Gas-chromatographic studies of the urinary androgenic steroids were performed and their significance has been considered.

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Nutritional Studies on the Entrants to an Old People's Home, with Particular Reference to Folic-acid Deficiency

A. E. READ,* M.D., F.R.C.P. ; K. R. GOUGH,† M.D., M.R.C.P. ; J. L. PARDOE,‡ M.B., B.CH. ;
ANNE NICHOLAS§

Since the introduction of reliable techniques for the detection of deficiency of folic acid there has been a gradual recognition that certain patients develop nutritional deficiency of this substance, with resultant megaloblastic anaemia. Most observers had previously felt that folic-acid deficiency was not common in well-nourished communities such as ours, and that it was confined to patients who could not absorb folic acid, who showed increased metabolic demands for folic acid, or who were taking drugs which interfered with its action. Nutritional deficiency causing a megaloblastic anaemia has been recognized in this country in middle-aged women (Gough *et al.*, 1963) and in other patients (Forshaw *et al.*, 1964). It seemed reasonable to suppose that the elderly might be particularly prone to develop nutritional deficiency of this substance, because of diminished financial resources, reduced mobility interfering with shopping, and apathy over food consequent upon old age and loneliness. It was therefore decided to survey a group of elderly subjects entering an old people's home which was run by the Welfare Committee of Bristol Corporation. The survey was

conducted during 1962–3, when 51 patients were seen. These were compared with a similar group of aged control subjects who were without apparent evidence of underlying disease. These patients were in the National Health practice of one of us (J. L. P.), and all volunteered for the study. The practice in question contains a fairly high percentage of retired elderly middle-class patients.

Patients Studied

Fifty-one consecutive patients were seen on arrival at the municipal home. Their ages ranged from 59 to 95, and 45 were 70 years and over. There were 17 men and 34 women. Two patients over 70 years old were uncertain of their exact age. A full clinical examination of the patients was performed, including a rectal examination. The weight was recorded and portable chest radiographs were also taken. An inquiry into each patient's financial, social, and nutritional background was made. If clinical and radiological examination showed no evidence of organic disease likely to cause folic-acid deficiency, the following tests were performed.

1. After 15 g. of oral L-histidine the urine was examined for formiminoglutamic acid (Figlu), using electrophoresis on cellulose acetate (Kohn *et al.*, 1961). Excretion of Figlu was estimated by

* Physician and Reader in Medicine, Department of Medicine, University of Bristol at Bristol Royal Infirmary.
† Lecturer in Medicine, Department of Medicine, University of Bristol at Bristol Royal Infirmary.
‡ General Practitioner, Portishead, Somerset.
§ Dietitian, Department of Medicine, University of Bristol at Bristol Royal Infirmary.

visual inspection of spots and expressed at 0, +, + +, or + + +.
A + + + spots represents excretion of >500 μg./ml. of urine.

2. Haemoglobin, packed cell volume, and white-cell count were
measured (Dacie, 1956).

3. Serum vitamin-B₁₂ levels were estimated microbiologically,
Lactobacillus leichmannii (normal 140–900 μμg./ml.) being used.

4. Serum folate levels were estimated microbiologically, *L. casei*
(normal level 5.9–21 mμg./ml.) being used.

5. In some patients vitamin-C levels were estimated by the method
of Roe and Kuether (1943) but using the buffy coat of blood
samples. This estimation correlates well with clinical evidence of
deficiency.

6. In certain patients folic-acid-clearance tests were performed as
described by Chanarin *et al.* (1958).

7. Dietary intake of folic acid, ascorbic acid, iron, vitamin B₁₂,
protein, and total calories of patients and control subjects was
assessed, and figures for these were calculated (McCance and
Widdowson, 1960).

These procedures having been carried out, the patients were
not seen for a further six months, when clinical examination,
reweighing, and special tests were repeated. Patients who had
died or obviously deteriorated during this period of time or who
were ill were excluded from the series in order that changes in
nutrition could be attributed to the duration of stay at the
home. There were five deaths, and four other patients were
clearly deteriorating—two from unknown causes and two with
neoplastic disease. There were also two discharges, so that after
initial acceptance 11 patients could not be further studied for
these reasons.

Clinical Examination.—Of the 51 patients initially examined
clinical evidence of anaemia was confirmed in six, the haemo-
globin in each case being 70% or less. These patients were
excluded from the survey, as they had an established anaemia of
some degree on arrival at the home. Of these six patients the
anaemia was due to iron-deficiency following gastrectomy in
two, to undiagnosed pernicious anaemia in two, to rheumatoid
arthritis in one, and to nutritional folic-acid deficiency in one
(this case is separately reported below). Fifteen patients
were described as " wasted " (weight <7 stone ; 44.5 kg.),
and eight were mentally confused. Apart from wasting,
mental confusion, and senility, the condition of all the other
patients was considered to be fair, though some had condi-
tions common in the elderly, such as Parkinsonism, Paget's
disease, and mild congestive heart failure, and three patients
had an atrophic sore tongue—two of the latter had megalo-
blastic anaemia (one had pernicious amaemia and one was
folic-acid-deficient), the third had a low serum folate and
excreted a marked excess of Figlu. With the previous 11
exclusions and the six associated with anaemia, 17 were there-
fore excluded, so that 34 patients could be followed.

Social Aspects.—It must be obvious that the entrants to a
municipal home are likely to be those without friends or
relatives or whose presence could not be further tolerated by
their families. Many of our patients lived alone or with aged
relatives who were equally unable to look after themselves.
Death or illness of a partner or relative was a common cause
for admission. Confirmatory evidence of poor living condi-
tions and of a disinclination to look after themselves was
apparent in our patients. They rarely went out and personal
hygiene was often poor. The majority were existing on an old-
age pension alone (£2 14s. a week), only 10% had applied for
National Assistance, and only two had a pension from other
sources.

Results

Haemoglobin Levels

Haemoglobin levels (Fig. 1) in the patients (excluding the six
who had clinical anaemia) are contrasted with those in our
control subjects. It will be seen that, even allowing for ex-
clusion of these six patients, there is a significant reduction of

haemoglobin levels in the remainder, so that eight others
(three men and five women) had haemoglobin levels less than
80%. The differences between male patients and controls is
significant (t=5.59 ; P<0.0001), but there is no significant
difference between female patients and controls.

After at least six months' stay in the home eight of the
patients (34) considered suitable for inclusion in the survey
showed a rise in haemoglobin (>5%) (five without iron
therapy). In six of the eight patients the initial values were
less than 80%. In two patients haemoglobin levels remained
unchanged (less than 80%). In three patients with normal
haemoglobin levels on admission there was a fall to less than
80% after six months—one of these having developed a bleed-
ing gastric carcinoma, and two others developing anaemia
without apparent cause. These three subjects were excluded
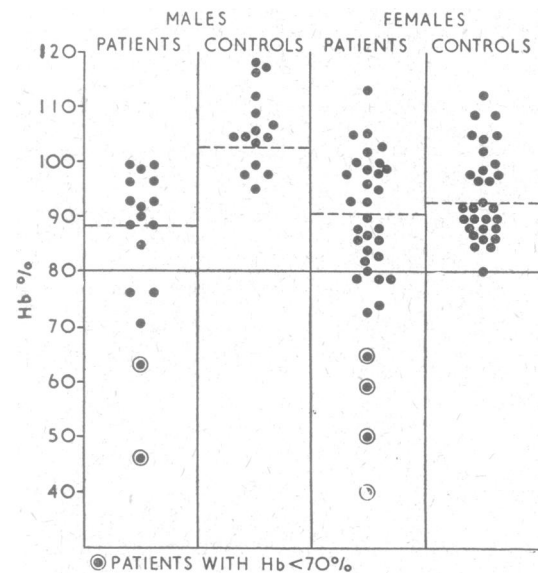from the follow-up series.

FIG. 1.—Haemoglobin levels in patients and controls. Dotted lines
indicate mean values.

Serum Folate Levels

In 50 of the 51 patients folate levels (Fig. 2) were measured
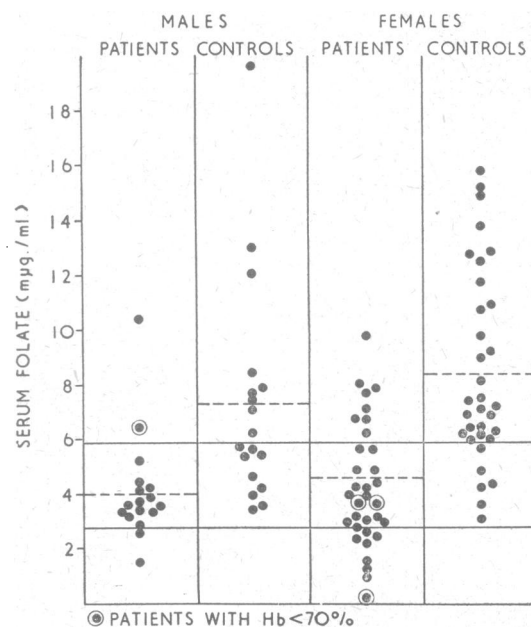and were found to be below 6 mμg. in 40 and below 3 mμg. in

FIG. 2.—Serum folate levels in patients and controls. Dotted lines
indicate mean values.

10. Only 10 patients had levels in the accepted normal range (6–21 mμg./ml.). In the six excluded anaemic patients folate levels ranged from 0.1 to 6.5 mμg., the lowest being in a patient with nutritional folic-acid deficiency, whose case is recorded below. Of the 10 patients with folate levels below 3 mμg. all but two had normal haemoglobin levels. No control subjects had folate levels less than 3 mμg., but in 15 controls the level ranged from 3 to 6 mμg./ml. There was a significantly lower serum folate level in both male and female patients compared with the controls (males t=2.91, P<0.01 ; female t=5.26, P<0.001). There was also a significantly greater scatter of folate values in controls·than in patients.

After a stay in the home there was a rise of serum folate levels in only seven of the 23 patients with subnormal levels who could be followed ; in each case the level rose to normal (>6 mμg./ml.). In none of the eight patients with very low levels did a rise to the normal level occur. It is significant that two patients with very low folate levels were clearly deteriorating when seen on the second occasion and had already been excluded from the follow-up.

Figlu Excretion

Figlu excretion (Fig. 3) after histidine-loading was satisfactorily completed in 50 patients, and in 31 of them the amounts excreted were in excess. Four of six excluded patients with severe anaemia excreted Figlu. Of the remaining 25 seven of eight with a + + + Figlu excretion had folate levels below 6 mμg./ml. There was, however, no close relation between less marked Figlu excretion and serum folate levels—positive Figlu excretion (+ or ++) occurring in three patients with normal folate levels, and negative Figlu excretion occurring in 12 patients with serum folate levels less than 6 mμg./ml. Fifteen control subjects excreted Figlu, only one showing a greater than (+) excretion.
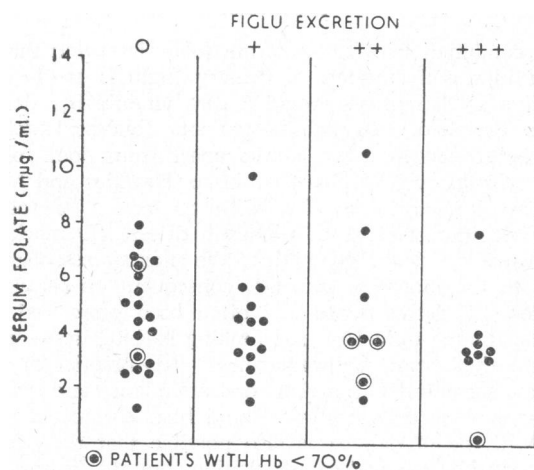

FIG. 3.—Figlu excretion in relation to serum folate levels in 50 patients.

Figlu excretion returned to normal in 17 of the 23 patients who were followed for six months ; it remained elevated and unchanged in four and increased in two others. Eight patients excreting excess Figlu died, deteriorated, or were discharged.

Of the 17 patients whose Figlu excretion decreased there was an increase in serum folate level of 1 mμg. or more in eight, in six it was unchanged (three of these six having levels in normal range), and in three it fell. In the three patients whose folate level fell despite the disappearance of Figlu, there was no apparent clinical change or deterioration. Only four patients excreted more Figlu after a six-month stay in the home than they did on admission, and in two of these the folate level was still low (3.0 and 4.1 mμg.) on re-estimation. In the third the folate level was normal and remained un-

changed. The fourth patient had a very low serum folate level (1.4 mμg./ml.) which remained unchanged, the patient dying shortly after the second examination.

Vitamin-B$_{12}$ Levels

Vitamin-B$_{12}$ levels were measured in 48 patients. There was no significant difference between serum vitamin-B$_{12}$ levels in male patients and controls, but some difference was seen in the female patients and female controls, the patients having a lower level (t=3.33, P<0.005). Two female patients with pernicious anaemia were not included in these results, but five other patients, four of them females, had levels less than 140 $\mu\mu$./ml. None of these five patients was anaemic.

Vitamin-C Levels

In eight patients vitamin-C levels ranged from 6.3 to 14.7 mg./100 g. (Table I). In each of these the serum folate was less than 6 mμg., and four of them excreted Figlu (+ or ++). There was no clinical evidence of scurvy. Vitamin-C levels were remeasured in the eight patients after a six-month stay in the home, and in all but one of the seven with the lowest levels it increased, the increase ranging from 1.1 to 8.4 mg./100 g. These patients were all apparently well. A rise in vitamin-C level was not seen in one patient with a low level, who was obviously deteriorating (Case 5, Table 1), and in the patient with the highest level (Case 8).

TABLE I

No.	1st Vit. C (mg./100 g.)	2nd Vit. C	Serum Folic-acid Level (mμg./ml.)	Folic-acid Clearance	
				3 min.	30 min.
1	9·2	13	4·5	—	—
2	6·3	10	3·4	160	30
3	7·0	9·9	5·1	—	—
4	9·1	14·3	5·4	142	47·7
5	7·1	7·2	4·3	—	—
6	9·6	18	3·8	108	82
7	6·6	7·7	4·1	96	21
8	14·7	14·0	4·4	115	29

Folic-Acid Clearance

Folate clearance tests (Table I) were performed in five patients. In all of these the initial serum folate levels were between 3.4 and 5.4 mμg./ml., and only one patient was excreting Figlu. In each case the 3-minute and the 30-minute figures were in the normal range.

Diet and Weight

At the best a dietary history can give only a rough indication of nutritional status, and in the elderly patient further inaccuracies must arise. However, by including patients who could give a reasonable account of their food intake, and excluding those who were ill, confused, or forgetful, some useful information was obtained.

Dietary histories were obtained from 31 entrants to the home and from 35 elderly controls (>70 years of age). It will be seen (Table II) that there was a significant difference between these groups with respect to folic-acid, iron, protein, and total calorie intake.

With respect to total calories, six patients (two males and four females) were existing on diets containing less than 1,000 calories a day, and a further six (two males and four females) were taking between 1,000 and 1,200 calories a day. Only one of our controls was having less than 1,200 calories. Certain points concerning diets of individual patients are worthy of

note, as they indicate the type of problem encountered. Thus one elderly woman fed her cats on more expensive fish than she bought for herself, while an elderly man begged scraps from his neighbours and yet kept and fed 13 cats in a filthy squalid flat. Other patients living with their children declared that they existed on scraps left over after their grandchildren had eaten, though these accusations may have been due to paranoid delusions. On the credit side several elderly men were keen gardeners and produced a constant supply of fresh vegetables.

TABLE II.—*Dietary Intake*

		Males		Females	
		Patients (11)	Controls (11)	Patients (20)	Controls (24)
Folic acid (μg./day)	{ Mean	31·3	52·6	33·2	52·7
	{ S.D. ..	± 18·5	± 7·5	± 3·5	± 11·9
		t = 3·53.	P < 0·01	t = 5·10.	P < 0·001
Ascorbic acid (mg./day)	{ Mean log value	1·308	1·378	1·146	1·372
	{ S.D. ..	± 0·225	± 0·221	± 0·271	± 0·151
		t = 0·73.	P = Not sig.	t = 3·32.	P < 0·01
Iron (mg./day)	{ Mean	6·38	9·33	6·64	9·10
	{ S.D. ..	± 2·51	± 2·31	± 2·64	± 0·151
		t = 2·87	P < 0·01	t = 3·09.	P < 0·01
Protein (g./day)	{ Mean log value	1·643	1·865	1·630	1·785
	{ S.D. ..	± 0·164	± 0·063	± 0·147	± 0·089
		t = 4·18.	P < 0·001	t = 4·39.	P < 0·001
Calories/day	{ Mean	1,295	2,234	1,357	1,867
	{ S.D. ..	± 364	± 441	± 419	± 341
		t = 5·45.	P < 0·001	t = 4·45.	P < 0·001

* Log values have been used in respect of ascorbic acid and protein in order to normalize the distribution.

The diet given to the inmates at the home was analysed ; it will be seen that with moderate helpings a diet containing adequate intake of the various foodstuffs (Table III) was provided. Further, it is likely that additions bought from pocket-money or given by visiting relatives were made. A rough note of each patient's food intake was provided by the staff when the patient attended the second clinical examination, and all but seven were found to be eating well. This accorded well with the gain in weight commonly noted. Of the 34 subjects who were followed, a gain in weight of >4 lb. (1.8 kg.) (and not due to fluid retention) occurred in 20, and in seven (Fig. 4) this was 10 lb. (4.5 kg.) or over. Only five patients lost weight—four less than 4 lb. (1.8 kg.), though loss of weight was common in those deteriorating and not included in the survey.

TABLE III.—*Calculated Average Daily Dietary Intake of Patients Over a Four-week Period*

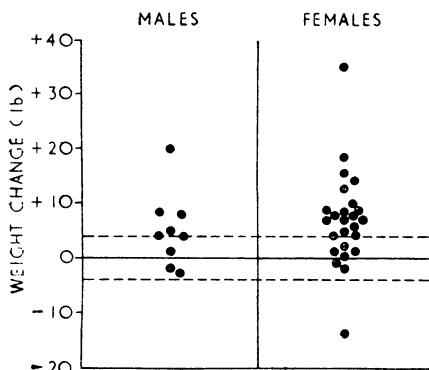|	Average Daily Intake					
	As. Acid mg.	B₁₂ μg.	Folic Acid μg.	Fe mg.	Protein g.	Total Cals.
Week I	13	2·9	46·3	5·3	52·3	1,659
Week II	19	5·7	62·9	12·2	52·6	1,579
Week III	12	2·9	46·3	5·8	52·2	1,707
Week IV	11	2·9	44·8	5·7	50·6	1,627
Average	13·75	3·8	50·75	7·25	51·9	1,643

FIG. 4.— Weight change in patients after six months' institutional care.

Report of Case of Megaloblastic Anaemia Due to Nutritional Deficiency of Folic Acid

An 82-year-old spinster was first seen in May 1962 during the routine survey of new admissions to the local authority home. She had been living with her 84-year-old sister under very poor conditions, and admission to the home had been arranged at the request of the general practitioner. She was mentally confused and it was impossible to obtain an accurate dietary history, although the diet had consisted mainly of bread-and-butter, biscuits, and tea. She denied symptoms of any sort when first seen, and during the first few days of admission had a very poor appetite, and refused most of the cooked food offered to her. She was incontinent of urine and faeces. She was seen two days after admission and transferred to the Bristol Royal Infirmary.

On examination she was frail, with obvious malnutrition, anaemia, and senile purpura. There was marked papillary atrophy of the tongue. The nails were thin and flattened. Oedema of the ankles was present. There were no other abnormal physical findings.

Investigations.—Haemoglobin 30% (4.5 g./100 ml.) ; P.C.V. 14% ; M.C.H.C. 32%. Blood film: the red cells showed anisocytosis with many macrocytes ; the polymorphs showed a right shift, and platelets were scanty. Bone-marrow examination revealed fully developed megaloblastic changes. Serum iron 106 μg./100 ml., serum vitamin B₁₂ (initial) 50 μμg./ml., serum folate 0.1 mμg./ml. Urinary excretion of Figlu (+ + +). Jejunal biopsy normal. Dietary history: estimated daily intake of folic acid 20 μg.

Progress.—She was given physiological doses of folic acid (50 μg./day). A reticulocyte peak of 15% was reached on the 12th day of treatment. The haemoglobin level rose to 70% by the time she was discharged back to the local authority home. The serum level of vitamin B₁₂ also rose to 160 μμg./ml. on the folic-acid therapy alone. As her deficiency of folic acid was gradually corrected she became less confused and also began to take the hospital diet with relish. When last seen, three months after her return to the home, she had gained a stone (6.4 kg.) in weight and was reported to be in good spirits and eating well.

Discussion

The combination of a low serum folate level and the excretion of increased amounts of urinary Figlu is good evidence of folic-acid deficiency, provided that vitamin-B₁₂ deficiency can be excluded. In elderly patients folic-acid deficiency could be related to other factors apart from poor folic-acid intake. Drugs such as phenobarbitone (Hawkins and Meynell, 1958) are known to interfere with the action of folic-acid, and, more important still, neoplastic disease (Dymock, 1964) could cause deficiency due both to the anorexia associated with it and to the increased demands consequent on cellular proliferation. Sedative drugs had often been prescribed in our patients, though only 10% were taking barbiturates—the common sedatives being phenothiazines. Our practice of reviewing cases six months after their first attendance and discarding those who were deteriorating should have eliminated most of those with neoplasia. It is also possible that the occasional patient could have had malabsorption, but this is rare in the elderly and likely to have been detected by clinical examination.

Allowing for these possibilities, it seemed that there was evidence of folic-acid deficiency, as judged by the serum folate level (serum level of folate <6 mμg.) in 40 (80%) of the 51 patients, and even if we exclude the six patients who were grossly anaemic the proportion with low levels is still 67%. That this is an unduly high figure is suggested by the fact that the control elderly subjects, as judged by serum folate levels, also showed deficiency in 15 out of 51 subjects—that is, in 30% the levels were <6 mμg./ml. This figure is in excess of that quoted for a series of normal patients in a younger age group, in whom 19% of females and 10% of males showed similar low figures (Gough et al., 1964). It is thus possible that the serum folate level normally falls with old age, a response perhaps to a normal fall in intake and possibly reduced demands consequent upon slower cellular activity. Equally it may mean

that the normal control range quoted by Waters and Mollin (1961) is unduly high. The normal folate clearance might be cited in favour of this, though it is possible that it merely means that deficiency, though present, was not severe. Whatever the explanation, the difference between controls and patients is still statistically significant.

Very low folate levels (<3 μg./ml.) were seen in nine patients and in none of the controls. The excretion of Figlu in excess amounts after histidine-loading is supporting evidence of deficiency, and this occurred in 31 (62%) of 50 patients, though the relationship to the serum folate level was not a precise one. Four patients excreted Figlu with a normal serum folate level, but 25 others excreting Figlu had low folate levels. It is perhaps of interest at this point to note the frequent finding of a very low folate level (<3 mμg./ml.) and increased Figlu excretion in patients with a normal haemoglobin and apparently normal red-cell morphology. In this range megaloblastic changes are normally seen. It is, however, possible that bone-marrow examination would have shown some evidence of megaloblastic erythropoiesis. Vitamin-B_{12} deficiency was not an important factor in producing evidence of folic-acid deficiency, as there were only two patients with pernicious anaemia in this group, both of whom were excluded, though five other patients had low vitamin-B_{12} levels without megaloblastic change or anaemia.

It seems justifiable to attribute folic-acid deficiency in most of these patients to poor nutritional intake. Support for this comes from the poor diet that they were taking prior to admission. A significant dietary deficiency of folic acid, iron, protein, and total calories was present when compared with a similar group of control patients. Ascorbic acid intake was only significantly different in female patients, so that it is unlikely that this factor was a major one in determining the availability of folic acid in the tissues. A further factor in support of a dietary deficiency of folic acid and other substances comes from the beneficial effects of taking the diet available in the home, which was apparently of sufficient calorie and folic-acid content to reduce urinary Figlu excretion in 17 out of 23 patients, and to produce an increase in weight in a similar number.

The diet as supplied and calculated gives an adequate intake of calories for the generally low daily activities of an elderly patient in a supervised home. This allows for the fact that a reduction of 25% of intake below that for a young adult is assumed (2,200 and 1,800 calories a day are accepted as the energy requirements for ordinary living, excluding any form of work, of an adult male and female) (B.M.A. Report of the Committee on Nutrition, 1950). The dietary intake of protein and folic acid is also adequate, allowing for a similar reduction of intake in the elderly. The vitamin-C allowance, according to calculations and without supplements, however, is probably only just sufficient, although the serum levels of some patients studied rose with the stay in the home. The dietary folate intake supplied did not cause a rise in the serum folate level. Nor presumably would it have been possible to increase serum folate levels on such a diet without supplements of folic acid. For example, a 25% increase in total dietary intake (which most elderly people would find excessive) would apparently have increased the intake of dietary folic acid by only about 12 μg.

A factor of importance not taken into account could be the varying availability of foodstuffs containing folic acid throughout the year. It is likely that serum folate levels vary according to dietary intake, and winter levels, when fresh green vegetables are not so freely available, may be considerably below those found in the summer months. This may have explained the failure of folic-acid levels to rise in some patients, because comparisons were made between admission levels during the summer and follow-up figures in the winter. A similar factor could explain the failure of vitamin-C levels to rise significantly in all patients studied. Foodstuffs con-

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taining folic acid are largely those which contain vitamin C, and megaloblastic anaemia responding to folic acid can occur in scurvy (Zalusky and Herbert, 1961). Vitamin-C levels were low in our patients, and levels rose, though not to normal values, after a six-month stay in the home.

If we accept malnutrition as the factor responsible for folic-acid deficiency then the basic cause is simply the poor financial state, loneliness, apathy, and inability to obtain fresh vegetables because of infirmity so common in the elderly patient. Of these factors apathy seems of some importance, as it was striking how often elderly patients improved—starting to eat and putting on weight—once the misery of living alone or in an unwanted atmosphere was left behind. Unfavourable comments are often made about homes run by municipal authorities, but many elderly patients are far better looked after than they had been before admission. Further, the home that we studied was a large one (total patients 560) —in fact, a modernized "workhouse"—and it is likely that even better results could be obtained in the smaller municipal houses now being provided.

The implications of these studies are obvious. Everyone concerned with the welfare of elderly people is fully aware that attention to their plight is a most important and urgent matter. We have directed our investigations at only one facet of malnutrition in these patients—namely, folic-acid deficiency—and it is highly probable that other deficiencies exist, such as hypoproteinaemia and metabolic bone disease (Gough et al., 1964). The value of full clinical and haematological examination of all entrants to old people's homes is also clear, though the general practitioners responsible for care in this home would have found it impossible to deal with the extra work involved, since care of the inmates formed but a small part of their practices. Also, routine pathological investigations could not be made without reference to the hospital services. The problem is one of some magnitude, for there are 1,000 patients in homes for the elderly in Bristol alone.

Conclusions

It seems likely that regular vitamin supplements would be of value to the elderly person living alone. As regards folic acid, dosage should be in the "physiological" range (25–50 μg./day) as otherwise precipitation of neuropathy in patients with vitamin-B_{12} deficiency could occur. There were in fact two patients in our series with undiagnosed pernicious anaemia, and five others had low levels and could have been latent examples of the disease.

The difficulties to be met in trying to get the elderly subject to take vitamin supplements would be considerable (though easier in a municipal home, where the need for such therapy seems less). Though it may be questioned what harmful effects low levels of folate and increased values for Figlu excretion have, the fact that progression to severe megaloblastic anaemia can occur is well illustrated in Case 1; and, of course, many examples of nutritional deficiency of this type have been recorded in other groups of patients. It seems, however, that folate levels are a useful measure of malnutrition in subjects on a mixed animal and vegetable diet, as in this country, and serve to focus attention on generalized malnutrition, which, to some degree, is so common in many elderly patients.

Summary

Of 51 patients admitted to an old people's home and followed for six months folic-acid deficiency as judged by a low serum folate level was present in 40 (80%) and in 34 (67%) of those without severe anaemia (Hb<70%). Folate levels failed to rise with the diet provided, but Figlu excretion, previously increased in 31 of 50 patients (62%), was returned to normal in 17 of 23 patients followed. Vitamin-C levels rose but not to normal,

and all except 5 patients gained weight. The patients showed greater frequency of folic-acid deficiency than a group of aged control subjects, and their diets contained, prior to admission to the home, less folic acid, iron, protein, and total calories. The implications of these studies are discussed.

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Physiological and Clinical Assessment of the Effect of the Musculotropic Agent Mebeverine on the Human Colon

A. M. CONNELL,* B.SC., M.R.C.P.ED.

It is possible to achieve smooth muscle spasmolysis by two methods which are pharmacologically distinct. Anticholinergic drugs, such as belladonna, act by blocking cholinergic fibres, while other preparations, such as papaverine, have a direct effect on smooth muscle. Anticholinergic preparations have been widely used as smooth-muscle relaxants. Success in this respect has been limited on account of their widespread effect through the organism. In order to achieve a therapeutic result at one site it is usually necessary to administer doses likely to produce effects elsewhere in the body, with resulting undesirable side-effects. On the other hand, a direct musculotropic drug such as papaverine does not have these effects (Goodman and Gilman, 1955). Unfortunately, papaverine has not been shown to be effective in the treatment of bowel disorders. Kralt *et al.* (1960) showed that in animals phenylethylamine derivatives of resperine had little or none of the central nervous effect of the parent compound but did have strong papaverine-like spasmolytic effects with less marked atropine-like effects. One of these compounds, Mebeverine,† has been shown to have virtually no atropine-like action as tested by the lacrimation response, the sialogic response, and the inhibition of gastric secretion in cats. Dose for dose it was three times as potent as papaverine in inhibiting the peristaltic reflex of the guinea-pig ileum and 20 to 40 times more powerful in inhibiting the sphincter of Oddi (Lindner *et al.*, 1963). The pharmacological properties of this compound have been extensively studied by Lindner *et al.* (1963), who have shown it to be remarkably free of untoward effects. In man no atropine-like effects could be established.

This paper assesses Mebeverine physiologically with regard to its affect on the motility of the colon and small intestine in man and clinically by a double-blind controlled trial of its effect on the irritable colon syndrome.

1. Effect on Motility of Colon and Small Intestine in Man

The patients were studied using either miniature balloons or a pressure-sensitive radio telemetering device of high sensitivity. The tubes were inserted into the colon through a sigmoidoscope, which was then withdrawn, and manoeuvred until the miniature

balloons lay at approximately 25, 20, and 15 cm. from the anus respectively. Subsequently the patient was allowed to rest for at least 30 minutes before a recording was begun. Full details of the method and procedure have been described elsewhere (Connell, 1961). This method was used to study the pelvic colon.

The pressures in the small intestine and the proximal colon were studied, using a miniature ingestable radio transmitter whose frequency of oscillation is altered by external pressure. These changes are detected by an external aerial and receiver system and displayed on a suitable recorder (Connell and Rowlands, 1960). Full details of the technique and its application to the study of the small intestine and ascending colon have been described elsewhere (Connell *et al.*, 1963).

Subjects and Procedure

The effect of Mebeverine on the sigmoid colon was studied during the course of routine motility studies in patients suffering from the irritable colon syndrome. In 10 patients Mebeverine was administered by a slow intravenous injection of 50 mg., and in one by an intramuscular injection of 75 mg. The effect of a slow intravenous injection of 50 mg. was tested in the small intestine (ileum) in two normal subjects and on the caecum in two subjects, one normal and one suffering from the Zollinger-Ellison syndrome. In all cases a basal recording lasting from 30 minutes to one hour was obtained, after which the patient received a control injection of intravenous saline. Thirty minutes later the Mebeverine was given and the recording continued for at least 30 minutes. Records were analysed over the 15-minute period following the control injection and the 15-minute period following the injection of Mebeverine. This analysis was made in respect of (1) the percentage of the term of analysis in which activity was present (percentage

* Institute of Clinical Science (Department of Surgery), Queen's University, Belfast. Lately Member of the Scientific Staff, Medical Research Council, Gastroenterology Research Unit, Central Middlesex Hospital.
† Not yet available in the United Kingdom, but is marketed in certain European countries.