response observed with yeast. This leads me to think that there may be a Wills's factor after all, despite the modern tendency to explain the action of yeast in terms of folic-acid conjugates. It is true that folic-acid conjugase inhibitors make microbiological assay of yeast difficult. This difficulty does not apply to assays in the rat which were used as a check in this instance.

I should like to thank my colleagues: Dr R. B. Thompson who has been responsible for marrow cultures, Dr W. Walker, who followed the survival of transfused erythrocytes, Dr L. W. Carstairs for intubation of the small intestine. In addition I should like to thank the medical, nursing and lay staff of the Hospital and Medical School and many general practitioners for their co-operation. Dr E. Lester Smith supplied the whole of the vitamin B_{12} used in this investigation and Dr W. F. J. Cuthbertson was responsible for microbiological assays. I should like to thank both these members of the Research Division of Glaxo Laboratories Ltd. for their co-operation, and Glaxo Laboratories for a research grant made to King's College which provides for the Research Fellowship now held by Dr R. B. Thompson.

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The Place of Diet in the Treatment of the Sprue Syndrome

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Clinical aspects of the sprue syndrome

In preparing this talk, I have been conscious of the fact that it has to be presented to a somewhat mixed audience, possibly including some who are uncertain as to what is meant by 'sprue'. For this reason, it is perhaps better first to say a few words about what is meant by this term.

My own clinical interest in the subject has been based on cases that I have seen in recent years in Britain, in India and Burma, and in the United States of America, but

I must confess that, like most workers on the sprue syndrome at the present juncture, I have not been carrying out carefully controlled experiments on various dietetic modifications.

Sprue is a syndrome that occurs in adults in this and other temperate countries, where it is known as idiopathic steatorrhoea. It also occurs in the tropics, or in Europeans returning from tropical countries, and it is then known as tropical sprue. Something similar, seen in infants, is known as coeliac disease, and some of the patients with idiopathic steatorrhoea have had coeliac disease in childhood. The chief features of the sprue syndrome are fatty diarrhoea, loss of weight, anaemia which is frequently associated with a megaloblastic marrow as in pernicious anaemia, and evidences of deficiency of vitamins and other nutrients such as calcium. In coeliac disease the anaemia is usually of the iron-deficiency type. The clinical features can be explained by malabsorption of various dietary factors including fats, haemopoietic factors, and vitamins. The primary cause of this malabsorption is unknown, but Frazer (1949) who has summarized the various views, himself believes that the main feature is defective absorption of particles of fat which he believes can normally be absorbed, in part, as neutral fat. If the illness is prolonged, it is said that atrophic changes may be seen in the mucous membrane of the small intestine, but our knowledge about this is incomplete. Sometimes the diagnosis of sprue is wrongly made in patients suffering from other diseases such as intestinal tuberculosis.

Dietetic treatment

Until 1947 the main plank in the treatment of sprue in its various forms was dietetic, and this was supplemented by injections of liver extract. The diets used in recent years have been based on those published by Fairley (1930), and most experiments with the dietetic treatment of sprue since then have been concerned with various modifications of Fairley's diets, or others of a similar nature. The sprue patient is unable to deal adequately with fats and, to a lesser degree, with carbohydrate, and so the obvious thing to do is to restrict these and, in the acute stage, when diarrhoea is severe, to give only a small total quantity of food. Accordingly, Fairley produced a series of five graduated diets, the caloric value of which varied from 770 to 3020 Cal. The ratio protein:fat:carbohydrate in the first two diets is 1·0:0·3:1·1, and in the third and fourth the carbohydrate is raised to 1·3. Protein is best supplied as lean rump steak, very carefully prepared without skin, fat or gristle, and lightly cooked. A modification that I have tried and found successful under the conditions encountered is one where the lean meat was replaced by skim milk. Diets of this type are described in the Army Manual on Diseases of the Tropical and Sub-Tropical Areas (Anonymous, 1946). In this connexion, following the work of Fairley (1932), a special high-protein milk powder, known as Sprulac (Cow and Gate Ltd., Guildford), was produced commercially for the treatment of sprue. We have not adhered strictly to such diets here, but have suited the feeding to the symptoms. If the symptoms are very marked, restrictions must be severe but, in the average case, an initial diet supplying 1600–1800 Cal. is usually satisfactory. In the period of convalescence, and for some time after, suitable convalescent feeding will be required. The main basis is that overdone meats, fats, fried

foods, milk, cream, butter and starchy foods are eliminated or severely restricted. In some patients the limitation has to be continued; we have found that the main thing is to suit the diet to the individual, who has to avoid those substances causing symptoms such as diarrhoea or flatulence. The diet has frequently to be supplemented by vitamins, calcium, and, in the past, by liver injections. I would emphasize that in our experience here it has rarely been necessary to commence therapy with the rigid Fairley type of diet. An increase of dietary fat does not reduce the percentage of fat absorbed, and we have tended not to adhere to a very severe diet or a very strict one, but to allow the patient to eat fats within the limits of his tolerance. In the past little attention has been paid to the salt content of the sprue diet, but Black (1946), working with tropical-sprue patients in India, showed that they had an abnormal loss of sodium, and to a less extent of chloride, in the faeces. When these patients, who of course were in the tropics, were given 15 g. daily of salt in the diet, sodium and chloride were retained, the signs of dehydration disappeared, and the blood pressure rose. We should therefore make sure that a patient with sprue has sufficient salt in the diet.

In Table 1 there is given an analysis of the response of twelve patients suffering from the sprue syndrome, who were treated with diet, supplemented where noted with liver therapy; one patient died of the illness, despite the measures taken; as regards the others, the immediate response to treatment was good in ten cases, although the haematological response at this stage was poor in all the patients. These patients were seen again at intervals of from 1 to 7 years. Four patients with idiopathic steatorrhoea then showed definite clinical improvement, and three others, one with idiopathic steatorrhoea and two with tropical sprue, had no symptoms or signs and two of them had completely normal blood counts at intervals respectively of 1, 6 and 6 years after they were first treated in the hospital wards. These three patients were then taking normal diet and no other treatment. Only one patient, who was not improving, was adhering to a strict diet, whereas the others were avoiding fats to varying extents.

In general it has been found that idiopathic steatorrhoea is more difficult to treat than tropical sprue. Miller & Barker (1937) have given an account of the response to treatment by diet and liver injections of thirty-three cases of the sprue syndrome; they found that liver therapy was sometimes effective where dieto-therapy failed. However, in their series no patient was able to stop specific treatment completely without having a relapse. Interpretation of response to treatment has to be made with caution because of the cyclical nature of the illness (Keele, 1946).

Pteroylglutamic-acid therapy

Since pteroylglutamic acid (folic acid) was synthesized in 1947, attention has swung largely from diet to the use of this drug in sprue therapy. A paper on this subject has been published from this department (Davidson, Girdwood & Innes, 1947), and it was shown that there was no benefit in coeliac disease, but that there was some control of diarrhoea and clinical improvement in the adults. When the marrow was megaloblastic there was haematological improvement. This was a short-term experiment; what of the long-term view?

The administration of folic acid has been continued for periods of some 1–2 years

Table 1. *Response to dieto-therapy in some patients suffering from sprue*

Case no.	Diagnosis	Sex	Age	Features on admission	Treatment	Immediate response (2 months)	Final response (2 years)	Treatment after discharge
1	Idiopathic steatorrhoea	M.	61	Stools, bulky only Tongue, nil General condition, poor Hb., 9·6 g./100 ml. Rbc., 3·07 M.	Diet, liver injections, proteolysed liver, yeast	Stools, 2 SF* Tongue, nil General improvement Hb., 10·4 g./100 ml. Rbc., 3·01 M.	Constipated Tongue, red General condition, good Hb., 10·7 g./100 ml. Rbc., 4·31 M.	Low-fat diet
2	Idiopathic steatorrhoea	M.	51	Stools, severe diarrhoea Tongue, nil General condition, poor Hb., 13·8 g./100 ml. Rbc., 3·1 M.	Diet, liver injections	(5 weeks) Stools, 2–3 L* Tongue, nil General improvement Hb., 12·3 g./100 ml. Rbc., 3·1 M.	(2½ years) Stools, 3–4 L* Tongue, nil General condition, fair Hb., 12·4 g./100 ml. Rbc., 3·6 M.	Avoids greasy foods
3	Idiopathic steatorrhoea	M.	29	Stools, 2–3 L* Tongue, nil General condition, fair Tetany Hb., 11·4 g./100 ml. Rbc., 5·1 M.	Diet	(3 weeks) Stools, 2 N* Tongue, nil Generally no change No tetany Hb., 10·5 g./100 ml.	(2¼ years) Stools, 2 N* Tongue, nil Generally no change No tetany Hb., 8·3 g./100 ml. Rbc., 4·59 M.	Fairly strict diet for 2 years. Worse since he stopped it
4	Idiopathic steatorrhoea	M.	35	Stools, 2–3 L* Tongue, ulcers General condition, fair Hb., 13·3 g./100 ml.	Diet	(3 weeks) Stools, 1–2 N* Tongue, nil General improvement	(5 years) Stools, 1–2 N* Tongue, nil General condition, good Hb., 12·7 g./100 ml. Rbc., 3·87 M.	Fairly strict diet for 1 year then avoided fats
5	Idiopathic steatorrhoea	M.	53	Stools, 5 L* Tongue, nil General condition, poor Hb., 11·8 g./100 ml. Rbc., 2·48 M.	Diet, liver injections	(5 weeks) Stools, 3 L* Tongue, nil General slight improvement Hb., 10·4 g./100 ml. Rbc., 2·88 M.	(2½ years) Stools, 1–2 L* Tongue, nil General improvement Hb., 10·1 g./100 ml. Rbc., 3·11 M.	Low-fat diet, Sprulac, liver injections, Marmite
6	Idiopathic steatorrhoea (old coeliac disease)	M.	44	Stools, 1–2 SF* Tongue, nil General condition, poor Hb., 12·7 g./100 ml. Rbc., 3·66 M.	Diet, liver injections, proteolysed liver, vitamin C	(6 weeks) Stools, 1–2 SF* Tongue, nil Generally no change Hb., 13·0 g./100 ml. Rbc., 3·65 M.	(1 year) Stools, 2 SF* Tongue, nil General condition, poor Hb., 11·5 g./100 ml. Rbc., 3·01 M.	High-protein, low-fat diet, liver injections

7	Idiopathic steatorrhoea	M.	42	Stools, 8–10 L* Tongue, nil General condition, poor Hb., 9·6 g./100 ml. Rbc., 2·68 M.	Diet, liver injections, riboflavin, ascorbic acid, yeast, nicotinic acid	(6 weeks) Stools, 2–3 L* Tongue, nil General condition, poor Hb., 11·8 g./100 ml. Rbc., 3·37 M.	(2 years) Stools, 3–4 SF* Tongue, nil General condition, poor Hb., 11·8 g./100 ml. Rbc., 3·61 M.	Strict diet, liver injections, vitamins
8	Idiopathic steatorrhoea	F.	55	Stools, 4–5 L* Tongue, glossitis General condition, very poor Hb., 11·0 g./100 ml.	Strict diet, liver injections, casein hydrolysate, vitamins	(5 weeks) Died	—	—
9 (Outpatient)	Idiopathic steatorrhoea	F.	53	Stools, 10 L* Tongue, glossitis General condition, poor Hb., 13·3 g./100 ml. Rbc., 4·46 M.	Normal diet, aneurin	(6 months) Stools, 2 N* Tongue, nil General condition, good Hb., 13·0 g./100 ml. Rbc., 5·0 M.	(1 year) Stools, 1–2 N* Tongue, nil General condition, good Hb., 13·3 g./100 ml. Rbc., 4·52 M.	No treatment
10	Tropical sprue	M.	65	Stools, 1–2 SF* Tongue, nil General condition, good Hb., 9·6 g./100 ml. Rbc., 2·55 M.	Restriction of dietary fats, liver injections	(3 weeks) Stools, 1–2 SF* Tongue, nil General condition, good Hb., 12·1 g./100 ml. Rbc., 3·5 M.	(7 years) Stools, 2–3 SF* Tongue, red General condition, fair Hb., 10·7 g./100 ml. Rbc., 2·68 M.	Slight restriction of dietary fats, liver injections, proteolysed liver
11	Tropical sprue	F.	50	Stools, 5–6 L* Tongue, glossitis General condition, poor Tetany Hb., 11·3 g./100 ml. Rbc., 4·5 M.	Very strict diet, Sprulac	(2 months) Stools, 1–2 SF* Tongue, improvement General condition, improvement Hb., 13·0 g./100 ml.	(6 years) Stools, 1–2 N* Tongue, nil General condition, much improved Hb., 15·1 g./100 ml. Rbc., 4·85 M.	(1) Repeated hospital admissions for 3 years. Strict diet, calcium, vitamins, liver injections (2) Been on normal diet for 3 years, no therapy
12	Tropical sprue	M.	47	Stools, 4–5 L* Tongue, nil General condition, very poor Hb., 9·9 g./100 ml. Rbc., 2·75 M.	Diet, liver injections, blood transfusions, Adexolin	(6 weeks) Stools, 1–2 SF* Tongue, nil General condition, improvement Hb., 13·5 g./100 ml. Rbc., 4·65 M.	(6 years) Stools, 2 N* Tongue, nil General condition, good Hb., 14·5 g./100 ml. Rbc., 4·37 M.	Norma ldiet, avoiding fish

Rbc. red blood cells, M. million.
* Indicates number of stools daily and whether loose (L), semi-formed (SF) or normal (N).

in a series of sprue patients, and the haematological results have been much more satisfactory than those obtained from previous efforts at treatment by diet or by liver injections.

Clinically, as is shown in Table 2, seven out of eleven patients showed clinical improvement, and three did not improve, when pteroylglutamic acid was used. In addition, one tropical-sprue patient became so much worse with folic-acid therapy that she had to discontinue this form of treatment after 7 weeks, whereas one patient with

Table 2. *Clinical response to folic-acid therapy of some cases of sprue*

Case	Diagnosis	Sex	Dosage of folic acid (mg. daily by mouth)	Time of administration	Response			Importance of di during folic-aci treatment
					General	Stools*	Tongue	
A	I.S.	M.	10	1 year†	Not improved	2 N→1 SF	Normal→Pain	Slight fat restricti necessary
B	I.S.	M.	5	1 year 8 months	Not improved	2 L→N	Nil	Important
C	I.S.	F.	10 5	8 months 4 months	Slightly improved	1 N→N	Nil	Not important
D	I.S.	M.	10	1 year	Much improved	4 L→N	Nil	Not important
E	Tr.S.	M.	20	9 months	Not improved	5 L→4–5 L	Nil	Important
F	Tr.S.	F.	20	1 year	Not improved	3 SF→3 SF	Nil	Very important. Crude liver inject more important
G	Tr.S.	M.	5	1 year 6 months	Much improved	7 L→N	Nil	Very important
H	Tr.S.	F.	10	9 months	Slightly improved	2 SF→2 SF	Nil	Important
I	Tr.S.	M.	2·5	1 year 8 months	Much improved	2 L→N	Glossitis→Nil	Not important
J	Tr.S.	M.	20 10 2·5	5 weeks 6 months 6 months	Much improved	2 SF→N	Nil	Important
K	Tr.S.	F.	5 10	2 weeks 5 weeks	Not improved	3–4 L→5–6 L	Nil	Very important. Crude liver injec important

I.S. idiopathic steatorrhoea; Tr.S. tropical sprue.
* Indicates number of stools, daily and whether loose (L), semi-formed (SF) or normal (N).
† Varying doses were given in the first 6 months but averaged in that period 13 mg. daily.

tropical sprue and one with idiopathic steatorrhoea, who are not included in the table, were able to stop folic acid after a few weeks as their blood counts and clinical state were normal. No deterioration was found during a follow-up period of over a year. A fourteenth patient, who had shown no response to any form of treatment for idiopathic steatorrhoea over a period of years, also showed no clinical or haematological response to folic acid. Table 2 also shows the extent to which diet was important in the treatment of the patients who were receiving folic acid.

How folic acid acts is uncertain. It does not increase fat absorption, but possibly directly or indirectly improves absorption of water and salt. It may have some effect on the absorption of dietary salt, or on intestinal secretion which had not been reabsorbed as in the normal person.

Vitamin B_{12} therapy

Recently, enthusiastic reports have been given of the effects of parenteral administration of vitamin B_{12} in the treatment of the sprue syndrome (Spies, Suarez, Garcia Lopez, Milanes, Stone, Lopez Toca, Aramburu & Kartus, 1949). We are at present, in Edinburgh, treating some sprue patients in this way, but it will be surprising if

vitamin B_{12} is effective where potent purified liver extracts failed, and therefore one would expect to find some patients failing to respond to vitamin B_{12} and then responding to folic acid.

Response to treatment

To summarize the present position as regards the treatment of the sprue syndrome in the adult, it seems in the light of experience gained in the recent war that some patients with tropical sprue of recent onset may recover without any treatment on returning to temperate regions. Many men developed sprue while in India, but only 1073 were sent back to Britain between 1943 and 1946 (Keele, 1949). Some had lost their symptoms before they reached the United Kingdom; others recovered in hospital with no treatment, with dieto-therapy, or with diet and liver injections. Some 200–300 were invalided out of the army, and many responded to folic acid treatment. Idiopathic steatorrhoea is more difficult to treat, but some patients respond to dieto-therapy, sometimes with only moderate restriction in fats and carbohydrates. On occasion, parenteral liver therapy gives a better response than diet alone, but whether vitamin B_{12} will be as effective remains to be seen. Folic acid benefits many patients.

There is no doubt that pteroylglutamic acid is a very valuable weapon which should perhaps be used in all cases of tropical and non-tropical sprue, but even when it is used the diet cannot entirely be neglected. The clinical and haematological responses to these haemopoietic agents do not always run parallel, and it seems likely that, as the disease progresses, there may be a progressive lack of absorption of haemopoietic agents. Probably in the early stages vitamin B_{12} is not absorbed, and so there will be a haematological response to liver or to vitamin B_{12}. Later there is also a failure of absorption of folic acid conjugates, and so the tissues are depleted of folic acid. At this stage, liver therapy, vitamin B_{12} therapy and treatment by dietetic means are all likely to be unsuccessful, and the only substance that will produce haematological benefit if the marrow is megaloblastic is free folic acid. Undoubtedly, however, other unknown factors are involved because, as we have seen, anaemia may persist despite folic-acid therapy. Once irreversible changes occur in the mucosa of the small intestine, the chances of restoring the patient to normal health are slight.

Pteroylglutamic acid has unfortunately made little difference to the treatment of coeliac disease in the infant or child. The main basis of treatment in this condition is dietetic. The banana has been much publicized in connexion with the treatment of the condition, but in general it does not have any magical properties. The problem is to persuade the child to eat the sort of diet that he can tolerate—low in fat, high in protein, and containing carbohydrate in forms that will not increase the diarrhoea. Why these children do not respond to pteroylglutamic acid like the adult is unknown.

Some of the problems of the sprue syndrome

There are certain major problems to be solved about the place of diet in relation to the onset of sprue. During the war against the Japanese, although sprue was fairly common amongst British troops in India and Burma, it was not seen in malnourished British prisoners in Japanese P.O.W. camps, and there has been no suggestion that it

has developed since their release. Gilroy (1949) has suggested that this might be due to lack of fat in the diet of the prisoners. If this is so, does it mean that a low-fat diet used therapeutically will prevent further development of changes in the intestinal wall? We have seen nothing here to suggest that this is so. The patients who respond well to folic-acid therapy have, in many instances, increased the fat in their diet without evidence of detrimental results.

It is usually said that sprue is virtually unknown amongst Indians, and yet, during the war, Indian troops were affected in large numbers with a condition similar to sprue once they were sent to Burma and the eastern parts of India. Malnutrition in jungle fighting may have been a factor. Some of these men died, and were found to have atrophy of the mucosa of the small intestine, a change that occurs in monkeys fed a diet similar to that of poor Indians (Rao, 1942), but British troops developed sprue when sent to the eastern parts of India, and Leishman (1945) records that in one R.A.F. unit, within 3 weeks of its arrival in the Chittagong area, 10 % of its personnel was down with diarrhoea which rapidly developed into the full sprue syndrome. This indicates that a major factor in connexion with the onset must be geographical in some direct or indirect way. Stefanini (1948) has referred to an outbreak of sprue in Italian prisoners of war in India. There were four camps. The population was similar in each and the diet was similar, but sprue developed in only one camp which was at a higher altitude and had a longer rainy season. Why then is sprue not commonly seen in poor Indians? Is this because of faulty observation? The poor Indian obtains most of his fat from cooking oils, and if he uses 1 oz. of oils in the day, he obtains about 30 g. of fat. How much fat is needed in the diet for sprue to develop? Sprue is very common amongst the malnourished people of Puerto Rico, as has been shown by Spies, Suarez and their co-workers in a series of papers (cf. Spies *et al.* 1949). These patients respond dramatically to pteroylglutamic acid, even if the faulty diet is continued. The discrepancy in the recorded results of treatment may be because the American workers are dealing with patients suffering from primary malnutrition, whereas British workers are dealing with a condition found in well-fed Europeans who have visited the tropics.

Possible importance of the intestinal flora

It is well known that both folic acid and vitamin B_{12} are synthesized in the intestine of man by intestinal bacteria, and that these factors may be destroyed by other bacteria. Preliminary experiments to see to what extent folic acid and vitamin B_{12} are to be found in the small intestine of fasting pernicious-anaemia patients and in controls showed no evidence of significant amounts of either until the large intestine was reached; no sprue patients were available at the time, but in one patient with ulcerative colitis folic acid was present in the contents of the lower end of the small intestine to the extent of 1·2 mg./100 ml. (Girdwood, 1949). This matter is undergoing further investigation, but it may be that the intestinal flora is of importance in this way in malnourished patients suffering from steatorrhoea, whether the malnutrition be primary, or secondary to malabsorption. This, too, may be of importance in relation to the diet prescribed, and may explain some of the discrepancies found in different investigations. For instance, the Indian troops in Burma were taking suppressive

mepacrine and were chlorinating their water. This may have been of importance in relation to their intestinal flora.

Sprue-like states in animals

In animals a sprue-like state can be produced in several ways. McCarrison (1921) produced diarrhoea in monkeys by dietetic means, and by adding fat to his basal diet produced a condition more akin to sprue. Folic-acid deficiency in various animals, whether produced by dietetic means (Miller & Rhoads, 1932–3) or by the use of folic-acid antagonists (Thiersch & Philips, 1949) may give rise to a sprue-like state. I have seen sections of the small intestine of animals given folic-acid antagonists showing atrophy of the epithelium as in the late stages of sprue.

Conclusions

It seems to me that the so-called sprue syndrome may be a mixture of more conditions than we realize; some of the possibilities are summarized in Table 3. Primary malnutrition may give rise to diarrhoea and atrophy of the small intestinal wall. If the

Table 3. *Some of the mechanisms that may give rise to steatorrhoea*

Primary malnutrition → small-intestinal changes → diarrhoea
Primary malnutrition plus sufficient fat in the diet → steatorrhoea
Folic-acid deficiency (dietetic or from folic-acid antagonists) in animals → diarrhoea → small-intestinal changes → sprue-like stools
Unknown factors, possibly including those environmental and hereditary → 'the sprue syndrome' in its various forms (usually with steatorrhoea) → malabsorption → secondary malnutrition and deficiency of various substances including folic acid → further intestinal changes → steatorrhoea, if sufficient fat in diet

patient has enough fat in the diet there will be steatorrhoea. To what extent is primary folic-acid deficiency of importance in this respect? We do not know the cause of idiopathic steatorrhoea or of the tropical sprue syndrome or of coeliac disease, but certainly, frequently, despite what has been said to the contrary, it cannot be dietetic. I feel sure that in many cases it is curable in the adult, especially in the tropical form, if treated early enough and treated properly. On the other hand, if it is allowed to go on for a prolonged period the changes in the gastro-intestinal tract will be permanent and irreversible no matter what treatment is given. The changes and the clinical picture will then be similar to what is seen in people suffering from continued severe primary malnutrition.

It may seem that I am departing far from the stated title of this communication, but it is of importance to know the mechanism of the therapeutic agents that are used, and the aim of treatment must be to give the most efficacious therapy at an early stage. It may be that folic-acid deficiency is what causes progressive changes in the intestinal wall, and that this does not happen in pernicious anaemia because folic-acid conjugates are absorbed. It may be that the disease cannot progress if fats are eliminated sufficiently from the diet. All this is mere speculation, but it appears to me that it is important to investigate this further, dietetic surveys forming one line of approach,

to see to what extent the incidence of steatorrhoea is related to the quantity and character of the fats in the diets of various peoples; it does not appear probable, however, that this will give the whole answer. Finally, I would make a plea for the abolition of the term 'sprue' which has come erroneously to be used as a synonym for the condition of steatorrhoea.

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