B.C. 5,000. Glands, liver, spleen normal. Died a month later
74	M 73	Glandular enlargement..	11·0	4·3	100	Reticulosis	1·20	—	Very little weight loss
75	F 41	Pernicious anaemia refractory to vitamin B_{12}	9·3	3·04		Pernicious anaemia; gastric carcinoma; metastases	1·16	—	
76	F 76	Iron-deficiency anaemia	6·2	3·03	47	Inoperable carcinoma of transverse colon	1·04	—	No weight loss
77	M 45	Lymphadenoma ..	8·6	—	125	Renal carcinoma	0·98	8·65	Normal renal function. No weight loss
78	M 71	Follicular reticulosis (biopsy diagnosis)	12·7	4·35	—	Follicular reticulosis	0·97	4·57	
79	F 62	Refractory iron-deficiency anaemia	5·4	2·9	50	Carcinoma of jejunum	0·796	4·61	
80	M 52	Glandular enlargement..	14·9	4·98	—	Follicular reticulosis	0·762	—	
81	M 49	Lymphadenoma ..	12·0	4·25	—	Lymphadenoma	0·75	3·6	No weight loss
82	M 62	Iron-deficiency anaemia	4·6	2·97	6	Carcinoma of stomach and liver	0·71	—	
83	M 63	Same patient as Case 82 a year later	9·0		47	,, ,, ,,	0·112	1·64	No clinical deterioration, but mass larger
84	M 32	Anaemia	7·6	2·31	—	Acute lymphatic leukaemia	0·715	3·5	Three weeks' illness
85	M 69	Jaundice	11·3	—	50	Carcinoma of liver	0·601	—	Serum bilirubin 120 mg./100 ml.
86	F 46	Uterine carcinoma; secondaries	3·5	1·67	125	Uterine carcinoma; secondaries	0·472	2·29	
87	M 48	Lymphadenoma ..	14·2	5·19	60	Lymphadenoma	0·46	12·8	
88	F 39	Pain in back—for investigation	9·0	3·1	125	Multiple myeloma	0·343	3·38	No weight loss
89	F 59	Chronic myeloid leukaemia	8·4	3·28	25	Chronic myeloid leukaemia	0·325	6·55	W.B.C. 384,000
90	F 22	Lymphadenoma ..	7·5	2·4	110	Lymphadenoma	0·221	—	Very little weight loss
91	M 34	Glandular enlargement..	14·8	—	47	,,	0·142	5·75	
92	F 32	Multiple myeloma ..	12·3	—	57	Multiple myeloma	0·134	2·91	
93	M 37	Lymphadenoma ..	8·5	3·08	—	Lymphadenoma	0·133	—	
94	F 42	Emaciation	10·2	3·55	120	Carcinomatosis	0·100	8·4	
95	F 66	Anaemia	6·6	2·80	8	Lymphosarcoma	0·084	3·35	No hepatic or glandular enlargement. Spleen just palpable. No weight loss
96	M 66	Chronic lymphatic leukaemia and cardiac failure	11·1	3·44	—	Chronic lymphatic leukaemia and cardiac failure	Negligible	Negligible	

TABLE III.—*Folic-acid Excretion in Patients with Chronic Infections or Associated Conditions*

Case No.	Sex and Age	Diagnosis	Hb (g.%)	R.B.C. (mil./c.mm.)	E.S.R. (mm./hr.)	Years of Illness	Urinary Folic-acid Excretion (mg./24 hrs.)	Urinary C.F. Excretion (μg./24 hrs.)	Remarks
97	F 27	Rheumatoid arthritis ..	8·6	—	60	6/12	4·23	—	
98	M 23	Pulmonary tuberculosis		—	5	6	3·49	—	Extensive bilateral
99	F 26	P.U.O.	12·5	4·88	5	1½	3·48	5·73	Temperature to 103° F. (39·4° C.), good general condition
100	M 37	Pulmonary tuberculosis		—	52	2	3·34	—	Bilateral
101	F 23	P.U.O.	12·4	4·14	18	3/12	3·23	6·5	Temperature to 99·5° F. (37·5° C.)
102	M 47	Pulmonary tuberculosis	—	—	2	3	3·01	—	Large cavity
103	F 52	Chronic bronchitis with acute recurrence	14·0	—	100	20	2·98	—	
104	M 62	Pulmonary tuberculosis	—	—	35	1½	2·62	—	Bilateral
105	M 53	,, ,,	—	—	47	2	2·59	—	,,
106	M 67	,, ,,	14·2	—	26	Many	2·43	4·07	Extensive unilateral
107	F 21	Undulant fever ..	15·2	—	12	2/12	2·38	11·2	
108	F 43	P.U.O.			22	1½	2·38	—	Lost 3 st. (19 kg.)
109	F 63	Rheumatoid arthritis ..	9·9	3·37	5	3	2·30	2·79	
110	F 70	Severe chronic bronchitis with heart failure	13·0	4·5	40	Many	2·2	—	Much wasted
111	M 48	Pulmonary tuberculosis	—	—	40	1	2·14	—	Extensive bilateral
112	M 52	P.U.O.	13·4	5·82	130	4/12	1·79	—	Temperature to 101° F. (38.3° C.)
113	F 53	Chronic pneumonia with eosinophilia	11·0	3·86	74	1½	1·74	—	
114	M 46	Sarcoidosis	14·6	5·01	—	Recent	1·15	2·15	Splenic enlargement only. Diagnosis after splenectomy
115	F 45	Pulmonary tuberculosis amyloid liver	—	—	55	13	1·14	6·13	
116	F 50	Lupus erythematosus disseminatus	7·4	3·58	110	2	0·95	—	
117	F 50	Rheumatoid arthritis ..	14·8	—	35	2/12	0·825	—	Did not respond to salicylates
118	M 26	Subacute bacterial endocarditis (untreated)	11·0	3·63	76	1	0·14	—	

not received folic acid, vitamin B_{12}, or citrovorum factor, 7 cases of megaloblastic anaemia of pregnancy, and 1 case of idiopathic refractory megaloblastic anaemia.

TABLE IV.—*Folic-acid Excretion in Megaloblastic Anaemia (Untreated)*

	No. of Cases	Folic-acid Excretion (mg.) Following a 5-mg. Test Dose given Subcutaneously
Pernicious anaemia	20	0·066–3·08 (mean 1·55)
Intestinal malabsorption	2	0·126, 0·299
Pregnancy (megaloblasts, not transitional erythroblasts, present) ..	4	1·33, 1·50, 2·37, 2·64
Idiopathic refractory megaloblastic anaemia	3*	1·58, 1·75, 3·84
	1	1·92

* Received 15 mg. of folic acid by injection.

In all these patients the marrow was frankly megaloblastic: examples where transitional erythroblasts were found are recorded separately (Girdwood, 1953).

It will be noted from Table IV that in megaloblastic anaemia of pregnancy folic-acid excretion may be normal. Of the 20 pernicious-anaemia patients, 9 had an excretion of less than 1.5 mg.

Discussion

These results suggest that the folic-acid excretion test may have a limited place in the investigation of puzzling cases. Many more cases must be studied before we can say to what extent the test is of value in differentiating between such conditions as aplastic anaemia and aleukaemic leukaemia or simple iron-deficiency anaemia and iron-deficiency anaemia associated with advanced malignant disease. It is obvious that a "negative" test (normal excretion) is of no assistance to the clinician in the diagnosis of malignancy, since in 14 cases a normal excretion of folic acid was found. On the other hand, where there is no evidence of intestinal malabsorption, prolonged fever, megaloblastic anaemia, a large effusion or generalized oedema, and where renal function is not impaired, a "positive test" (an excretion of less than 30% of a 5-mg. test dose) would appear to suggest the presence of malignancy. Further investigations may show additional exceptions to this generalization. It is important that an exact dosage of folic acid should be given, and the urine collection must be complete. We have found that a repetition of the test dose may give a less abnormal finding on the second occasion, possibly because the first 5 mg. of folic acid partially corrects the folic-acid deficiency in the tissues.

It is not certain what a diminished urinary excretion of folic acid indicates. In nutritional megaloblastic anaemia, and in untreated cases of intestinal malabsorption, the presence of megaloblasts in the marrow is taken to indicate deficiency of folic acid or of vitamin B_{12}. In untreated pernicious anaemia, in which the primary deficiency is believed to be of vitamin B_{12}, folic-acid excretion following a test dose is frequently low, but can be normal. Moreover, transitional erythroblasts rather than true megaloblasts may be found in association with either a normal or an abnormal output of folic acid. The excretion in megaloblastic anaemia of pregnancy may be normal or abnormal, and this is discussed elsewhere (Girdwood, 1953). In malignant disease the amount of the test dose of folic acid excreted may be much diminished, but megaloblasts are only very rarely found in the marrow. They were not seen in any of the cases reported here.

One possible explanation both of the absence of megaloblasts and of the low urinary excretion of folic acid would be that the tumour tissue competes with the host for folic acid or its derivatives, but not to the extent of depriving the red-cell precursors of enough folic acid for maturation along normoblastic lines. Such a possibility is understandable where there is widespread malignancy as in leukaemia (for example, Case 84, in which the illness had been of only three weeks' duration and there would hardly be time for any other mechanism to play a part). The occurrence of megaloblastosis cannot be related directly to the degree of impairment of urinary folic-acid excretion, since the mechanism of production of megaloblastic change in the marrow varies in different conditions. It is possible that where the primary fault is virtual absence of folic acid or associated substances from the diet, or malabsorption of the folic-acid group of vitamins, a greatly diminished urinary output of administered folic acid will be associated with megaloblastosis; but we have seen that where the primary fault is the absence of vitamin B_{12}, or where there seems to be mal-utilization of folic acid in the body (for example, pregnancy megaloblastic anaemia) this relationship does not necessarily hold.

Other modes of production of the apparent folic-acid deficiency in cases of malignant disease that merit consideration are deficient intake due to anorexia with resulting primary malnutrition, and diminished absorption produced by widespread metastases or some other means.

It seems unlikely that either of these mechanisms could operate without significant weight loss occurring, and there was little or no weight loss in Cases 74, 76, 77, 81, 84, 88, 90, 95, and 114. Moreover, in Cases 77 and 114 there was no evidence at operation of any cause for intestinal malabsorption. This was true also at post-mortem examination in Cases 88 and 95.

In contrast, there was very severe primary malnutrition of many years' duration in Cases 40, 41, and 42, as established by a detailed dietetic investigation. An important source of calories for Case 40 was whisky. Case 41 weighed only 4 st. 12 lb. (30.8 kg.): a fat-balance test in this patient revealed normal fat absorption. A post-mortem examination of Case 42 revealed no abnormality other than generalized wasting.

Nevertheless these patients, while excreting less of the administered folic acid than did most of the other control cases, were able to excrete 1.5 mg. or more.

It is, of course, possible that several factors operate to give a diminished folic-acid excretion in some patients with malignant disease. Thus it would be reasonable to assume that intestinal malabsorption was an important cause in Case 79. Recently a folic-acid-absorption test has been devised for measurement of absorption of folic acid from the alimentary tract (Girdwood, 1953), and it may be that the application of this test to cases similar to those in Table II will be of value.

The data given do not indicate whether the result of the folic-acid-excretion test is of help in assessing the prognosis or of value in considering the best method of treatment to adopt, especially in patients with leukaemia or some form of reticulosis. Case 63 had a normal folic-acid excretion and died within three months. Case 87 had a very abnormal excretion, but is alive and well following *x*-ray therapy.

Summary

A test dose of 5 mg. of folic acid was given subcutaneously to 148 patients. The urinary excretion of folic acid usually exceeds 30% of the test dose, and an excretion of less than 1.5 mg. is recorded as a "positive" test.

The test may be positive in megaloblastic anaemia, but there is no evidence that anaemia in itself gives a diminished excretion.

Where renal function is good and the patient does not suffer from megaloblastic anaemia, intestinal malabsorption, generalized oedema, a large effusion, or severe infection of long duration, a positive test is likely to indicate the presence of advanced malignant disease. It is, however, possible to have advanced malignancy with a negative folic-acid test.

This work was made possible by the kind co-operation of many physicians, surgeons, and nursing sisters in numerous hospitals in Edinburgh and district. I wish to thank them, Mr. Robert Brown, for performing many of the assays, and Professor L. S. P. Davidson for helpful advice. Financial assistance was obtained from the John Risk Bequest. Dr. A. T. Mennie, of Lederle Laboratories Div., Cyanamid Products Ltd., kindly supplied the folvite.

References

Bethell, F. H., Meyers, M. C., Andrews, G. A., Swendseid, M. E., Bird, O. D., and Brown, R. A. (1947). *J. Lab. clin. Med.*, **32**, 3.

Girdwood, R. H. (1951). *Edinb. med. J.*, **58**, 309.

—— (1952a). *Blood*, **7**, 77.

—— (1952b). *Biochem. J.*, **52**, xxvii.

—— (1953). *Lancet*, **2**, 53.

Sauberlich, H. E., and Baumann, C. A. (1948). *J. biol. Chem.*, **176**, 165.

Swendseid, M. E., Swanson, A. L., Meyers, M. C., and Bethell, F. H. (1952). *Blood*, **7**, 307.

Teply, L. J., and Elvehjem, C. A. (1945). *J. biol. Chem.*, **157**, 303.

THE PREVALENCE OF FOOT DEFECTS AMONG WARTIME RECRUITS

BY

D. HEWITT, M.A.

A. M. STEWART, M.D., F.R.C.P.

AND

J. W. WEBB, M.B., D.P.H., D.I.H.

(Institute of Social Medicine, Oxford)

There is a general, if unconfirmed, impression that foot defects are common, painful, and incapacitating enough to justify more attention than they have hitherto received from epidemiologists. A recent survey in Luton has indicated the number of persons who themselves complain of foot trouble (Dykes, Grundy, and Lee, 1952), but assessments of incidence based on clinical observations are mainly confined to children (Emslie, 1939; Wilkins, 1941), young women (Alford and Gorrie, 1952), and aged persons (Sheldon, 1948). In the present investigation the registers of Civilian Medical Boards, which are more fully described elsewhere (Martin, 1949; Clements and Pickett, 1952) have been used to obtain an estimate of the prevalence of foot defects in men of working age and, where possible, to identify predisposing factors.

The registers used in the present survey relate to men who were called up in 1941 and examined in Leicester. According to the official instructions circulated to the Medical Boards, "special attention should always be drawn to the defects which may cause a man to be classified in one of the lower grades of fitness for military service, or which may influence decision on possible claims for pension in the future: these should be described as in a clinical report." The instructions stress the importance of recording all types of foot defect and state that a detailed examination of the feet may be omitted only if a man is so severely disabled in other respects as to be totally unfit for military service. There were 358 such cases in the Leicester records. After the exclusion of these, and of a further 93 over 45 years of age, there remained 22,843 men between the ages of 17 and 44, of whom 3,287 (14.4%) shared 4,160 foot defects.

Age Distribution and Interrelation of Foot Defects

The distribution of foot defects by age and diagnosis is shown in Table I. The two categories of flat-foot distinguish cases in which the arch could be restored by standing on tip-toe (mobile, or A cases), and cases in which the

TABLE I.—*Foot Defects Recorded at Specified Ages: Men Examined at Leicester in 1941*

Defect	Cases per 1,000 Examinees Aged						Total No. of Cases
	17–19	20–24	25–29	30–34	35–39	40–44	
Of longitudinal arch:							
Flat-foot (A cases)	38·9	38·6	36·7	39·0	36·6	45·6	880
,, (B ,,)	8·5	11·6	20·4	24·6	34·8	38·2	502
Pes cavus	5·2	7·9	10·7	11·2	14·4	12·7	233
Of forefoot:							
Hammer-toe ..	20·5	32·5	44·1	48·4	61·9	67·1	1,003
Hallux valgus ..	13·9	15·1	26·0	33·5	40·0	46·9	640
,, rigidus ..	2·3	1·8	7·4	7·3	8·4	6·0	126
Overlapping toes ..	12·0	12·7	17·2	21·1	22·7	20·1	405
Other:							
Callosities	5·0	5·5	10·7	21·1	25·8	26·2	356
Miscellaneous ..	0·8	0·5	0·9	1·0	0·4	0·0	15
No. of examinees ..	4,835	3,786	2,153	5,082	5,496	1,491	22,843