

THESIS PRESENTED FOR  
THE DEGREE OF DOCTOR OF MEDICINE.

TROPICAL SPRUE :

A DISCUSSION OF THE AETIOLOGY, DIAGNOSIS  
AND TREATMENT WITH A DESCRIPTION OF  
NINE PERSONAL CASES  
TREATED WITH  
FOLIC ACID.

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## INTRODUCTION.

Since sprue was first described by VAN KETELAER in 1672 in the Dutch East Indies and in 1766 by HILLARY in the Barbados, the aetiology of the disease has remained obscure.

During this last war large numbers of troops were stationed in India and the Far East and the incidence of sprue increased out of all proportion to the increased European population in these areas. The hygienic conditions and the physical tasks imposed upon these men were different from anything undertaken by a white population in the Far East within living memory, and it is hardly a matter for surprise that these cases presented certain differences from the classical sprue seen in the pre-war years.

The onset was more sudden and in many cases the course was more acute and the response to therapy was often quicker than was seen before the war.

The problem attained such proportions as to warrant the setting up of a Sprue Research Team by the India Command.

Interest in the disease has been quickened by the published work of various members of this

Research Team and also by Professor A.C. FRAZER'S work on the physiology of fat absorption.

During the past three years SPIES, at Birmingham, Alabama, has performed clinical trial of folic acid in the treatment of Sprue with strikingly good results.

The objects of this thesis are to present a critical review of recent work on sprue and to assess the value of folic acid therapy as a therapeutic advance.

THE FIRST DESCRIPTION OF TROPICAL SPRUE IN THE  
ENGLISH LANGUAGE,

Written by William HILLIARY, M.D., in 1766.

"And I shall begin with the Description of a Disease, which I think I may safely say is new and has never yet been described by any Author, neither Ancient nor Modern, not even by any of the Arabian Physicians; most of whom lived and practised in the hot countries of Persia, Syria, Arabia and Aegypt; but of late years has become endemical and frequent in Barbadoes and other West India Islands.

The Patient who labours under this Disease, usually first complains of an uneasy Sensation or slight burning Heat about the Cardia, or upper Mouth of the Stomach; which comes slowly on, and gradually increases and rises up the Oesophagus into the Mouth, without any Fever, or the least feverish Heat, or much pain attending it; most commonly without any observable Intemperance or Irregularity in living or without any Surfiet, taking cold or any sort of Fever or other Disorder, which it can be attributed to.

Soon after this burning Heat little small Pustulae or Pimples, filled with a clear acrid Lymph, no bigger than a Pin's head begin to rise; generally first on the End and Sides of the Tongue, which gradually increase in Number, not in Magnitude, and slowly spread under the Tongue and sometimes to the Palate and Roof of the Mouth, and the Inside of the Lips; and soon after this the skin which covers those Pustulae, slips off, and the Tongue looks red

and a little inflamed, though not swelled, yet is almost raw like a Piece of raw Flesh, and is so tender and sore that the Patient can eat no Food but what is soft and smooth, nor drink anything that is Vinous, spirituous or the least pungent without acute Pain; so that some suffer much from the want of proper Food. In some Ptyalism comes on, and continues a long time, which is so far from being of any service, or giving any Relief to the Patient, that on the contrary it drains and exhausts the Fluids of the Body, and greatly wastes and sinks them.

In this State they continue several Days or Weeks and sometimes for Months, sometimes a little better, then worse again; and after a considerable time, sometimes longer, and sometimes shorter, the Pustulae will disappear and the Mouth grow well, without any Medicines or Applications, or any Manifest Cause, and continue so for several Days or Weeks; ..... Diarrhoea comes on, and continues longer or shorter in different Patients .....; and in all it greatly wastes their Flesh and Strength and sinks their Spirits very much. The diarrhoea after continuing a longer or shorter Time, sometimes stops without taking any Medicines, or doing anything to stay it, and the Patient thinks himself better for a short Time, and sometimes for a longer Time: but in general the Acrid Humour soon returns to the Mouth again, with all the same symptoms but sometimes increased or aggravated; and after some

Stay there it removes from thence to the Stomach and Bowels again; and thus a Metastasis of the Humour from the Mouth to the Bowels and vice versa, is frequently and sometimes suddenly made, without any manifest or perceptible Cause.

The Patients are all along without any Fever or Feverish Heat .....

The frequent Metastases which this Acrid Humour makes from the Mouth to the Stomach and Bowels, and from those to the Mouth again, greatly emaciate and weaken and consume the Patient.....whence a true Atrophy is produced which at the last either sinks the Patient, or brings on a Marasmus, which soon ends in Death.

As it is a new Disease, we must give it Some Name; shall we call it an Aphthoides Chronica, or an Impetigo Primarum Viarum? or what? But I will not dispute with any about its Name, as that is only a Dispute about Words; and if any Person will give it a better Name, I will readily agree with him and thank him also."

(From "Observations on the Changes of Air and Concomitant Epidemical Diseases in the Island of Barbadoes" by William HILLARY, M.D., 1766, page 227 et seq.; L. Hawes, W. Clarke and R. Collins in Pater-noster-row, London).

The disease was described before this by VAN KETELAER, a Dutch Physician, in 1672, so that HILLARY'S claim to be the first to describe it is not a true one, but HILLARY'S description is well worth preserving as a clear record of much accurate clinical study.

THE PHYSIOLOGY  
OF  
FAT ABSORPTION

THE PHYSIOLOGY OF FAT ABSORPTION.

Any investigation on the aetiology of sprue must be preceded by a survey of the most recent work on the physiology of fat absorption because, whatever theories may be propounded about this disease, steatorrhoea is one of its essential features.

The theory that fat is completely emulsified, saponified and hydrolysed into soaps, fatty acids and glycerol, then absorbed through the villi of the small intestine and resynthesised, was based on the work of VERZAR and McDOUGALL who propounded this theory in 1936 and named it the lipolytic hypothesis of fat absorption.

This work is sufficiently well known not to need further elaboration here, but in 1938 FRAZER published the first of his experimental findings which suggested that an alternative theory needed consideration, and this he has called the partition theory.

A review of his work is now necessary as it seems to throw considerable light on the problems bound up with sprue, and his work will be quoted at length and one of his tables reproduced in full later. He has divided the study of fat absorption from the lumen of the small intestine to the corium of the villus into four stages - viz:

1. Changes in the Intestinal Lumen.
2. Changes at the outer border of the Intestinal Cell.
3. Changes in the Cell.

#### 4. Changes at the inner border of the Cell.

##### 1. CHANGES IN THE LUMEN.

The two main biochemical changes here are emulsification and hydrolysis.

(a) EMULSIFICATION. This process occurs in the intestinal lumen down to a particle size of less than 0.5 $\mu$ , and it is the mechanism of this which needs clarification. The PH of the intestinal contents in the upper two-thirds is around 6.5, and the only emulsifying system effective in vitro at this PH was the triple combination of fatty acid, bile salt and monoglyceride. Acid soaps have been thought to produce this fine emulsification but their action is inhibited by the presence of calcium and by a PH less than 7.5.

FRAZER found that material obtained from the intestinal lumen by intubation contained the same combination of fatty acids, monoglycerides and bile salts as he had shown essential in vitro to produce full emulsification. He sums up by saying: "It may be concluded that of the various emulsifying mechanisms suggested, it is only the Triple combination of fatty acid /Bile salt/monoglyceride which has been shown to be effective under the conditions prevailing in the intestine. The various components of this system are readily available due to lipolysis and bile secretion. Phospholipid, cholesterol and other substances may perhaps be secondarily involved in the interfacial film, but it seems they are not essential to the fine emulsification of fats in the

intestinal lumen." He then suggests that this emulsification may exist to provide an increased interfacial area for subsequent hydrolysis or that it may be concerned with the absorption of unhydrolysed fat in a finely particulate state.

(b) HYDROLYSIS OF THE TRIGLYCERIDES TO FATTY ACIDS AND GLYCEROL. This is generally

agreed to be the function of Lipase, the exact nature of which substance or substances is not yet clearly defined. It is probably better to restrict the term Lipase to those enzymes which act chiefly on the glycerides of the long chain fatty acids.

The Partition theory of fat absorption differs from the lipolytic theory in that it postulates that hydrolysis is only partial in the lumen of the intestine and that a proportion of fat is absorbed in its triglyceride form, a possibility which has not been recognised by those who support VERZAR'S theory of complete lipolysis and absorption as fatty acids.

If the partition theory is accepted, failure of lipolysis cannot be such an important factor in deficient absorption of fat as it has been regarded until now because, if it is accepted that fat can be absorbed as a triglyceride, then complete hydrolysis is no longer an absolute essential preliminary step.

In vitro, experiments have demonstrated that lipolysis is markedly retarded at the PH of most of the intestinal contents and further, that when 20-30% of fatty acid has been liberated there is practical cessation of hydrolysis.

"As hydrolysis proceeds it is inevitable that the fatty acid formed will accumulate at the oil/water interface, and it is equally certain that this fatty acid will eventually displace the enzyme from the oil surface and bring lipolysis to a stop.

It seems that unless the fatty acid can be removed from the oil/water interface, lipolysis will be restricted to about 30% in the short time available in the intestine.

The fatty acids can only be removed from the interface as water soluble compounds or complexes.

If the fatty acid itself is water soluble no accumulation will occur. This can be clearly demonstrated with tributyrin which can be rapidly and completely hydrolysed.

The long chain fatty acids may be removed as soaps. This occurs readily at PH 8.5 but only to a limited extent at PH 6.5.....

It may therefore, be concluded that so long as the PH of the intestinal contents is in the region of 6.5 the hydrolysis of long chain fats will tend to be restricted to 30% or less.....

In the case of short chain fats such as tributyrin unrestricted hydrolysis is to be expected." (FRAZER 1946).

## 2. PASSAGE OF FAT THROUGH THE STRIATED BORDER OF THE INTESTINAL CELL.

In order to establish the particulate theory of fat absorption it was necessary to demonstrate that it was possible to pass fat in its particulate form

through the outer border of the intestinal cell.

The effective emulsifying system has already been demonstrated by intubation experiments and the membranous structure of the outer border of the cell (the Brush Membrane) has been described by BAKER (1942) as being traversed by tiny canals which will allow the passage of particles about  $0.3\mu$  in diameter.

FRAZER (1946) used paraffin to demonstrate the absorption of unhydrolysable material and it was emulsified to a particle size of less than  $0.5\mu$  and then introduced into the duodenum of rats.

Residual biochemical analyses and histological preparations have shown that the paraffin was absorbed through the brush membrane and into the cell, the main factor appearing to be the particle size which must be fine enough to traverse the canals described by BAKER.

Whether or not unhydrolysed fat can be conveyed further along the absorption pathways has yet to be shown but enough has been done in the experiments just described to cast considerable doubt on the hypothesis of complete lipolysis of fats in the intestinal lumen.

FRAZER (1946) is of the opinion that the force which determines the passage of particles through the membrane is related to electrolyte concentrations on either side and this becomes more interesting in view of the findings of BLACK (1947) regarding the dehydration and salt deficiency found in cases of

sprue seen by the Sprue Investigation Team. These findings will be referred to later.

### 3. CHANGES IN THE INTESTINAL CELL.

#### (a) RESYNTHESIS.

Fatty acids and glycerol have been shown to resynthesize triglycerides readily in vitro and, given suitable conditions, it is reasonable to suppose that this process will occur in vivo, but, as stated earlier, if an appreciable portion of the fat is absorbed into the cell in its unhydrolysed state, then resynthesis may not be of great importance in normal fat absorption.

#### (b) PHOSPHORYLATION.

It is generally agreed that phospholipids are formed in the intestinal cell but the function of this process is not understood as yet.

FRAZER (1946) suggests two possible functions which, until now, have not been described. He points out that, as the emulsified fat in the intestinal lumen is negatively charged, it would flocculate in the presence of plasma proteins at the PH of the blood. This flocculation of the chylomicrons which are seen at the height of fat absorption does not occur and their behaviour is similar to that of a lecithin stabilized emulsion and, moreover, these particles cease to be stable when heated with lecithinase, thus indicating the essential involvement of phospholipid in the stabilizing film.

The second function of phospholipid may be con-

cerned with the passage of fat through the inner membrane of the cell into the corium of the Villus and, in view of the defects in phosphorylation that have been suggested by STANNUS (1942) and LEISHMAN (1945) to be important aetiological factors in Sprue, this second hypothesis as to the function of phospholipid provides an explanation of the manner in which deficient phosphorylation may impede fat absorption and promote steatorrhoea.

(c) ABSORPTION OF FATTY ACIDS.

It is suggested that the fatty acids are absorbed as water soluble compounds and in support of this it is pointed out that certain short chain fatty acids are themselves water soluble. It is possible that the long chain fatty acids, which are not water soluble, are absorbed as soaps and as this hypothesis may have an important bearing on the production of the diarrhoea that accompanies steatorrhoea, it will be referred to again later.

It has been shown by intubation that the theory that fatty acids are absorbed as water soluble complexes with bile salts does not conform, in the molecular ratios required for this hydrotropic action, with the actual conditions found in the intestine.

The observations made previously on the removal of fatty acid from the oil/water interface are in support of the hypothesis that fatty acids are absorbed in a water soluble form.

4. PASSAGE OF FAT THROUGH THE INNER BORDER OF THE  
INTESTINAL CELL.

FRAZER (1946) has demonstrated that small doses of choline will cause fat to move from the interior of the intestinal cell into the corium of the villus: this effect occurs immediately after the administration of choline and appears to be specific for this substance and it still occurs after atropinisation.

By feeding rats on olive oil and water and then cutting sections of the jejunum it has been shown that fat globules accumulate in the interior of the cell and finally block the cells: if however olive oil and choline are administered, masses of fat move into the areolar tissue of the villus and the cell is cleared.

5. THE DISTRIBUTION OF FAT IN THE BODY.

Marked differences occur in the distribution of fatty material in the body and these depend on the chemical composition of the fat ingested.

Animals were fed with triglyceride or its constituent fatty acids and the distribution pathways were compared with those following the feeding of animals with glycerol.

FRAZER (1946) makes the following statement on the subject:

"Thus, triglyceride gives rise to large globules in the intestinal cell, to a milky appearance of the lacteals, to a characteristic systemic lipaemia, and

to deposition in the fat depots. On the other hand, the ingestion of fatty acid causes none of these changes, but in contrast a granular deposition in the intestinal cells, an increase of particulate material in the portal blood and deposition in the liver. It is suggested that after feeding a long chain triglyceride, a large proportion, probably 60%, is absorbed unhydrolysed in particulate form, and this material passes by the lacteal-lymphatic pathway to the systemic blood and fat depots. If fatty acid is absorbed, however, it passes mainly by the portal vein to the liver. Under normal conditions of fat absorption, several factors will determine the distribution of the fatty material. The type of triglyceride ingested may affect the extent of hydrolysis; with long-chain fats restriction may occur but with short-chain compounds hydrolysis is likely to be complete. Thus, tributyrin cannot be recovered from the chyle or the fat depots after absorption, but triolein can be found in both. The extent of hydrolysis of the long-chain fats will also be influenced by the PH conditions in the intestine. If the PH is 8.0 more fatty

acid is likely to be absorbed, but if it is 6.5, as usually found in most of the intestine, a larger proportion will be absorbed in particulate form. It is clear, therefore, that considerable variation may occur in the distribution of fatty material after absorption without necessarily changing the total quantity of fat absorbed."

The distribution of absorbed fats may be followed in the systemic circulation by means of chylomicron counts and can be checked by differential analyses of blood fat but, as yet, no satisfactory method is in use for determining the distribution of fat to the liver by the portal vein in the human subject.

## THE CLASSIFICATION OF FAT ABSORPTION DEFECTS.

The following table classifies fat absorption defects on an Aetiological basis in accordance with the findings given previously.

### FIG. 2 (after FRAZER).

#### A. INTRALUMINAR FAULTS.

##### 1. Defective Emulsification.

- (a) If lipolysis does not occur.
- (b) If bile salts are excluded from the intestine.
- (c) Due to mechanical interference such as lack of intestinal motility or entanglement of the components of the emulsifying complexes.

##### 2. Defective Hydrolysis.

This is so rarely found that it is doubtful whether it is a factor in defective fat absorption even in advanced pancreatic disease.

- (a) Defective alkalinity of the PH of the contents of the lower ileum or functional abnormality of this portion of the intestine may cause a fat absorption defect which may be seen in some cases of Regional Ileitis.

#### B. MEMBRANE FAULTS.

- ##### 1. Structural abnormality in the outer membrane of the Intestinal Cell.

Table showing the main points of difference between lipolytic and partition hypotheses (after FRAZER) 1946

	Lipolytic Hypothesis	Partition Hypothesis
1. Changes occurring in the lumen of the intestine		
(a) Emulsification		
i. Mechanism	Acid soap	Triple complex: fatty acid, bile salt/lower glyceride
ii. Function	To promote hydrolysis	To disperse unhydrolyzed fat preparatory for absorption
(b) Hydrolysis		
i. Extent	Complete	Partial.
ii. End products	Fatty acid and glycerol	Fatty acid, di- and mono- glycerides and later glycerol
iii. Function	Essential preliminary to absorption	Provides 2/3 components of emulsifying system. Partitions fat into fatty acid and glyceride fractions
2. Passage through the outer membrane (free border) of the intestinal cell		
(a) Structure of brush border	Solid pavement	Canal structure
(b) Fatty acids	Pass through the membrane as soluble complexes with bile salts	Pass through the membrane either as soluble compounds or complexes
(c) Glycerides	Do not pass through the membrane	Pass through the membrane as finely dispersed emulsion of negatively charged particles less than 0.5 $\mu$ in diameter
(d) Adrenal cortex	Not concerned here	Controls normal electrolyte balance which is closely related to the absorption of charged particles
3. Changes occurring in intestinal cell		
(a) Resynthesis	Essential part of mechanism. All fatty acid converted back to triglyceride	Not an essential part of the absorptive mechanism
(b) Phosphorylation	A stage in resynthesis of triglyceride fat	Not concerned with resynthesis but occurs at oil/water interface, as an essential change in interfacial structure, and probably elsewhere
(c) Adrenal cortex	Essential for normal phosphorylation	Not concerned in phosphorylation
4. Distribution of absorbed fatty substances in the body		
(a) Fatty acid fraction	After resynthesis the triglyceride passes up lacteals and thoracic duct into systemic circulation. Negligible amounts pass up portal vein to liver	Mainly passes by the portal vein to the liver
(b) Glyceride fraction	Not absorbed as such. Resynthesized from fatty acid and glycerol as described above	To systemic blood via lacteals and thoracic duct and so to the fat depots

This is practically impossible to prove at the present time.

2. Changes in the forces acting through the membrane may occur in conditions in which the electrolyte metabolism is altered. This possibly explains the moderate fat absorption defect which may occur in Addisons disease and in adrenalectomised animals. It may also be a factor in the defective fat absorption of Sprue as BLACK has shown defective salt metabolism coupled with dehydration occurs in this disease.

C. INTRACELLULAR FAULTS.

1. Interference with phosphorylation due to
  - (a) Enzymic deficiency.
  - (b) Deficiency or lack of raw materials for phosphorylation.

STANNUS observations and those of LEISHMAN seem to show that this is a very important factor in the aetiology of the Sprue Syndrome.

D. DISTRIBUTIVE FAULTS.

1. Obstruction of the pathways, e.g. obstruction of the Lacteals.
2. Due to a change in the normal proportions of fat absorbed in particulate and non particulate form.

It has been shown that in most cases of Sprue 60% to 70% of ingested fat is absorbed from the intestine without any apparent systemic lipaemia, such as is characteristic in normal subjects one and a half hours after a fatty meal. This point will

not be discussed further at present as any attempted solution can only be theoretical and the possibilities will be considered in a later stage of this thesis.

E. UNCLASSIFIED.

Various surgical conditions such as after gastrectomy and in cases of Gastrocolic fistula.

METHODS OF STUDY OF FAT ABSORPTION IN MAN.

Only by a knowledge of the amount of fat ingested in the diet as well as the quantity passed out in the faeces can the fat absorption be estimated. Even under these conditions the test should be carried out over a five day period and BLACK, FOURMAN and TRINDER (1946) are of the opinion that nine days samples should be collected for analysis.

Sprue diets are deficient in fat and, unless a definite amount is given in the diet during the period of the test, deceptively low excretory values will be obtained.

The normal human being should absorb 94% of ingested fat even when the intake is increased from the standard 50 G daily to 100 G or more. Less than 90% absorption is definitely an abnormally low figure.

A more accurate method of assessing the Fat Balance would be to use "labelled" fats and a new technique is being devised by FRAZER at the present moment.

To assess the changes in the lumen of the intestine intubation and removal of the intestinal contents has been performed.

After determining the presence of alimentary enzymes, the state of emulsification is examined by dark ground illumination and, should emulsification be impaired, the material is tested to determine which component of the intestinal emulsifying system is absent by adding the various constituents individually to different samples of the intestinal content, incubating them at body temperature, and then seeing in which sample emulsification takes place.

Finally a differential analysis of the fatty material is carried out.

"In the normal subject the alimentary enzymes are present in fairly constant amounts, the fat is finely dispersed or is readily emulsified by the standard technique, the interfacial film has the properties of a negatively charged interface and lecithin is not essential to stability, the acetyl value of the glyceride fraction indicates the presence of mono- and di-glycerides up to 30%, and the proportion of fatty acid to glyceride only exceeds 30% when very small quantities (less than 500 mg.) of fat occur in the sample." (FRAZER 1946)

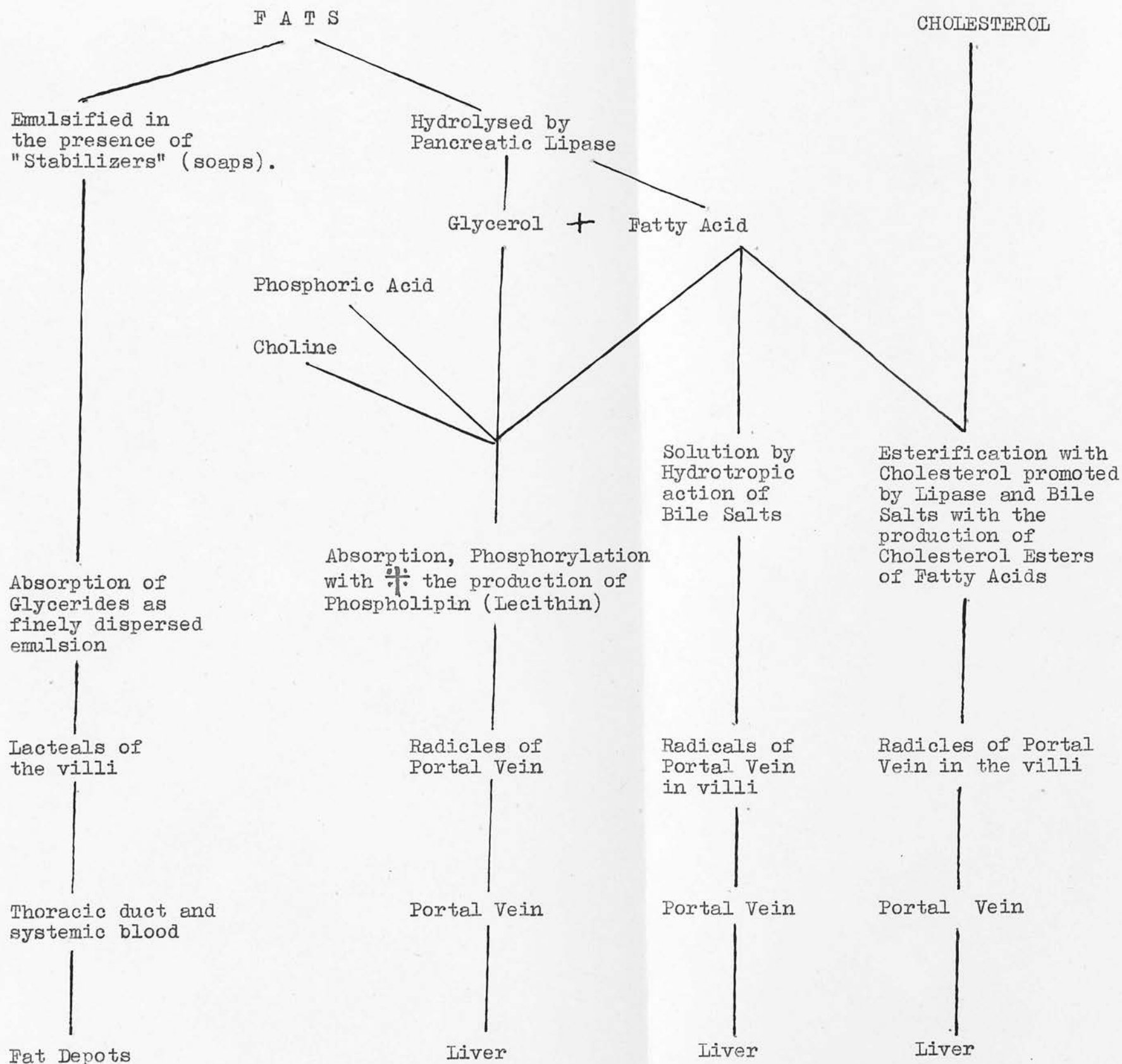
Chylomicron counts to assess the changes in the fat content of blood specimens taken at short intervals can be employed to follow the systemic distribution of fatty material after a meal.

At present there is no satisfactory method for following the portal distribution of fat to the liver.

FIGURE 3.

## A DIAGRAMMATIC SCHEME ACCORDING TO THE "PARTITION" THEORY -

showing the main paths followed by the two fractions: neutral (unsplit) fat and fatty acid (split fat). The  $\frac{\oplus}{\oplus}$  represents the suggested point of failure in sprue. (after STANNUS 1942).



THE  
BIOCHEMICAL CHANGES  
IN  
SPRUE

## THE BIOCHEMICAL CHANGES IN SPRUE.

The defective absorption of fat is demonstrable by excessive excretion in the stools and the establishment of an adverse fat balance.

Investigation of the carbohydrate and mineral metabolism in cases of Sprue has demonstrated that there is a profound disturbance of absorption which is not limited to fat alone.

Water and salt metabolism are closely associated and, apart from giving rise to the well known muscular cramps, salt deficiency has far reaching physiological effects upon the organism. BLACK (1947) has shown that the water salt metabolism is upset in Sprue far more often than was appreciated formerly and his work will be discussed in some detail.

The importance of dehydration, with which the salt metabolism is closely associated has been stated as follows:

"When it is realized that the sodium in the Sodium Chloride supplies 90 percent of the metallic ions in tissue fluid and the chloride 70 per cent of the acid electrolyte, its importance will be obvious and, further, there is practically no mobilizable store of Sodium apart from that in the body fluids.

There is therefore a disturbance of the acid-base balance which is of considerable importance in an already wasted patient.

The mechanism of osmotic control of the tissue fluids, already profoundly disorganized by dehydra-

tion, is further harassed and tissue metabolism may give up the unequal struggle." (MANIFOLD, 1947).

The carbohydrate metabolism is also affected and, after a test dose of glucose, the curve in sprue, both tropical and non tropical, is either flat or may rise only gradually and fall very slowly to its original level. (HANES and McBRYDE, 1936)

The nitrogen metabolism does not appear to be so badly affected as that of the other constituents of the diet but in cases with severe cachexia and wasting it must be depressed.

The observations of SNELL (1939) bear out this statement.

As regards vitamin utilisation, more work is still required to show how important this factor is in the development of sprue; the therapeutic response to liver, Nicotinic acid, riboflavine and Brewer's Yeast would appear to indicate deficient utilisation of the Vitamin B<sub>2</sub> complex.

The Biochemical findings will now be discussed systematically and in more detail.

#### FAT METABOLISM.

##### THE FAT CONTENT OF THE STOOL.

The calculation of the percentage of fat in a single stool sample is no longer regarded as a satisfactory index to the amount of fat passed in the stools over a period of time because, even if the fat intake is known, the non fatty residue varies so much from time to time that the percentage of fat in the stools may be appreciably altered from day to day.

Also variations occur in normal people fairly commonly in the amount of fat absorbed from day to day and these phasic variations make it unsound to rely on stool findings in single specimens.

"In addition to these difficulties the normal physiological range has not been satisfactorily agreed, and figures for the upper limit of normal faecal fat are given by various authors as ranging from 15 to 50 per cent." (HUTCHINSON 1919, FOWWETHER 1926, SHELDON & HARRISON 1927: HARRIS & HARRIS 1942).

"It can be seen by reference to our findings in individual cases that a high dried faecal fat percentage was found in some of the control series. Furthermore, in a number of abnormal subjects the diagnosis could not have been made had attention been paid only to this percentage.

This method of investigation thus cannot be relied upon for the differentiation of the normal from the abnormal unless the observed defect is gross, and in such cases there are invariably other associated symptoms and signs upon which a diagnosis could also be made.

For similar reasons the method is of no value in determining the case of <sup>w</sup>steatorrhoea as has been assumed in many investigations." (FRAZER 1946).

It is now generally accepted that the only accurate method of calculating fat absorption is to give a known quantity of fat in the daily diet for at least two days before the test, then to collect

the stools over a period of 2 to 5 days and estimate the fat excreted in the stools over that time.

The difference between the fat ingested and that excreted represents the fat absorbed, and normal subjects should absorb 95% of their fat intake: excretion of above 10% of the fat ingested is regarded as definite evidence of deficient absorption.

BLACK, FOURMAN and TRINDER, (1946) while working with the Sprue Research Team recommended that at least four days stools should be examined at a time. This they repeated on three separate occasions in order to get an accurate estimate of the fat absorbed and, during their research, they examined five hundred such four day specimens.

In order to detect minor degrees of Sprue they gave 100 G of fat daily and did colonic washouts and found that the total fat excreted should not normally exceed 10 G per day, and this figure is confirmed by the findings of COOKE, ELKES, FRAZER, PARKES, PEENEY, SAMMONS and THOMAS (1946).

They further found that the typical bulkiness of the sprue stool was not entirely due to its excessive fat content but that an increase in water and non fatty dry matter were also factors, and as the case improved, not only did the fat content diminish but also the amount of non fatty solids in the stool.

Further, they observed that little fat was present in an unsplit form and HINDS HOWELL (1947) has stated that an increase of split fat in the stools is one of the earliest signs of sprue.

BLACK, FOURMAN and TRINDER however found that neutral fat, when added to a sprue stool and incubated, was rapidly split and this finding causes some doubt as to the usefulness of assessing the split fats as apart from the neutral fats. This subject will be discussed in full later.

The study of stools by the Sprue Research Team has thrown doubt on some traditional beliefs about the appearance of stools in Steatorrhoea.

They point out that many stools which have a high fat content are well pigmented and are not unduly bulky: it has been known for some time that on exposure to sunlight colourless stercobilin will go darker and, if the stool is not unduly bulky, it may soon assume a very normal appearance to a cursory examination.

They found that individual stools in patients with steatorrhoea may be normal in appearance and fat content because cases of sprue often avoid fatty articles of diet and therefore excessive excretion will only be discovered by giving a known quantity of fat in the diet.

It was observed that attacks of watery diarrhoea may occur in sprue and, as this diarrhoea is allayed by sulfaquanidine, a mistaken diagnosis of dysentery may be made even though the typical exudate of bacillary dysentery is absent.

#### CARBOHYDRATE METABOLISM.

HAYNES and McBRYDE (1936), described the flat or very gradually rising curve of the blood

sugar slowly falling to the resting level which follows the ingestion of a test dose of glucose in cases of sprue and idiopathic steatorrhoea.

CRAWFORD (1939) discussed the same finding in coeliac disease and THAYSEN (1935) and HARDWICK (1939) showed that after the ingestion of glucose the increase in blood sugar is often less than 40 mgs per 100 ccs., but that intravenous injection of glucose (20 G in 50 ccs. distilled water) is followed by the normal rapid rise and fall of the blood levels. These findings clearly indicate an impairment of absorption of glucose from the intestine.

MAEGRAITH, et. al. (1945) investigated the contemporaneous absorption of glucose and fructose in cases of tropical sprue in order to compare the absorption of a sugar (glucose) which is absorbed mainly after phosphorylation with one (fructose) which, as VERZAR (1936) has shown, passes across the gut membrane by simple diffusion. They gave 100.G Sucrose by mouth after preliminary starvation for 24 hours and estimated the glucose and fructose levels in the blood every half hour for two and a half hours and they found that in active cases the glucose curve was flat, the maximum rise above the fasting level seldom exceeding 20 mgs. per 100 ccs., whereas the fructose absorption curve was always within normal limits.

As the patient improved the glucose absorption curve slowly changed until, in the convalescent stage, it approximated to normal.

FOURMAN (1947) investigated the changes in the blood phosphate after the ingestion of glucose and fructose in cases of sprue. His purpose was to investigate the cell as well as the plasma changes in phosphate with glucose and fructose in order to compare the absorption of glucose and fructose in sprue. He points out that the blood-fructose curves after a fructose meal are not a satisfactory measure of absorption because even in normal people the increment in blood fructose is only about 10 mg per 100 ccs., and depends largely on the efficiency of the liver in converting fructose to glucose rather than on the speed of absorption. For this reason he casts doubt on the claim of MAEGRAITH that fructose absorption is normal in sprue.

He found that there was no demonstrable difference between the absorption of glucose and fructose in patients suffering from tropical sprue when investigated along these lines, and that the organic phosphate changes after giving both glucose and fructose were diminished or reversed in some sprue patients, indicating that the absorption of both these sugars is impaired.

#### DEHYDRATION AND BLOOD SODIUM CHLORIDE.

It has long been realised that in late stages when the patient is emaciated dehydration also is present and dehydration has been described as a terminal change found at autopsy.

Clinicians have also been aware that acute or terminal cases of sprue often give low blood

pressure readings, the systolic reading being below 100 and the diastolic between 50 and 70.

THAYSEN (1932) suggested adrenal deficiency as being the cause of Hypotension occurring in cases of Steatorrhoea in this country but no evidence in support of this has been forthcoming.

Episodes of dehydration and salt deficiency were described in cases of Coeliac Disease Steatorrhoea by PRUNTY and MACONN (1943) but BLACK (1946) first investigated these changes in cases of tropical sprue and drew attention to their comparative frequency, a fact which had not hitherto been appreciated.

He suggests that the chief cause of the salt deficiency is due to its loss in the stools either as unabsorbed dietary salt, or in the intestinal secretion which has not been reabsorbed in the usual way and quotes VISSCHER, FLETCHER, CARR et. al. (1944) to establish the point that the absorption of sodium, chloride and even of water is not a simple process of diffusion but an active process which may well be impaired in sprue.

He points out that water and salt deficiency are of great therapeutic importance as the usual sprue diet only contains a normal salt intake and that this amount should be augmented.

The sprue diet only contains 5 Grams of salt whereas a daily intake of 15 Grams is recommended in the tropics for patients with diarrhoea.

He found that restoring the salt and giving

sulphaguanidine to stop the diarrhoea would reverse a state in which the patients seemed likely to succumb and put them into a condition to benefit from therapy.

Between 5 and 10 per cent of his patients developed a low blood pressure, asthenia and signs of peripheral failure and ten such cases had low serum sodium and a low plasma volume in relation to their body weight.

In these cases an abnormal loss of sodium and, to a lesser degree, of chloride occurred in the faeces whereas, in the urine, sodium was not excreted and the chloride content was below normal.

These cases responded to a high salt intake and the signs of dehydration disappeared.

In no case did BLACK find any evidence of adrenal dysfunction.

These findings, coupled with FRAZER'S theory that electrolyte unbalance may prevent the absorption of particulate fat, are possibly of great importance in explaining certain features of the more acute cases of sprue.

CALCIUM DEFICIENCY. Low blood calcium figures have been shown to occur in cases of tropical sprue (HANES and McBRYDE 1936) and even lower figures have been demonstrated in Idiopathic Steatorrhoea and Coeliac Disease: in fact HAMILTON FAIRLEY (1936) differentiated between Tropical Sprue on the one hand and Idiopathic and Coeliac Disease on the other, on the grounds that the hypocalcaemia of Tropical sprue

does not cause osteomalacia or bony deformities and gross osteoporosis is rare.

Deficiency of calcium is seen more frequently in coeliac disease and non-tropical sprue than in the acuter tropical forms of the disease and tetany, osteoporosis, skeletal deformities and pathological fractures are described.

SNELL (1939) found that the serum phosphatase in cases of Idiopathic Steatorrhoea is usually normal but BENNET, HUNTER, and VAUGHAN (1932) claimed that in certain cases it was increased and they postulated that the unabsorbed fatty acids in the bowel may form soaps with the calcium and thus prevent its absorption. FOURMAN (1947) found no significant difference from normal in the blood phosphatase in cases of Tropical Sprue.

MAEGRAITH et. al. (1945) found no great deviation from normal calcium levels in cases of tropical sprue even during tetany, thus confirming the observations of FAIRLEY (1936).

#### IRON AND MAGNESIUM.

Iron excretion has been investigated and was found to be excessive in the stools and this is seen especially in cases with hypochromic anaemia. (WINTROBE 1942).

Attention was drawn to the low level of magnesium in the plasma by MAEGRAITH et. al. (1945) who found it to be as low as 0.75 mg. per 100 ccs and 1.2 mgs per 100 ccs respectively, in two

acutely ill patients who were in tetany. In both cases the magnesium was restored to its normal level when convalescence was reached. In this connection MAEGRAITH (1947) drew attention to the low magnesium intake of sprue diets which are deficient in green vegetables. The plasma phosphorous level is variable and may be below 3.5 mgs per cent but has been recorded above 5 mgs. (WINTROBE 1942).

#### NITROGEN METABOLISM.

This does not appear to be radically altered.

KEELE (1946), in a series of ten cases found the nitrogen to be in positive balance but in cases with severe cachexia SNELL (1939) pointed out that the blood protein may be lowered and the albumin-globulin ration reversed.

THE AETIOLOGY OF SPRUE

- (a) The identity of the disease
- (b) Geographical Distribution
- (c) The role of Infection with a discussion of "Hill Diarrhoea."
- (d) A Resumé of the Recent Work done
- (e) The role of Vitamins
- (f) The role of fat ingested in the diet.

THE AETIOLOGY OF SPRUE.

A discussion of the aetiology of the Sprue Syndrome is a matter of great complexity and difficulty because sprue has been linked and coupled with so many other conditions that it is difficult to define the limits of the syndrome, although an attempt has been made to do so in the section on the Diagnosis.

WINTROBE (1942) would even include Pernicious Anaemia in the Sprue Syndrome on the strength of the similarity of the blood picture and MANSON-BAHR (1943) would include Pellagra, on the grounds that the gastro-intestinal disturbances may resemble Sprue, and he claims this as a distinct link between the two conditions quoting MANNING (1909), who referred to pellagra as psilosis pigmentosa, in support of this conception. In one review of the syndrome (1941) he actually refers to it as the "Pernicious Anaemia - Pellagra - Sprue Syndrome." It is considered inadvisable to include these in the Sprue Syndrome, as both pellagra and pernicious anaemia have an aetiology which is well understood and can therefore be treated with success. The aetiology of the steatorrhoea of sprue is not understood: its origin is unknown and its response to treatment may be variable.

Apart from this basic difference the clinical picture of typical sprue is clearly defined from the two conditions just mentioned and it is felt that no useful purpose can be served by bringing them into the discussion.

The non tropical steatorrhoeas variously known as idiopathic steatorrhoea, non tropical sprue (THAYSEN, 1935) and coeliac disease resemble tropical sprue very closely and some authorities state that there is no essential difference between them.

Thus VEDDER (1940) queries the existence of any essential differences between tropical and non tropical sprue.

He points out that the symptoms of tropical sprue may not develop until the patient has returned from the tropics and has resided in a temperate climate for many years and he postulates that cases of non tropical sprue are not recognised early, last longer and therefore the symptoms are more pronounced.

This view has been expressed with many variants by a number of workers.

THAYSEN (1935) considers that all these conditions are variants of the same disease process and he uses the term "non tropical sprue" to describe his cases and, having examined 10 cases in detail and finding no evidence of previous coeliac disease, he states it as his opinion that this condition is not a late stage of coeliac disease as was thought to be the case by BENNETT, HUNTER and VAUGHAN (1932).

BENNETT and HARDWICK (1940) refer to idiopathic steatorrhoea as "adult coeliac disease" and consider that coeliac disease, whether in children or in adults, is a separate disease from tropical sprue, pointing out as the main points of difference that coeliac disease is mainly a disease of childhood whereas tropical sprue affects adults, that megacolon

is common in adult coeliac disease and almost unknown in tropical sprue and that rickets and deformed bones are found in coeliac disease alone (this last point of difference was first noted by FAIRLEY in 1936).

The case for considering idiopathic steatorrhoea as adult coeliac disease cannot yet be considered proved but, apart from this point, the differences between the two conditions pointed out by BENNETT and HARDWICK are not denied.

It may be argued that the essential pathology of all these conditions is the same and that the difference is merely one of the acuteness of the onset and course of the illness, but this will not explain two features in which tropical sprue differs from the non tropical steatorrhoea, namely, the marked tendency to remission and relapse in the tropical disease, and the long interval that often elapses between residence in the tropics and the brisk onset in this country of rapidly developing sprue identical with that seen in the tropics. The remission and relapse is a striking feature of tropical sprue: most cases respond to therapy and a cure is effected but a relapse is always a possibility and may occur years after the patient has been residing in temperate climates; when these relapses occur they may be very acute and, especially in the days before liver therapy, they might well prove fatal.

This characteristic is completely unlike coeliac disease or idiopathic steatorrhoea and

seems to demarcate these conditions from tropical sprue.

The long interval that can elapse between return to this country from the tropics and the first signs of sprue has been cited by VEDDER (1940) as supporting evidence of the identity of tropical sprue with "non tropical sprue."

This feature is one of the most extraordinary of several inexplicable characteristics of tropical sprue and MANSON-BAHR and WILLOUGHBY (1930) describe cases that have begun, apparently de novo, twenty five or even forty years after the patient has left the endemic area. There would appear to be some justice in querying whether residence in the tropics can possibly be a factor in producing a disease which only reveals itself for the first time twenty years after leaving the endemic area, but these cases produced the clinical features of tropical sprue, which are more acute in their onset and respond more readily to therapy than the "non tropical sprue," and therefore this occurrence would seem to be against the identity of the two conditions rather than an argument in its favour.

Biochemically there is a great resemblance between the two conditions: the faeces have a similar composition, the fat and sugar absorption tests are similar and the blood chemistry does not differ appreciably in the two conditions.

On the whole tropical sprue is an acuter disease with relapses and remissions and in many cases episodes of dehydration, which are not seen

in idiopathic steatorrhoea. Until we have a clearer conception of the aetiology of sprue or of idiopathic steatorrhoea it will be impossible to say with certainty whether these conditions are or are not essentially the same and, in our present state of ignorance, it is not easy to see any advantage to be gained from identifying them with each other.

Clinically, there are definite differences and, for this reason, only tropical sprue will be discussed in this thesis and any mention of sprue will refer to the condition seen in the tropics only.

Many factors appear to enter into the aetiology of sprue and many theories have been propounded to account for its origin.

STANNUS (1942) made a very complete and critical review of the ideas extant at that time and pointed out that: "Since there is no general agreement between the views expressed and since no one of the authors gives anything more than a tentative explanation of the facts, no apology is needed for also entering this speculative field."

Between 1942 and the present much work has been done which seems to have cleared the picture somewhat, especially the work of FRAZER on normal fat absorption and the work of various members of the SPRUE RESEARCH TEAM, but the fundamental factor or factors which will produce sprue after subjecting a healthy subject to them are still unknown and speculation and theory are still necessary when discussing the aetiology of this syndrome.

Before embarking on a detailed discussion of recent work and ideas it is necessary to consider certain facts which are connected with the incidence of this disease.

1. CLIMATE AND GEOGRAPHICAL CONSIDERATIONS.

The incidence of sprue is very widespread; it is seen in Ceylon, Assam, Bengal, Madras, Burma, Malaya and Southern China and, to a less extent, in the West Indies and the Southern States of America.

For some reason the disease is rare in the African continent but occasional cases do occur. DREW et al (1946) report an authentic case from North Africa; LEISHMAN (1945) mentions a case in which the disease originated in Durban, and MANSON-BAHR (1941) saw a case from Nyasaland. A few typical cases occurred in Egypt during the 1939-45 war, mostly among the troops who were stationed in the Western Desert and living on a diet which contained little fresh food of any kind.

Greece and Italy also produced occasional rare cases. The disease is so rarely seen in Brazil that DE FIGUEREDO, in 1941, reported "the first case of Tropical sprue in Brazil."

It is worthy of note that the incidence of sprue appears to be related to humidity as well as heat and the ARMY SPRUE RESEARCH TEAM noted that the maximum number of cases developed in May and June when the barometric pressure was at its lowest, the temperature was high and the humidity was at its peak: they emphasise that the incidence was at

its highest in the highest temperature areas.

Under conditions which prevailed in the Far East before the last war, Europeans were only affected usually after a period of years of residence in the tropics and ASHFORD, reviewing the incidence of the disease in Puerto Rico, found that the longer white people resided in endemic zones, the higher was the incidence among them. This confirmed the general impression formed clinically before the war by physicians who were seeing cases of Tropical sprue.

As has been stated previously, some cases only develop manifestations of the disease many months or even years after their return home from the tropics and MANSON-BAHR (1941) states: "The tendency to remissions is one of its chief characteristics, and most extraordinary of all is its latency in which it surpasses almost any other chronic disease. It can commence apparently de novo twenty five or even forty years after the patient has left the supposedly endemic area. Several instances of this have come under the reviewer's observation."

It has long been supposed that cases who have been invalided home and cured tend to relapse if they are sent back to an endemic area again but FAIRLEY (1936) stated that this was not the case and DE LANGAN and LICHTENSTEIN (1936) state that, although a return to cooler climes is desirable it is not essential and, if properly treated, sprue can be cured quite well in the tropics.

In view of the well known tendency to relapse and remission it is unwise to regard any case as being finally cured but there is no evidence that relapses are commoner if the case returns to the tropics after clinical cure than if he is kept in temperate climates.

During the past war our troops in India and Burma were affected by a type of sprue which was more acute and quicker in its onset and development than the cases seen under peace conditions. Men who landed fresh from the United Kingdom became ill within a few weeks and within two months or so had lost twenty pounds in weight.

KEELE (personal communication 1947) pointed out that these cases differed from the previous descriptions of sprue in the repeated relapse and remission soon after the onset and probably in curability by diet and liver. He points out that in civilian life no Europeans would be submitted to similar circumstances of hardship and dietary monotony for long enough to produce this clinical picture.

One case, very like these wartime cases, was seen personally in 1937 in British Guiana. A half-caste clerk joined the British Guiana-Brazil Boundary Commission from Barbados and within three months of living in very primitive conditions in the "bush" he had developed steatorrhoea and glossitis and had lost over two stones in weight. He was sent to Georgetown where he was treated on Fairley's high

protein, low fat diet and made a complete clinical recovery.

## 2. RACIAL CONSIDERATIONS.

Tropical sprue is not so common among the coloured inhabitants of endemic areas as it is among Europeans but the old view that they were never affected by it is now disproved. It can and does affect Indians, Negroes, Chinese and other coloured races but not so commonly as it occurs in Europeans.

It is a personal impression that when it does affect natives it affects the clerk type of native who is living on a higher ration scale than his compatriots and whose diet often contains European fats. Anglo-Indians who take a European diet are certainly liable to be affected by Sprue.

During the war large numbers of Indians were affected by a marasmic condition characterised by severe wasting, steatorrhoea, macrocytic anaemia and evidence of specific deficiencies of the vitamin B2 complex. WALTERS (1947), JONES et al (1944) and TAYLOR and CHUTANI (1945) described outbreaks of this condition and from the reports it is difficult to differentiate this condition from sprue. In fact many observers have stated that had this illness occurred in Europeans it would certainly have been diagnosed sprue and LEISHMAN (1945) writes that he is convinced that these men were cases of sprue. Unfortunately however, proper facilities for investigating these cases were not available owing

to other demands on the Medical Services and the true nature of these cases cannot be determined.

There is no doubt that many deficiency states were complicated by diarrhoea and anaemia and other symptoms which have been attributed to vitamin deficiency: the whole story of the marasmic conditions among Indian troops is still very confusing and it is felt that any opinions expressed can only be based on conjecture.

### 3. PERSONAL AND ENVIRONMENTAL FACTORS.

ASHFORD, studying the disease in Puerto Rico, found that the disease affected the well-to-do rather than the poorer classes and that it was a disease of towns rather than of rural areas.

DE LANGAN and LICHTENSTEIN (1936) describe it as a disease of the rich:

ASHFORD noted that sedentary workers were more prone to develop sprue than those who led an active life and he described people "with a naturally weak constitution" as being especially liable to it.

HOTZ and ROHR (1938) have described instances where coeliac disease and non tropical sprue affected more than one in the same family but no other workers have noted this coincidence as a feature of the disease and it has never been noted as a feature of tropical sprue.

All ages appear to be liable to the disease though its commonest incidence before the war was in middle age; MANSON-BAHR (1941) found that sprue was rare below the age of 15.

The widespread incidence of acute sprue among our troops in India during the war appears to indicate that environmental factors such as poor hygiene, environment and housing conditions, irregular and maybe inadequate rations, excessive physical effort and humid climates must have played a part in the enormous increase in incidence as compared with the Army in India under peace time conditions.

There is also another feature that must be considered.

Even where troops were under the poorest conditions and the incidence of sprue was very high there were always a large number of troops who did not suffer from sprue.

In fact more troops did not succumb to the disease than those who did fall victim to it. The identical conditions of feeding and environment imposed on such a large number of men for so long would appear to indicate that there is a personal factor which influences the incidence of sprue. It is well known by every practitioner in this country that certain individuals cannot take fatty foods without becoming "bilious" and complaining of spots before the eyes, nausea and indigestion and, in severer cases, actual vomiting. On the assumption that people, who in temperate climates were intolerant of fat, might be particularly liable to develop sprue when exposed to the dietary changes and environment of the tropics twenty five consecutive cases were questioned personally on this point. Only 3 admitted any intolerance to fats at all and no

case of pronounced "bilious" tendency was found.

Englishmen as a race are not fond of greasy foods and practically every case questioned stated this, but this dislike of fats was confined to actual fat on meat and did not include fried foods, cream or butter.

It is possible that persons with a weak link in their processes of fat metabolism are candidates for sprue when they go to endemic areas but, if this is so, the defect is not familial as sprue does not exhibit any familial tendency.

#### 4. THE ASSOCIATION OF SPRUE WITH INFECTIONS AND OTHER DISEASES.

MANSON-BAHR and WILLOUGHBY (1930) found a previous history of amoebic dysentery in 32% of 200 cases of tropical sprue, but this figure is open to the criticism that there is no evidence to show that it is any higher than the number of people who would admit to a past history of amoebic dysentery were 200 subjects, who were not suffering from Sprue but who had sojourned for long periods in tropical countries, interrogated. LEISHMAN (1945) only obtained a history of amoebic dysentery in 4% of his cases.

In the Western Desert of Libya a sprue-like syndrome was noted as an occasional sequel to prolonged dysentery especially among recently captured German prisoners of war and in many cases these men had remained on duty for many weeks, either in the Western Desert or elsewhere, in spite of the fact that they were suffering from chronic dysentery. Dysentery, both amoebic and bacillary, was rife

among the Prisoners of War in Japanese hands and it would be reasonable to suppose that, were dysentery a factor in the aetiology of sprue, a certain number of these men would have developed the disease. In Changi Camp alone 16,000 cases of dysentery occurred during the first month of confinement and, although the incidence fell as camp hygiene improved, it was always a major medical problem which necessitated special dysentery wards in the camp hospital. In spite of this the incidence of sprue was practically non-existent. This point will be discussed more fully later but it is made at this juncture in order to support the statement that no real evidence has yet been produced to show that previous dysentery is a factor in the production of sprue and, in view of the fact that amoebic dysentery is a disease of the large intestine whereas the absorptive failure of sprue is in the small intestine, it seems unlikely that any association between sprue and amoebic dysentery is of more than coincidental significance.

Yeasts of the *Monilia* type have been thought to be connected with the incidence of Sprue. MACKIE and CHITRE (1929) and later PASRICHA and LAL (1939) found that monilia is almost equally prevalent in the stools of healthy and diseased individuals in the tropics and that there was no justification for regarding them as of aetiological importance in sprue.

LEISHMAN (1945) uses a wider conception of the term "infection" to embrace a change in the predominating intestinal flora and he puts forward the

hypothesis that such a change, by inhibiting the biosynthesis of the vitamin B<sub>2</sub> complex in the intestine, may interfere with the process of phosphorylation; such a change in flora might follow unaccustomed diet.

FRAZER (1947) also suggests that it may be coincidental in some cases of sprue that bacteria of the intestine may compete with their host for certain substances which are essential to the nutrition of both.

This theory will be discussed later in this thesis.

No conclusive evidence has yet been produced to show that malaria, alcoholism or any intestinal infection or infestation is a factor in the production of sprue.

Many cases of "sprue-like" symptoms due to other disease have been reported by various writers among whom are HURST (1942), FAIRLEY and MACKIE (1937), and VAUX (1943) but in these cases the steatorrhoea was due to obstruction of the lacteals and the cases did not fall into the category of proper sprue.

There is, however, one condition which is very closely related to the sprue syndrome, which it precedes so often that many observers refer to it as "Para Sprue" and that is the condition known for many years in India as "Hill Diarrhoea."

HILL DIARRHOEA is a form of diarrhoea which occurs in areas of India subject to marked seasonal change. It is seen during the hot and humid season

of the year and the advent of cool, dry weather will often stop in a few days a diarrhoea which has lasted for months. A sea voyage often has the same effect in causing the diarrhoea to remit.

In a certain number of these cases the diarrhoea does not cease, especially if the sufferer goes down to the plains just before the end of the hot season, and the case ultimately reveals itself as unmistakable sprue.

This diarrhoea has none of the exudates of dysentery and it used to be said that the stools did not contain an excess of fat but, as these patients often limit their fat intake, and as this statement is based on fat estimations of isolated stools, it must be accepted with reserve until fat balance estimations have been done on a series of cases.

It is often very difficult, owing to the lack of adequate laboratory facilities, to differentiate this condition from an attack of dysentery of low virulence, in which the dysenteric organisms are overgrown by other intestinal saprophytes. A number of cases seen personally in Rangoon were eventually diagnosed as dysentery instead of the Hill Diarrhoea with which they were sent down from North Burma.

In the cases which are definitely not due to dysentery there seems no reason to believe that they are not a mild form of sprue - the Larval sprue of MANSON-BAHR (1940). There is no reason to suppose that sprue, in its early stages, will not be reversed if fat is excluded from the diet or living

conditions change and, until a series of these cases have been investigated with properly controlled fat balance estimations, it cannot be accepted that there is any grounds for regarding them as a separate clinical entity. It is often very difficult to decide at what time a case of sprue in the tropics had its inception; close questioning will often reveal an attack of diarrhoea some months or weeks previous to his present illness. Moreover, it is remarkable how far advanced in the disease a patient can be without his noticing anything wrong.

It was often possible in Burma for a Medical Officer to see that a man was ill when examining him on a parade owing to his emaciation, and often these men would insist that they were perfectly fit and well although they might have lost a stone or more during the past fortnight.

These cases, of short duration usually, did very well on dietary measures alone and did not even need to leave the endemic area.

"Larval sprue," "parasprue" and "prosprue" are terms which various workers have employed to describe this type of diarrhoea which often escapes detection as sprue for many months.

KEELE (1947), in a personal communication, expresses much the same opinion: he states that a great deal of so-called hill diarrhoea is really dysentery.

He is of the opinion that the remainder often merely represent a mode of onset of sprue, but only if it persists for 2 or 3 months or more. He saw



this form of "incomplete sprue" in 3 to 6% of his cases but he thinks it is commoner than this figure would indicate.

The facts stated above have been productive of many theories which have been very completely reviewed and criticised by STANNUS (1942) and only the more recent work and theories on the aetiology need be discussed further.

VERZAR and McDOUGALL (1936), believed that all fat was split by lipolysis in the small intestine and that neutral fat, which makes its way into the lacteals, is resynthesised in the intestinal mucosa from fatty acids formed by the lipolysis higher up in the small intestine. FRAZER (1946) pointed out that this lipolytic theory would not account for certain observations made by himself and his co-workers and has produced the particulate theory of fat absorption which is now more generally accepted than VERZAR and McDOUGALL'S hypothesis.

Apart from this concept, VERZAR and McDOUGALL stated that phosphorylation was essential for all fat absorption and they believed that phosphorylation in turn was regulated by the secretion of adrenal hormone. This finding was based on the fact that in Addison's disease they claimed to have found steatorrhoea, which statement is challenged by HURST (1942), and also on experiments performed on Adrenalectomised rats.

They state: "In all cases of disturbed or diminished activity of the adrenal cortex as in experimental B2 avitaminosis, pellagra, tropical and

non-tropical sprue and also in Addison's disease, disturbances of fat absorption have been seen."

BARNES et al (1939) repeated VERZAR's rat experiments and found that, provided adequate sodium chloride was administered, adrenalectomy does not affect fat absorption.

FRAZER (1946) pointed out that a low blood sodium is not uncommon in non-tropical sprue and that, while it may be corrected by administration of corticosterone, this does not produce a change in the fat absorption. He also mentions that no lesion of the adrenal cortex has yet been demonstrated at autopsy on sprue and suggests that any deficiency of adrenal cortical hormone, which may occur, might be due to prolonged steroid starvation. Furthermore, BLACK (1946), studying salt deficiency in tropical sprue found no evidence of adrenal deficiency in his cases and LEISHMAN (1945) found that these cases did not respond to desoxycorticosterone.

It therefore seems that a case has not been made for considering that deficiency of adrenal cortex is connected with the aetiology of sprue.

IZOD BENNET and HARDWICK (1940) postulated chronic jejuno-ileal insufficiency as the cause of sprue and suggested that this insufficiency might be total in as much as it affected secretion as well as absorption, but, in sprue secretion is not, as far as is known, affected, and moreover these workers

gave no indication as to the underlying cause of the insufficiency.

HURST (1942) believed that tropical and non-tropical sprue and coeliac disease are merely varieties of the same disorder, basing his statement on the fact that three characteristic and constant features are found in all three conditions, namely, (a) an excess of split fat in the stools but no excess of neutral fat, meat fibres or inflammatory material (b) the disappearance of the normal herring bone aspect of the valvulae conniventes of the duodenum as shown by X-ray examinations, and (c) the absence of any pathological changes at autopsy if the examination is done before post mortem damage occurs.

He suggests that the lack of fat absorption is due to paralysis of the musculares mucosae, which in turn may be due to absence of the normal stimulant of Meissner's submucosal plexus or the result of vitamin deficiency on the plexus. The paralysis of the musculares mucosae leads to loss of the pumping action of the villi by which HURST claimed the fat is conveyed from the lacteal radicles into the larger lacteals. HURST's theory is largely based on the findings of VERZAR, whose hypothesis he accepted.

As regards the absence of pathological changes in the intestine, this is now generally agreed, and the identity of the tropical and non-tropical forms of sprue has already been discussed.

As regards the mucosal pattern being connected with fat absorption, STANNUS (1942) points out that similar X-ray patterns occur in other conditions with defective fat absorption and are normal in infants and he believes that the altered X-ray pattern may be the effect of unabsorbed fat in the intestine, "due to its abnormal and bulky contents," and not the cause of it.

DREW and SALMON (1946) injected fatty meals into the intestine and noted that this did not affect the normal pattern in normal subjects and they claimed that this was against STANNUS's theory, but the comparison hardly seems to be a fair one inasmuch as the injection of one bulky meal into the intestine is not comparable with the situation produced by the continued presence of such meals over a long period of time.

Also WELLS and JOHNSON (1934) have shown that the villi may be quite motionless during absorption and that the converse may occur.

MANSON-BAHR (1941) suggests that deficient absorption of some constituent or constituents of the vitamin B2 complex may be an aetiological factor in sprue, qualifying this statement in 1943 by saying that the symptoms may be due not to a lack of vitamin but by failure to absorb it. He points out the great similarity between many cases of tropical sprue and pellagra and points out that pernicious anaemia may, in some cases, be very similar to sprue: he was so impressed by this similarity and by the response of certain features of sprue to nicotinic acid that in

1941 wrote the following: "..... it appears that in the disease group typified by the pernicious anaemia-pellagra-sprue syndrome the essential lesion is localised somewhere in the gastro-intestinal tract and is of such nature and extent as to interfere more especially with absorption of one or several of the vitamins essential to life." He terms this absorptive deficiency of the intestine "inefficiency" and he postulates a dysfunction of some specialised cells in the gastro intestinal tract and produces a diagram showing the sites of these cells, deficiency or "inefficiency" of which will produce pernicious anaemia, sprue and pellagra.

The possibility that vitamin deficiency is a factor in the aetiology of sprue will be discussed later and certain recent work will be reviewed.

Apart from this MANSON-BAHR's hypothesis is open to criticism on one or two counts. It is felt that it is going too far to associate two diseases, namely pernicious anaemia and pellagra, with sprue and make one syndrome out of these separate conditions. In pernicious anaemia and pellagra we have established the aetiology of the disease and we know what therapeutic measures will cure it but in the case of sprue we are not clear as to the aetiology.

Furthermore steatorrhoea is not an invariable feature of pernicious anaemia or pellagra. STANNUS (1942) points out that the geographical distribution

of pellagra and sprue is not the same and further draws attention to the fact that if the basic fault at the root of the aetiology of sprue is a failure to absorb vitamins, the response to nicotinic acid in small doses, on which this theory is based, cannot be explained.

Pellagra and sprue may exist together in the same case but not all skin conditions seen in sprue are pellagrous and many cases of sprue are seen in which there is no resemblance to pellagra. The existence of intestinal cells with a special function as regards the absorption of vitamins has yet to be demonstrated.

It is felt that while certain features of some cases of sprue are due to the condition known as vitamin deficiency, this term covering inability to synthesise vitamins as well as to absorb them, and that while some cases of sprue may closely resemble or be complicated by pellagra, that this is coincidental or a sequel to the condition rather than its primary cause.

STANNUS (1942) having reviewed the literature and criticised the outstanding views current at the time propounded his conception of sprue.

He agreed with VERZAR that a failure of phosphorylation was the primary cause of the failure of fat absorption in sprue but disagreed that this failure of phosphorylation was due to adrenal deficiency. He postulated that it was due to defective enzymic action.

He states: "The enzyme or enzymes which

catalyse phosphorylation - the "carriers" of phosphoric acid - probably have as the active part of the molecule coenzymes embodying some member or members of the vitamin B2 complex - all present in crude liver extracts. These many include riboflavine, nicotinic acid and pyridoxin. It may be remembered that choline is sometimes now included in the B2 complex.

Whether the same enzyme catalyses the phosphorylation of all the several substances is uncertain. Since normally the phospholipids (lecithins) synthesised by the intestinal mucosa from fatty acid, glycerol, phosphoric acid and choline contain unsaturated fatty acids it is possible that desaturation occurs at the same time as phospholipid synthesis. In view of the close association of pyridoxin with unsaturated fatty acids, it seems possible it may be at fault in sprue.

The nature of the fatty acids in the diet may be a factor in determining the geographical distribution of the disease.

The loss to the body of certain phospholipids containing highly unsaturated fatty acids may be a factor in the causation of the anaemia in sprue and of other nutritional anaemias."

He considers that the deficient absorption of fat is limited primarily to loss of power to absorb fatty acids and cholesterol and that the absorption of neutral fat is not affected (this would accord well with FRAZER's findings), but he also considers that there may be a secondary deficiency in neutral

fat absorption in consequence of non-absorption of fatty acid. He points out that there is a primary loss of power to absorb glucose, resulting in a flat glucose tolerance curve, and of galactose the glycerol formed by the splitting of neutral fat.

VERZAR showed that phosphorylation was necessary to glucose absorption and regards the flat sugar tolerance curve as strongly supporting the breakdown in phosphorylation. Fructose is normally absorbed without phosphorylation and MAEGRAITH et al (1946) investigated the absorption of glucose and fructose and found that, whereas the glucose tolerance curves were flattened in cases of sprue, the fructose absorption was unaffected. This is added confirmation of the phosphorylation theory as propounded by VERZAR and STANNUS.

From clinical observation it would appear that there is some difference in the degree in which phosphorylation of fats and sugars are affected in sprue.

It has been noted in several cases that although as the case improves under treatment, the flat sugar tolerance curve returns to within normal limits, the fat absorption is not affected *pari passu* and, if it ever returns to normal again, lags behind the recovery seen in the absorption of glucose.

Furthermore cases of sprue occur in which fat absorption is affected but the glucose tolerance test gives a normal curve.

Six cases out of the nine reported in Appendix 1 illustrate these observations. It may be as

STANNUS suggests that a different co-enzyme is required to catalyse phosphorylation of fats from that necessary in the case of sugars, or it may be that other factors than these co-enzymes are affected and prevent the normal absorption of fats. The anti-oxidants, of which one of the best known groups is the tocopherol series, may be at fault and, if deficient, would allow oxidation and non absorption of fat in the bowel. It is known that rancidity will destroy them and many fats eaten in the Far East are rancid. DARBY et. al. (1946) have found low tocopherol levels in three patients with sprue who were in relapse or early remission.

Be that as it may it does appear from clinical observation that, if a breakdown in phosphorylation is responsible for the defective absorption of both fat and glucose, there is a difference in the degree of breakdown in phosphorylation of fats as opposed to the defect as regards the phosphorylation of glucose. FOURMAN (1947) investigated changes in the blood phosphate after the ingestion of glucose and fructose in five normal subjects and four sprue patients and found no difference between the absorption of these sugars. It is considered that a good case has been made out for failure of phosphorylation being the cause of defective fat absorption but the next and obvious necessity is to determine the cause of this breakdown in phosphorylation.

STANNUS (1942) thinks that this is due possibly

to a lack of coenzymes 1 and 2 which catalyse phosphorylation and he points out that, as coenzyme 1 (diphosphopyridine nucleotide) consists of a molecule each of adenine, nicotinic acid amide united to a molecule of pentose, in turn connected to two molecules of phosphoric acid, there is some reason for believing that nicotinic acid may be implicated in phosphorylation. Riboflavine has also been stated to be a phosphate "carrier" so that "while nothing is known with certainty concerning the enzymes catalysing phosphorylation, it is probable that coenzyme 1 does play a part."

This hypothesis would explain the improvement seen in many cases after liver therapy and treatment with constituents of the vitamin B2 complex.

LEISHMAN (1945) working on the basis of STANNUS's assumptions has carried the process back a stage further. He points out that RHOADS and MILLER (1934) showed that parenteral liver extract in sufficiently large doses will control a case of sprue and that liver extract contains every known constituent of the vitamin B2 complex; that two of these, nicotinic acid and riboflavine, occur in the body in phosphorylated form as important components of tissue respiratory - enzyme systems, nicotinamide in the complex diphosphopyridine nucleotide or coenzyme 1 and, with slight modification, coenzyme 2, and riboflavine as yellow oxidase. He suggests that, in addition to their ability to accept and reject hydrogen, by virtue of which they catalyse oxidation, they can also accept and reject phosphoric acid and so

catalyse the process of phosphorylation.

He points out that in sprue one seldom obtains a history of deficient vitamin intake but he states "our whole conception of vitamin B deficiencies must now be recast in the light of recent knowledge of biosynthesis by intestinal bacteria. For example, by incorporating sterilising sulphonamides in the diet it was shown that all the identifiable B vitamins together with E and K were synthesised in a rat's caecum. Thiamin, nicotinic acid and biotin are synthesised within the human gut. The quantity of vitamin produced varies from person to person and is sensitive to changes in the diet but it can be considerable. In one riboflavine experiment ten times as much vitamin was excreted as was taken in the diet.

LEISHMAN then quotes the experiments of BENESCH (1945) who cultured material from a caecostomy both aerobically and anaerobically and found that under aerobic conditions, synthesis of nicotinic acid by intestinal bacteria took place. When the culture was anaerobic the organisms grown destroyed a large part of the nicotinic acid already present in the medium. This suggests that in health an equilibrium exists between vitamin productive and destructive organisms and LEISHMAN suggests that on the strength of these findings we should now give a much wider meaning to the term "infection" so that it includes this disturbance of bacteriological equilibrium in the intestine.

An exogenous infection, itself not pathogenic, could swamp the normal synthesising bacteria or this

could result from a change in intestinal media such as could follow a change in diet or altered gastric activity.

Finally he suggests that such a change might merely be due to stagnation of intestinal contents.

The lines along which he urges future investigation should proceed are:

1. A series of vitamin excretion estimations in sprue cases and controls on a standard low vitamin diet, and
2. An investigation of the small intestine flora on the lines of Benesch to determine the relative proportion of aerobes to anaerobes and their ability to synthesise nicotinic acid and other constituents of the vitamin B complex.

This hypothesis has the advantage that it should be relatively simple to confirm or deny.

#### THE ROLE OF VITAMINS IN THE AETIOLOGY OF SPRUE:

The advocates of the theory that sprue is a disease due to deficiency or deficient utilisation of vitamins base their belief on the response of most cases to liver therapy, which observation was originally made by RHOADS and MILLER (1934).

Liver contains every known constituent of the B complex and of these, nicotinic acid and riboflavine, which are constituents of the B<sub>2</sub> complex, have been especially suspect as the substances deficiency of which is a primary factor in the production of sprue, because of the response of some cases to treatment with these substances.

LEISHMAN, as has been stated previously, regards this deficiency as being an interference with the biosynthesis of nicotinic acid and riboflavine in the intestine and a consequent interference with production of Coenzyme I.

MANSON-BAHR (1941) was among the first to suspect that deficiency of nicotinic acid might have a bearing on the aetiology of sprue. He noted that the glossitis of sprue and the glossitis of pellagra responded similarly to nicotinic acid therapy and, on the strength of this, suggested that the two conditions might be closely allied.

He stated that the action of riboflavine appears to be to heal the angular stomatitis which is frequently associated with sprue as well as pellagra. He stated that this therapeutic effect indicates that pellagrous stomatitis is due to Vitamin B<sub>2</sub> deficiency and went on to draw attention to the resemblance between the glossitis of sprue and pellagra on the one hand and that of pernicious anaemia on the other, and which he claimed also responds to nicotinic acid. He then reported a series of cases of sprue treated with nicotinic acid and noted its curative effect not only on the glossitis, but also on the gastro intestinal symptoms and the skin.

He noted that nicotinic acid would not affect the haemopoiesis - for this liver therapy was necessary.

On the assumption that deficiency of the vitamin B<sub>2</sub> complex was an aetiological factor in sprue, nicotinic acid and riboflavine usually com-

bined with liver therapy have been extensively prescribed in the treatment of the disease.

WINGFIELD (1946) states that he allows all his patients with sprue to take a full ward diet and get up when they wish and that he treats them with crude liver injections (4 cc. daily for one week and twice weekly thereafter), and to this he adds oral nicotinic acid 50 mgs. t.d.s.

This conception is open to criticism and cannot be regarded as proved.

As STANNUS (1946) points out, it is dangerous to assume that because a condition responds to therapy with a certain vitamin it is therefore caused by a deficiency of that substance.

KEELE (1946) has pointed out that glossitis and angular stomatitis may actually increase when the patients' dietary intake contains adequate quantities of nicotinic acid and riboflavine and furthermore, it has been noted that remission of the glossitis and stomatitis often occur in cases of sprue without any additional intake of nicotinic acid or riboflavine.

BLACK, BOUND & FOURMAN (1947) found that in 28 cases of sprue nicotinic acid and riboflavine given by injection did not cause clinical improvement nor increase fat absorption.

Another objection to the acceptance of a vitamin deficiency being a primary aetiological factor in sprue is the fact that prisoners of war in Japanese hands did not develop sprue.

These men lived for three and a half years on a diet that was deficient in practically every thing:

they developed many and varied deficiency syndromes including pellagra and beri-beri but sprue was virtually an unknown disease among them. This striking fact will be dealt with at greater length later but it is mentioned here because it is difficult, to say the least of it, to reconcile with a theory that postulates vitamin deficiency as the cause of sprue.

It may be argued that, as these prisoners were living on a diet deficient in fat, they did not manifest sprue during their captivity: this argument would be valid if several prisoners went down with sprue, which had been masked by fat deficient diets, when they started eating normal diets after their release but this did not occur. Many of them overate and developed transient diarrhoea but sprue was an exceedingly rare finding among released prisoners of war.

MITCHELL & BLACK (1946) saw only one case in the 577 cases of malnutrition they reviewed and MACFARLANE (personal communication 1947) states that he had a dysentery wing of 1200 beds in the Lahom Paton Allied P.O.W. hospital and he has only seen one case of sprue develop in his patients after release.

The writer has personally examined over 100 ex Prisoners in Japanese hands and, although practically every known deficiency syndrome has been encountered, no case of sprue was seen.

The response of sprue to pteroyl-glutamic acid (folic acid) is more dramatic in many respects than

that elicited by liver, yeast, nicotinic acid or riboflavine.

Folic acid is another constituent of the vitamin B<sub>2</sub> complex and DAVIDSON & GIRDWOOD (1947) are of the opinion that there seems to be little doubt that, in its free form, it is the factor essential for the continuation of normoblastic blood formation and that a deficiency causes reversion of the bone marrow to the megaloblastic state (the "megaloblastic arrest" of American authors). They point out that if free folic acid is given in pernicious anaemia, transformation occurs in the megaloblastic bone marrow together with an increase of free folic acid in the urine, but that with conjugated folic acid (pteroyl-heptaglutamic acid) as contained in yeast, no such transformation in the marrow or increase in the urinary free folic acid occurs.

When however liver extract is given the marrow transformation and also the urinary excretion of free folic acid occurs. Hence they assume that purified liver extracts contain a factor which allows the conversion of conjugated folic acid to free folic acid to take place.

They further state that this liberating factor, which they term L.F., is the product derived from interaction of Castle's intrinsic and extrinsic factor and is liberated in the intestine and stored in the liver.

They propose the hypothesis that the cause of pernicious anaemia is inherent in the inability of the body to convert conjugated folic acid to free

folic acid due to lack of L.F.

It would be an attractive theory that sprue was similarly due to a lack of L.F. and, to support this theory, it could be stated that folic acid improves the diarrhoea, the glossitis and the patient's sense of well being and, in many of the cases with macrocytic anaemia it will transform a megaloblastic bone marrow.

Against this theory however is the blood picture of sprue.

If, as DAVIDSON & GIRDWOOD postulate, a lack of L.F. causes Addisonian anaemia, this hypothesis is discounted immediately because a great number of cases of sprue show a hypochromic anaemia or no anaemia at all.

Furthermore the anaemia of sprue, even when it is macrocytic and the bone marrow is megaloblastic, rarely responds as completely to folic acid or to liver as does the anaemia of pernicious anaemia.

Moreover, folic acid often fails to restore the fat absorption completely back to normal.

In some cases it may be that lack of L.F. or free folic acid does play a part in the production of the clinical picture but, in view of the variable response of the blood and the fat absorption to its administration, it cannot be regarded as a primary factor in the aetiology of the disease.

Apart from the vitamin B<sub>2</sub> complex no case has been made out for regarding deficiency of any other vitamin as playing a part in the aetiology of sprue.

Some cases may be complicated by vitamin C

deficiency (MANSON-BAHR (1945) attributes certain skin rashes to this) or by deficiency of vitamin A or D, but these deficiencies, if they occur are coincidental and not fundamental deficiencies.

There at the present time, is the modern conception of sprue. It is becoming more and more widely accepted that a breakdown in phosphorylation is the primary cause of the defective fat absorption but, though ingenious theories as to the cause of the breakdown in phosphorylation have been advanced, they must be treated with reserve until further work has been done.

#### THE ACTUAL FAT CONTENT OF THE DIET.

This has not been so closely considered, one of the main reasons for this omission being that the fate of fats after ingestion by normal subjects has only recently been worked out by FRAZER, and as yet his investigations are incomplete.

There are however two incontrovertible facts that have emerged during the past few years that must direct our attention to a closer study of the breakdown constituents of the animal and vegetable fats that constitute the human daily fat intake.

The first is the occurrence of sprue in such large numbers among our troops during this last war and the fulminating and rapid onset of this disease, in many cases only a few weeks after landing in India fresh from the United Kingdom.

In some cases these men were accommodated under reasonable conditions and ate an adequate and regular diet but in others they were badly

accommodated in huts or in the open during the humidity of the monsoon and were called upon to make great physical effort with rations that were often inadequate and irregular. A classical example of this last type of case was seen among 80 Chindits who were kept on a K diet. The K diet, the constituents of which are given Appendix No. 2, is a compact emergency ration which is intended to feed a man for 2 days or, possibly a week at the most, until he can be supplied with fresh rations: it is not intended that men should subsist on it over long periods. In the case of the Chindits they were subsisted on this ration without a change of diet and they were able to eat it and enjoy it for the first week, after which anorexia, diarrhoea, nausea and, frequently, vomiting after eating it developed. Diarrhoea and flatulence appeared and three weeks later sore tongues so that these men developed sprue from a base line of good health inside 8 weeks, which is a great contrast to the slower development of the classical type of sprue seen before the war. In all 60 out of 80 cases sent in with symptoms of malnutrition were suffering from sprue.

The incidence of sprue among British troops in India and Burma during the last war reached such proportions as to become a serious problem. This exceptionally high incidence can be better appreciated when it is realised that out of 8000 men invalided home from the Far East for medical reasons there were 1000 cases of sprue.

This striking rise in the incidence of sprue

among our troops in the Far East during the last war is further shown by the following figures which give the number of men who were discharged from the army as being unfit for further service on account of sprue.

1943	-	6
1944	-	49
1945	-	196
1946	-	73
1947 (Jan-August)		13

The number of men stationed in the Far East did undoubtedly increase between 1943 and 1945 but not sufficiently to account for an increase of discharge from the army due to sprue of from 6 to 196.

The second striking fact appears at first to be a paradoxical finding in direct contradiction to what has just been stated.

From what has been said it would be expected that the conditions under which our prisoners in Japanese hands had to live would have produced an exceedingly large number of cases of sprue. They were housed in primitive conditions; they were worked mercilessly and their diet was reduced to a very low scale.

Notwithstanding this and contrary to expectations these people did not develop sprue. Brigadier J. BENNET, the present Consulting Physician to the British Army, was himself a prisoner in Japanese hands and he has sent a personal communication on the incidence of sprue in the prisoner of war camps which is quoted here in full.

"THE OCCURRENCE OF SPRUE IN PRISONERS OF WAR  
IN FAR EASTERN CAMPS.

"The heavy incidence of bacillary dysentery and deficiency of the Vitamin B complex in Singapore camps in 1942 directed attention in cases of bowel disorder to possible evidence of the emergence of clinical features suggestive of the sprue syndrome.

During the first six months of captivity in Singapore the diet consisted of unpolished rice 500 g., meat or fish 50 g., fresh vegetables 100 g., and its fat content was mainly represented by 5 g. of cooking oil and an uncertain issue of 15 g. of canned milk. During this time severe cases of dysentery frequently showed complete desquamation of the thick, dirty yellowish-white fur on the tongue leaving a painful raw red surface. In association with this, palatal erythema was usually seen. Many of these cases showed persisting diarrhoea not easily referable to an unresolved dysenteric lesion by the presence of pus in the stools or evidence obtained on sigmoidoscopy. The stools tended to be liquid and faecal without demonstrable blood or mucous; they seldom showed evidence of active fermentation and were not bulky. A few cases developed a moderate degree of anaemia, investigation of which showed a mucous gastritis with a tendency to low levels of H.Cl secretion and a blood picture of a normocytic and normochromic nature. Up to August 1942, when I left Singapore, it could not be shown that these cases were in any way related to the sprue syndrome, and they were tentatively attributed to Vitamin B2

complex, possibly specifically one of nicotinic acid, deficiency conditioned by the dysenteric state. Cases of Wernicke's encephalopathy had previously been common in the same group and had been controlled to some extent by the prophylactic administration of Marmite or yeast tablets of Japanese origin.

In Formosan camps the diet was one in which unpolished rice was supplied along with about 8 ounces of poor quality vegetable. For long periods fat was represented by meagre quantities of vegetable oil, often averaging no more than 1 g. per day per head. Diarrhoea was very common and appeared to be attributed at first to mechanical irritation of the gastrointestinal tract and hyperactivity of the gastrocolic reflex. Its features, however, in some cases assumed a sprue like character with relapses and remissions of abdominal distension and explosive evacuations of stools which were occasionally frothy. These bowel movements were often confined to the early morning. Changes in the tongue were common. In the more acute cases the fungiform papillae were reddened towards the tip and erosions on the lateral border were common. In a few more protracted cases the tongue was large, of a reddish brown beefy appearance, somewhat bald, particularly in the dorsum and often fissured. These cases could be kept under control by careful attention to dietetic hygiene and the addition of yeast to the diet. Loss of weight was not much below the average in the camp as a whole.

The only case diagnosed as sprue in the Formo-

san camps that I am aware of was that of a young officer aged 30. He was seen in August 1943 after a year's captivity in Formosa. He gave a history of diarrhoea at sea in transit, of severe fever in January 1943. Following the latter diarrhoea had been present, stools frothy and the tongue sore. Motions varied from 6 to 10 daily. He had three further attacks of fever with tertian periodicity during this period. When seen in August 1943 he was very emaciated, weight 40 kilos (normal weight 70 kilos), with distended abdomen, frothy semi-liquid stools containing much undigested food, anaemia (hb 50% Tallqvist), enlarged spleen and enlarged tender liver. The malarial condition was rapidly cured by adequate treatment. The diarrhoea reacted very slowly to dietetic treatment combined with yeast, and any attempts to give even moderate amounts of starchy food such as rice gruel or small quantities of fat, caused an immediate relapse with severe distension and explosive bowel evacuations.

On a dietary regime commencing with fractional feeds of milk, bananas and white of egg, he was gradually restored to normal health and weight over a period of nine months. Glossitis occurred during the early stages of recovery but was otherwise not observed while under treatment. The diagnosis of sprue appeared to receive its main support from emaciation which was out of all proportion to that prevailing in cases with a similar history, and from the case being refractory to dietetic treatment of the kind which was well tolerated and successfully

employed in the type of cases referred to in the preceding paragraph."

TAYLOR, CRUICKSHANK, McFARLANE, HUSTON, GRAVES, HUNT & PHILLIPS, all of whom were themselves prisoners, have stated in personal communications that their experiences were in agreement with those of BENNET and that sprue was practically unknown among the prisoners of war in the Far East.

TAYLOR states that he remembers only one example of sprue among the prisoners in CHANGI camp and he was admitted to hospital before the commencement of captivity and remained in hospital until the prisoners were released. He concluded by stating "whether there were any more cases of sprue or not, it is certain that among the Singapore prisoners the disease was of the greatest rarity, and I believe this also applies to the prisoners in Burma and Siam".

CRUICKSHANK, in three and a half years saw two cases that could be clinically regarded as sprue and both these were Dutchmen who had suffered from the disease before the war in Java. He states "Watery diarrhoea was frequent in malnourished patients. The stools contained some pus cells, no excess of fat microscopically and undigested food at times."

"At post mortem these patients were grossly wasted. The small intestine was diaphanously thin with marked congestion and atrophy of the valvulae conniventes; some areas had a haemorrhagic appearance and in a small number of cases a plastic peritonitis associated with these areas. None of these, however, could be regarded as sprue."

The findings in the stool and the post mortem findings described by CRUICKSHANK certainly are not typical of sprue but appear to be due to changes of an irritative or inflammatory nature.

The prisoners of war hospital in Changi camp kept records which, considering the circumstances under which they were compiled, are remarkably complete.

A study of the "Annual Medical Reports of the P.O.W. Camp, Changi" from 1942 until 1945 confirms that sprue was virtually not encountered under these conditions.

In the 1943-44 report the following statement is made - "NON SPECIFIC DIARRHOEA:"-

"This was very common. In many cases it was probably due to Vitamin B2 deficiency, the bowel presenting an atrophic appearance, though no cases of obvious sprue were encountered."

Personal experience in examining a number of ex-prisoners who appeared for follow-up examinations and medical boards bears out this observation.

They gave histories and showed residual signs of every type of nutritional deficiency and intestinal infection and infestation: stories and residua of vitamin deficiency such as pellagra and beri-beri were very commonly encountered but in no case was there a history of sprue.

Thus, on the one hand, troops in India and Burma were developing sprue under the strain and hardships of war in very large numbers whereas prisoners of war, on the other, were not affected by it at all, although

their living conditions were as hard, and in a great many cases, worse than those of the troops who were succumbing to the disease.

In one respect however there was a great difference between the two groups and that was in the amount of fat and protein, especially animal fat and protein, in the daily diet. Two tables after BENNET are given in Appendix No. 2 showing the rations issued in No. 1 Prisoner of War Camp, Tariwau, and the average nutritive value of these rations per head daily. From these tables it will be seen that in 1943 the mean meat content of the ration was 0.099 G. daily, no fresh fish was issued and the average daily amount of dried fish per head was only 4.89 G. and only 0.69 G. of oil was supplied. The diet was made up with rice 410 G., soya beans 1.39 G., bean paste 4.169 G. and bean sauce 1.59 G. per man daily. This was a daily average intake of only 5.29 G. fat, 0.59 G. animal protein and 42.99 G. protein per man daily, the main bulk of the diet being 437.39 G. carbohydrate. In 1944 the situation improved considerably but the total fat intake only averaged 19.09 G. daily for a fit man and animal protein was only 3.19 G. daily, the total protein being 64.99 G. daily and the carbohydrate reaching an average of 639.39 G. daily.

There is no evidence that the protein metabolism is affected in the early stages of sprue and a positive nitrogen balance is the rule: the oedema, which may be due to low plasma protein, is a late manifestation or occurs while the case is recovering

under treatment.

It therefore would seem that the fat intake is important in the development of sprue and that unless an individual is ingesting a certain quantity of fat he will not develop sprue, even though he is subjected to all the other conditions that would favour the development of the disease.

It is reasonable to suppose that the prisoners of war would have contributed their rational quota to the total of patients with sprue had they not been under conditions which inhibited its development. Moreover it has also been well-known for some time now that if sprue is treated in its early stages it will clear up with dietary measures only and that a fat free diet with a high protein value will in these cases be successful.

KEELE (1946) who was seeing a very large proportion of early acute cases, found that dieting alone, using Hamilton Fairley's high protein, low fat and low carbohydrate diet, was successful in 67% of cases, the remainder requiring parenteral liver as well.

He also found that acute sprue has developed on a well balanced diet under jungle warfare conditions. These findings are strong support of the hypothesis that sprue can not develop unless there is an adequate level of fat in the daily diet and that, if fat is excluded from the diet even in the early stages of sprue, its development will be inhibited and the process will right itself, but, should fat persist in the diet for long after the disease process has

commenced, the full pathology will ensue and absorption of other dietary constituents will be impaired: at this stage the condition will not be inhibited merely by limiting the fat intake but will require replacement therapy with liver or folic acid also.

It is a time-honoured belief, now known not to be in accordance with fact, that native races are not affected by sprue. It is true that under normal conditions they are not affected to anything like the same extent as Europeans but it has been diagnosed among Indians and among West Indian negroes. ASHFORD studying the disease in Puerto Rico found that the disease affected the well-to-do rather than the poorer classes and that it was a disease of towns rather than rural areas and KEELE (1947) in a personal communication states that there is no doubt that steatorrhoea occurs in Indians, particularly those on relatively high fat diets, and that he saw several cases in Anglo-Indian civilians, who seem prone to it and who take a European diet. This bears out a personal impression gained in the West Indies from five cases of sprue seen in blacks in Trinidad and two cases seen in Burmese in Rangoon.

It is well known that the diets eaten by the poorer natives are deficient in fats and especially in animal fats, their fat intake being mainly in the form of vegetable oils, and this would appear to support the proposition that the type of fat ingested is an important factor in the aetiology of sprue.

WINTROBE (1942), discussing the treatment of sprue makes the following statement:

"Vegetable oil such as olive oil may be well tolerated when fats of animal origin cause diarrhoea." He quotes one of his severely ill patients who was able to take 1 oz. of olive oil daily.

It is therefore reasonable to suppose that the ingestion of animal fats may be more likely to allow the development of sprue than the ingestion of vegetable fats and STANNUS (1942) suggested that the nature of the fatty acids in the diet may be a factor in determining the geographical distribution of the disease.

The breakdown products of the various fats and their ultimate fate in the body have not yet been worked out completely in the normal subject and therefore it is prudent to speculate no further, but it is tempting to theorise that the fats themselves may produce a toxic factor, which may impede some catalysing "trigger" mechanism.

Additional factors may be the presence or absence of the anti oxidants, of which the tocopherols are among the best known, and the proportion of saturated to unsaturated fats.

It may be significant that the tocopherols are destroyed by rancidity and, as many animal fats, especially butter, frying fats and ghee become rancid in Eastern countries before they are eaten, destruction of the anti-oxidant substances may allow oxidation of the fats in the intestine with subsequent failure in absorption.

Low plasma tocopherol values in cases of active sprue are described by DARBY et. al. (1946).

THE DIAGNOSIS OF SPRUE.

## THE DIAGNOSIS OF SPRUE.

The typical case with diarrhoea, steatorrhoea, meteorism, progressive loss of weight, anaemia and signs of nutritional deficiency, occurring in an endemic area presents no great difficulty but sporadic cases often occur, in which the presenting features do not fit in with textbook descriptions of the illness, and in these cases the diagnosis may be very difficult. The work of the past ten years has increased this difficulty because it has shown that sprue, instead of being a clear-cut clinical entity with well-marked geographical limitations, is a condition of impaired fat absorption often accompanied by impaired haematopoiesis, which overlaps other disease entities in many respects.

It is therefore necessary to attempt to lay down the limits of the sprue syndrome and, in order to do this the findings will be described and an attempt will be made to indicate their importance as diagnostic criteria.

This is not an easy task because frequently it is only in its later stages that the symptom complex can be defined with any certainty.

### MODE OF ONSET OF THE DISEASE.

In many cases the diagnosis of sprue in its early stages is practically impossible because they merely present a long standing history of vague abdominal discomfort with attacks of fleeting diarrhoea and periods of constipation.

The attacks of diarrhoea are usually diagnosed

as dysentery, either amoebic or bacillary, or as "Hill diarrhoea."

It is considered that patients in endemic areas (cases) presenting this history should be investigated thoroughly for amoebic and bacillary dysentery and that, if repeated stool examinations and sigmoidoscopy prove negative, the patient should be given a known fat intake of either 100 gms. or 50 Gms. daily and then investigated for steatorrhoea. A diagnosis of "Hill diarrhoea" should never be accepted as it is felt that these cases will all be found to be either dysentery, sprue or some other known syndrome that is complicated by diarrhoea, if they are thoroughly investigated.

At this time the patient's nutrition is good and sprue is not thought of as the cause of his condition. One of the most common signs found in the abdomen is distention and any history of this or of flatulence should direct the examiner's attention to the possibility of sprue.

Many cases develop more acutely and produce the recognisable picture in a very short time and are not preceded by a long history of abdominal discomfort.

During the last war a great many cases presented this abrupt development of the symptom complex with rapid loss of weight.

Many cases in endemic areas have suffered from previous dysentery and this past history frequently overshadows the picture and clouds the diagnosis.

For this reason it is not advisable to go on

with anti-amoebic therapy when no indication for it is found in the stools or by sigmoidoscopy.

In some cases the presenting feature is soreness of the mouth, first noticed by the patient when he eats hot or spiced foods. This may be a fleeting occurrence which recurs later on in the disease.

On examination shallow ulcers, the aphthae tropical~~e~~ of earlier writers, may be seen along the sides of the fraenum of the tongue or in the buccal mucous membrane.

STEATORRHOEA: This finding is essential to the diagnosis of Sprue and, whether in the tropics or at home in European climates, the syndrome cannot be diagnosed unless it can be shown that the patient is excreting more of his fat intake than the normal human being. The importance of determining the fat balance over a period of not less than 48 hours as opposed to the estimation of the percentage of fat in an individual stool has already been stressed.

Having determined that the excretion of fat is excessive it is equally important to determine that this steatorrhoea is not secondary to other conditions which will be mentioned in the differential diagnosis, but is primary or idiopathic in nature; that is to say that, in our present state of knowledge, we cannot determine the cause of the failure of fat absorption, and it is to all appearances the primary lesion of the disease: there is no doubt that further research will reveal the cause of this dysfunction but at present it is obscure and, in order

to diagnose the condition of Sprue, the case must come into this category.

The typical sprue stool is so characteristic that, when present, it will indicate the diagnosis clearly. The original description of GEE (1888) in his paper "On the Coeliac Disease" is so accurate that, although it has been frequently quoted, no excuse is sought for plagiarising it yet again. "The signs of the disease are yielded by the faeces; being loose, not formed, but not watery; more bulky than the food taken would seem to account for; pale in colour, as if devoid of bile; yeasty, frothy - an appearance probably due to fermentation; stinking stench often very great, the food having undergone putrifaction rather than concoction. The pale loose stool looks very much like oatmeal porridge or gruel. True the dejections are faecal, more liquid and larger than natural; but they are not always more frequent than natural; it may be that the patient voids daily but one large loose whitish stinking stool."

This stool, although typical, is not always found when investigating a case of sprue. BLACK et al. (1946) have drawn attention to the attacks of watery diarrhoea, frequently mistaken for bacillary dysentery as they respond to sulpha therapy, which often occur during the course of sprue.

This watery diarrhoea may be almost choleraic in intensity.

FRAZER et al. (1946) and BLACK et al. (1946)

have also drawn attention to the fact that the stools may be of normal colour and consistence and yet the patient be excreting more fat than the normal subject.

HINDS HOWELL (1947) stated that an increase in the percentage of split fats in the total faecal fat is one of the earliest signs of sprue, but FOURMAN (1946) has demonstrated that if neutral fat is added to a sprue stool in vitro it will become split, and therefore it is felt that the importance of the actual percentage of split and unsplit fats in the stool is not of great diagnostic or prognostic importance.

The sprue stool does not usually contain undigested protein in the shape of muscle fibres.

#### SYMPTOMS AND SIGNS IN THE ALIMENTARY TRACT.

The sore mouth is often the first symptom to lead to the diagnosis of the disease and the patient often first complains that hot or spiced foods hurt his mouth.

Cheilosis is a frequent sign and, on examination of the tongue, it is found to be red, smooth and shiny or glazed in appearance, and it is painful especially at the tip and along the edges, which may be hyperaemic or even show tiny ulcerations. The edges of the tongue may be indented by the teeth in severe cases. On examining the fraenum tiny ulcerations may be seen along the sides of it.

The entire mucosa of the mouth may be red and sore and show similar small shallow ulcers. The

tongue and mouth may be so sore that a hungry patient may dread taking food and this may necessitate the diet being restricted to milk. In the early stages this soreness of the mouth is often only present for short intervals and KEELE (1946) has drawn attention to the frequent remissions at the commencement of the disease; he points out that the occurrence of the glossitis usually coincides with improvement of the patient generally and disappearance of his diarrhoea and anorexia, and he therefore terms it one of the symptoms of remission. Sometimes swallowing may cause retrosternal pain, indicating that the oesophageal mucous membrane is also affected.

Anorexia is a marked feature of sprue and always occurs in every case at some time or other. It too waxes and wanes and KEELE terms it one of the symptoms of relapse as it is accompanied by diarrhoea, loss of weight and deterioration of the patient's general health. In some patients this anorexia is especially marked as regards fats, which they know they cannot tolerate, and they seem to acquire a dislike for them. Distension and flatulence is one of the most constant features of sprue and nearly every case shows it during its course.

The abdomen is appreciably distended, usually in the mid line around the umbilicus, and percussion over this distension often yields a dull note, indicating that the distension is caused by masses of digested but unabsorbed food in the small intestine.

Thinness of the abdominal wall may allow peristalsis to become visible. Vague abdominal discomfort is practically invariable especially in the early stages and patients complain of an ill defined discomfort which they find difficult to describe. Barborygmi and a mild colicky contraction of the gut often troubles them and they suffer from eructations.

Vomiting is an uncommon symptom of sprue though it may occasionally be seen. Heartburn, often described as epigastric pain, is a frequent symptom of sprue. It is usually transient and may recur at intervals and diagnoses of peptic ulcer have been made in cases in which heartburn is a predominant feature.

The diarrhoea has already been described: urgency of defaecation is frequently confined to the early morning and wears off as the day goes on.

Some patients complain of periods of constipation.

Pruritus may occur in some cases.

#### GASTRIC ACIDITY.

Complete achlorhydria is not so common as hypochlorhydria, which is present in the majority of cases; some cases may show normal gastric acidity curves.

Achylia Gastrica does not occur in sprue and histamine will yield some secretory response.

#### GLUCOSE TOLERANCE TEST.

A comparison of the blood sugar curve when glucose is given by mouth with the curve when it is

given intravenously may be a very helpful finding in doubtful cases. If the oral curve is flat and the intravenous curve is normal it indicates deficient absorption from the intestine. Not all cases of sprue present the typical flat blood sugar curve after the oral administration of glucose but, when present, it is a sign of great value in confirmation of the diagnosis.

#### X-RAY APPEARANCES OF THE ALIMENTARY TRACT.

RHOADS and MILLER (1934) described the characteristic appearances of the small bowel radiologically but GOLDEN (1941) has conclusively proved that these appearances, though seen in all cases of sprue at some time during its course, are not specific for sprue. He has described similar appearances in Vitamin B deficiency, worm infestation, chronic nephritis and post irradiation enteritis. He suggests that the changes seen in sprue are due to deficiency of some factor causing atrophic changes in the autonomic nervous plexus in the wall of the small bowel such as have been described in Vitamin B deficiency.

DREW, DIXON and SAMUEL (1947) used radiology as a method of assessing recovery from sprue and detecting cases likely to relapse, and they claim that clinical and radiological estimations were of equal value in assessing recovery.

The radiological changes in sprue are classified under four headings:

- (a) CHANGES IN MOTILITY. Although the meal

may pass through the small bowel more quickly in the early stages of the illness, in the established case delay is the prominent feature. In the small bowel the appearances of films taken at intervals change so little that they give the impression of being cast in wax and this unchanging radiological pattern has been described as the "Moulage Sign."

(b) CHANGES IN TONICITY. Areas of segmentation (hypertonicity) alternate with hypotonic areas of dilatation: these changes are best seen in the middle third of the ileum according to DREW, DIXON and SALMON and are not seen in the jejunum or terminal third of the ileum to the same extent. They point out that in the early stages of sprue the jejunal mucosal pattern is exaggerated due to increased tonicity of the muscularis mucosae, whereas in the later stages this pattern is lost and flattened due to hypotonicity of this structure. This finding is compatible with the increased motility described in the early stages, which changes to a picture of delay in the later stages of the illness.

(c) PATTERN CHANGES IN THE MUCOSA. These changes are seen best in the middle third of the ileum and are described under four headings - viz, coarsening of the folds, irregularities of the folds, flocculation of the meal and obliteration of the folds.

The coarsening of the folds, widening of the valvulae conniventes and the replacement of the normal feathery mucosal pattern by a few coarse and

widely separated mucosal indentations is most obvious in the upper jejunum. As the disease progresses the valvulae conniventes become very regular and widely spaced.

The next phase is marked by the meal losing its smooth and uniform consistence and becoming granular in appearance and aggregated into floccules giving a fragmented appearance to the shadow.

In the terminal stages the mucosal folds of the bowel become obliterated and this change is best seen in the middle third of the ileum.

(d) CHANGES IN THE COLON. DREW, DIXON and SALMON found that there was some enlargement of the colon in most of the cases they investigated and stated that this enlargement appeared to be secondary to the large bulk of the faeces and was moderate in degree. As this moderate dilatation of the colon is present in many cases of tropical sprue they are doubtful whether it is useful, as has been suggested, to differentiate between sprue and coeliac disease.

To explain the colonic dilatation as being due to the large bulk of the faeces does not appear to be sound: the 26 cases investigated by these workers were convalescent and 12 cases were considered to have completely recovered and 9 only showed mild signs of sprue. Therefore, in these cases, bulkiness of the stools should not have been a feature and it would appear that atony of the colon, which persists after clinical recovery must be present to account for these radiological findings.

LOSS OF WEIGHT: Cases of sprue are invariably under weight and, though this is merely secondary to the failure of absorption, it is such an invariable finding that it is considered a basic and essential feature of the disease.

The case when seen may be in a phase of remission and not be actually losing weight, but he is under his normal weight: when he reaches his normal weight it is a sign of recovery and indicates that absorption from the intestine is re-established, although in many cases steatorrhoea and anaemia persist for some time after the body weight is restored to normal.

ANAEMIA is not a constant feature in sprue.

KEELE, who investigated over 600 cases of sprue, found that 35% of his cases showed normal blood counts and this is a far larger proportion than a study of the text books on the subject would indicate. In another 30% of cases he found a normal Haemoglobin and Red Blood Cell count but macrocytosis as the only divergence from normal. Thus 65% of his cases showed normal red blood counts and haemoglobin estimations and, in half of these cases, a macrocytosis was discovered as the only abnormality. It must be borne in mind that KEELE was coming in contact with the acute sprue syndrome which differs from the type of case seen in ordinary peace time conditions in its clear cut and almost fulminating onset and, under these conditions, it is reasonable

to postulate that there had not been time in many cases for the anaemia to develop. He himself states:

"At the onset of sprue the blood changes are slight even with profound loss of weight.

Dehydration may mask some changes. When anaemia develops it is macrocytic from the start in most cases. With remission the macrocytosis persists, the haemoglobin rising slowly. Reticulocytosis is not marked: normoblasts do not appear. As the patient reaches normal weight, and not before, the blood picture returns to normal."

Personal experience of chronic cases seen in this country is that the weight returns to normal in many cases a considerable time before the blood picture conforms to this clinical improvement.

The anaemia of sprue is not usually so severe as that seen in pernicious anaemia and, though in some cases it may be very profound, figures of 1.500.000 are unusual. The bone marrow, in cases with macrocytic anaemia, may show changes very like pernicious anaemia with hyperplasia of the cells of the erythrocyte series and megaloblasts predominating.

Normoblasts are also seen in the marrow in cases in which iron deficiency is a feature. In cases with hypochromic anaemia the marrow shows a relative as well as an absolute increase of normoblasts and contrasts sharply with the lack of red cells in the peripheral blood, this increase in normoblasts being approximately proportional to the degree of

anaemia. Sprue does not show the severe degrees of anaemia met with in cases of pernicious anaemia and poikilocytosis is not so pronounced.

"The deficiency of haemopoietic factor and iron in sprue probably accounts for the variability in size and haemoglobin content of the corpuscles as indicated by their colouring and yet an approximately normal mean corpuscular volume." (WINTROBE 1942).

"The blood picture changes as relapse and remission stages follow each other: as relapse occurs a hypochromic anaemia becomes macrocytic in type or, a normal haemoglobin content with macrocytosis as the only abnormality will become a macrocytic anaemia." (KEELE 1946).

Finally, it must be borne in mind that dehydration may mask an anaemia during the onset and relapse phases of the disease by producing haemoconcentration.

DEHYDRATION. The importance of dehydration as a feature of sprue has been largely overlooked until BLACK drew attention to it in 1946. Along with dehydration, a low B.P. and diminution of the blood Sodium content is also found and this may be coupled with pigmentation of the skin, which is so intense in some cases as to lead THAYSEN (1935) to raise the question of the possibility of suprarenal damage, but BLACK found no evidence of this in any of his cases.

In the advanced case with a dried tongue, sunken eyes and a blood pressure between 110 and 100

systolic there is no great difficulty in diagnosing dehydration but many cases do not present these florid signs until dehydration is well advanced. Also, dehydration occurs suddenly and progresses rapidly in the tropics, especially in patients with diarrhoea; in fact it may run ahead of its physical signs, and may be missed in the earlier stages unless the daily intake and excretion of fluid is charted as a routine.

The following case, seen personally, exemplifies this very important point.

A young soldier, aged 25, was admitted to Hospital in Rangoon as an obvious case of Sprue with diarrhoea and bulky, pale, frothy stools. He had travelled for six hours in a hospital train and, as the weather was hot and humid, he had sweated considerably.

On arrival he was febrile and complained of thirst but otherwise the dehydration was not very obvious.

His blood pressure was 105/65 and his urinary output was only five ounces in the first twenty four hours and, in spite of salt (grams 10 daily) and water (10 pints daily) his urinary output was only thirty ounces on the third day of his treatment in Hospital.

The fact that in tropical climates patients with diarrhoea are losing a great deal of fluid cannot be too strongly emphasised; not only may the timely hydration of these patients bring them out of

a seemingly hopeless condition into a state in which they can benefit from therapy but it may change the clinical picture by revealing an anaemia which has been hitherto masked by haemoconcentration.

Dehydration is not a feature of every case of sprue but when it is present its early diagnosis is of great importance.

THE GENERAL PHYSICAL AND MENTAL STATE OF THE PATIENT.

The patient usually complains of lassitude and a feeling of tiredness and inability to concentrate.

This tiredness may be so pronounced that even walking about in his room will exhaust him; this feature is well shown in case No. 3, who complained that even walking about his room exhausted him.

Emaciation and loss of weight is a very constant feature of sprue except in its early stages.

The loss of weight is often very rapid and the patient may lose 1 to 3 stones in weight in a matter of one to three months. The subcutaneous fat disappears and the skin is wrinkled and lies loosely over the body. If the case is seen during a remission phase he may not be actually losing weight but his weight is below his normal.

Oedema, especially affecting the legs and sacral area, is a frequent finding in sprue especially in cases who are responding to treatment. This oedema may be general in some cases. Petechial rashes used to occur in patients who were treated on milk and, as they disappeared when ascorbic acid was

given, they have been thought to be scorbutic in nature. These rashes usually affected the thighs but small subcutaneous haemorrhages on the hands have also been observed.

Dermatitis and subsequent pigmentation of the skin may occur, especially in elderly patients and it is commonly seen when they are convalescent. Pellagrous rashes with the typical raised edge may complicate sprue. Female cases often complain of menstrual disturbances and amenorrhoea is common. The onset of pregnancy exacerbates the symptoms of sprue.

The patient may suffer from distressing cramps due to calcium deficiency.

In a few cases tetany has been described but bony deformity or fracture is not a feature of tropical sprue.

Sprue patients are often very difficult to handle and require patient nursing because they become very bad tempered and irritable. Depression is also quite a common feature of the disease.

Occasionally patients complain of paraesthesiae, numbness and tingling in the extremities but actual cord lesions are very rare, though MANSON-BAHR (1945) states that they have been observed. Case No. 3 is an example of a patient who displayed tingling and paraesthesiae as a feature of his illness but MANSON-BAHR states that, in cases with severe anaemia, spastic paraplegia, ankle clonus, a positive Babinski sign and even complete paralysis of the lower extremities have been described. Such

cases are outside the personal experience of the writer.

### THE DIFFERENTIAL DIAGNOSIS OF SPRUE.

One of the main difficulties in the diagnosis of sprue is having in mind the possibility that the illness may be this disease instead of due to some other pathology. It appears to be far more common to miss diagnosing sprue than to diagnose sprue which eventually reveals itself as some other condition.

Once the possibility of sprue occurs to the investigator a fat balance test and the application of the diagnostic criteria should quickly confirm or disprove the possibility in most cases although certain cases may prove very difficult of definite diagnosis.

The diseases which may simulate sprue sufficiently to cause confusion fall into four groups and will be described under four headings.

#### 1. CASES WITH DIARRHOEA.

##### (a) THE DYSENTERIES.

BACILLARY DYSENTERY as a rule will cause no trouble as it is a more acute disease in its onset, runs a shorter and more acute course, does not exhibit steatorrhoea as a feature and the organism can in most cases be isolated without much trouble.

In some cases, however, confusion can occur, especially in two types of circumstances.

When the strain of dysentery bacillus is of low virulence the *b. dysenteriae* may be overgrown with *b. coli* and other intestinal organisms and may be very difficult to isolate. These mild cases

may not show the exudates of dysentery and, as they often are on a low diet, the fact that their faecal fat is low is not a finding of much value. They have often been diagnosed "Hill diarrhoea" or parasprue and the real nature of the disease has escaped detection for some time.

In the second type of case which has proved a pitfall a patient with undetected sprue complains of an acute attack of watery diarrhoea. BLACK (1946) describes this feature of the disease and points out that this diarrhoea usually responds to sulpha drugs. As the patient is usually on a restricted diet the absence of fat in his stools is to be expected and the attack may well be labelled dysentery, the true nature of the illness being overlooked for a considerable time.

The emaciation of dysentery is of more rapid development and, after treatment, the patient puts on weight again rapidly in comparison with sprue where the emaciation comes on after the disease is well established and the weight takes longer to recover. In the mild cases of dysentery the emaciation is in no way comparable to the extreme wasting of established sprue.

(b) AMOEBIC DYSENTERY in the active stages usually presents no great problem as the character of the stool and its exudates, the isolation of vegetative amoebae, sigmoidoscopic findings, co-existent hepatitis and the absence of steatorrhoea will in most cases clear up the diagnosis. The old

case of dysentery who has received one or more courses of treatment, often an incomplete course, can cause great difficulty. These cases are usually seen in this country and they give a history of amoebic dysentery and state that they are suffering from a recrudescence of the old trouble. They are often thin and are suffering from attacks of diarrhoea and on examination no cysts or amoebae are found and sigmoidoscopy reveals no sign of active amoebiasis.

It is notorious that amoebic dysentery after treatment may be followed by abdominal discomfort and occasional looseness of the bowels for months or even a year or two after treatment and that no signs can be found. These patients are often diagnosed as neurotics or anxiety states and it never occurs to the medical attendant to examine the fat excretion of these cases.

Cases which have been infected with amoebic dysentery as well as suffering from sprue can be most difficult to unravel. This problem was presented by Case No. 2, a nurse in the Queen Alexandra's Nursing Services who had had repeated courses of treatment both in India and in this country before she was admitted for investigation to Millbank.

It must be remembered that sprue may underlie the story of chronic and intractable amoebic dysentery and if this is done much time will be saved in arriving at the diagnosis.

GIARDIASIS may produce a fatty looking stool and may be confused with sprue.

(c) CARCINOMA OF THE COLON may simulate sprue especially if secondary deposits cause lacteal obstruction with consequent steatorrhoea but the diagnosis is not long in doubt if examination reveals the typical lymph glands or secondary deposits in the liver and a filling defect on X-ray examination: also the growth may be seen on sigmoidoscopy.

(d) ADDISONS DISEASE has been mistaken for sprue in cases which are suffering from diarrhoea, which often ushers in a crisis, when they are seen. Although, superficially, the disease has certain features in common with sprue a mistake in the diagnosis should be of very rare occurrence as the clinical picture differs from sprue in many respects of which the most important are, the absence of steatorrhoea, the distribution of pigmentation to the mucus membranes, the persistently low blood pressure and blood sodium and potassium findings. The asthenia of Addisons disease is marked but the wasting is not such a striking feature as one would expect to find in a case of sprue with comparable asthenia and hypotension.

## 2. CONDITIONS CAUSING STEATORRHOEA.

### (a) STEATORRHOEA DUE TO OBSTRUCTION OF THE LACTEALS.

In adults lymphatic obstruction of the lacteals may be due to intra abdominal carcinoma with lymphatic spread, lymphadenoma affecting the mesenteric

glands or to long standing Hirschsprung's disease. In children tabes mesenterica is the condition which mainly causes confusion.

Regional ileitis may also exhibit steatorrhoea as a feature in a few cases.

In all these conditions it is unlikely that the diagnosis will be in doubt for long as the clinical picture of the conditions mentioned is very unlike sprue in that a known cause for the steatorrhoea exists and can usually be found.

Any findings such as ascites, abdominal adhesions or tumours, enlarged lymph glands or hepatic enlargement are against a diagnosis of sprue: the X-ray findings in most of the conditions mentioned are typical of a different pathology from sprue and in no case will the X-ray changes described elsewhere in this thesis be found.

Finally the sugar tolerance test will give a normal curve and, in these cases of lacteal obstruction, the greater part of the fat in the stool is found in an unsplit condition.

(b) CHRONIC PANCREATITIS.

This condition, especially when it occurs in an endemic area, may cause considerable difficulty. It is the condition par excellence which may well cause an experienced physician much painstaking investigation before the diagnosis becomes clear.

In many cases a past history of jaundice, gallstones, cholecystitis or an acute febrile gastritis, or findings suggestive of cirrhosis of the liver may

indicate a pancreatic cause for the steatorrhoea and a finding of undigested meat fibres in the stools in the early stages when steatorrhoea has only just been detected is very much in favour of a chronic pancreatitis.

Diabetes is rare in chronic pancreatitis and only occurs in long standing cases in which the islets of Langerhans have been affected, but when it does occur it is a useful and valuable finding.

In exceptional cases diarrhoea is severe, there is complete anorexia and emaciation is rapid and these cases may closely resemble sprue except that the diarrhoea may be too severe and the wasting too rapid to fit in with the usual picture of the sprue syndrome.

Urinary diastase estimations are not of much help unless they show a marked increase in the urinary diastase, as normal findings do not exclude chronic pancreatitis as a possibility.

Glossitis and cheilosis are not features of chronic pancreatitis and, if they are found, will weigh the scales in favour of sprue. In Case No. 9 the past history of ulcers in the mouth was taken as being strongly in favour of sprue, although the stool findings resembled those of chronic pancreatitis.

In some cases jejunal intubation may be necessary to establish the diagnosis although even this may give very little information of value if trypsin is present in quantities which approximate to normal instead of being absent. FRAZER (1946)

states that Lipase is usually present but may be less than normal.

In most cases the diagnosis can be made after due consideration of the history and the clinical findings but exceptional cases may take some time before they reveal themselves as sprue or chronic pancreatitis. In cases of doubt the therapeutic test of treating the case as sprue is clearly indicated.

(c) HEPATIC DISEASE is a cause of steatorrhoea but should not be confused with sprue as a general rule.

In sprue the area of liver dullness is usually decreased due to a combination of meteorism and actual decrease in size of the liver whereas this does not obtain in hepatic disease except in cases of cirrhosis. In cirrhosis the history and signs of portal obstruction will usually direct investigations along the correct channels.

Jaundice is not a feature of Sprue Syndrome.

(d) STEATORRHOEA DUE TO GASTRO COLIC OR ENTERO COLIC FISTULA, should cause no difficulty as the history and X-ray findings will clear up the diagnosis.

### 3. CONDITIONS CAUSING STOMATITIS AND CHEILOSIS.

Where the first presenting sign of sprue is the stomatitis the condition may be very difficult to differentiate from aphthons stomatitis until the disease has progressed to a recognisable clinical picture.

In cases where the sore mouth is accompanied by a macrocytic anaemia, pernicious anaemia must be differentiated.

#### 4. CONDITIONS SHOWING FEATURES OF DEFICIENCY DISEASE

(a) STARVATION - such as was seen in prisoner-of-war camps should not cause any difficulty in diagnosis. The history of malnutrition, the absence of excessive excretion of fat and the response to an adequate diet are completely different from sprue.

Anorexia Nervosa - may be confused with the anorexia of sprue. The diagnosis may be difficult especially when, as in case No. 2 anorexia nervosa supervenes on sprue and perseverates the clinical picture and obscures an otherwise good therapeutic response.

(b) PELLAGRA may simulate sprue very closely indeed and, as a result of this similarity MANSON-BAHR (1943) was of the opinion that the two conditions were closely allied and MANNING (1909) referred to pellagra as psilosis pigmentosa. It is true that there may be a very close resemblance on clinical examination but a close study of the case will usually clear up the diagnosis. In pellagra there is a history of a diet low in protein and the constituents of the vitamin B<sub>2</sub> complex whereas sprue may attack persons whose diet is adequate.

The florid case of pellagra with the "magenta" tongue and the symmetrical skin lesions which display the hyperkeratotic border of MERK will present

no difficulty but some pellagrins do not exhibit the skin lesions - "pellagra sine pellagra" - and these cases may closely resemble sprue if diarrhoea is a feature of the disease.

The diarrhoea of pellagra is unusual until the disease is advanced and excessive fat excretion is not a feature of pellagra.

Erythema or itching of the skin is more a feature of pellagra than of sprue and if the lesions are symmetrical it is most suggestive of pellagra.

The tongue in pellagra is more of a red, angry and inflamed character than in sprue and KEELE never saw it in 600 cases of sprue. Any involvement of the spinal cord is evidence against a diagnosis of sprue and symptoms such as burning or numbness of the extremities make pellagra a more probable diagnosis. Fat balance tests should clear up the diagnosis and in cases of doubt the urinary nicotinic acid excretion test of HARRIS and RAYMOND may be useful.

(c) TROPICAL MACROCYTIC ANAEMIA - affects women usually and is much aggravated by pregnancy, when it assumes a frankly megalocytic type. Excessive excretion of fat is not a feature of this disease and the sugar tolerance test will not give the flat curve typical of sprue.

(d) PERNICIOUS ANAEMIA is not likely to be a cause of confusion: it is unlike sprue in many important features. Excessive fat excretion in the stool is not a characteristic of this condition and the wasting, which is so typical of sprue, is absent in pernicious anaemia.

Achlorhydria is a feature of pernicious anaemia but rare in sprue and the flat sugar tolerance curve is not found in pernicious anaemia.

T H E T R E A T M E N T O F S P R U E .

- A. GENERAL MANAGEMENT
- B. DIETARY TREATMENT
- C. TREATMENT WITH VITAMINS
- D. LIVER THERAPY
- E. TREATMENT WITH FOLIC ACID

THE TREATMENT OF SPRUE.

The treatment of sprue varies with the chronicity of the case as do the prospects of achieving beneficial results.

KEELE (1946) found that 67% of his cases responded to dietary measures alone, only 35% requiring liver therapy in addition, and it was a common finding in India and Burma that cases who were detected as suffering from sprue because of their emaciation on medical inspections did well on dietary measures and often did not have to leave the endemic areas.

These were acute cases and KEELE was dealing with an acuter type of sprue than was seen by physicians before the war and these are the cases which respond to the dietary restrictions without the need arising for substitution therapy.

WINGFIELD (1946) differed from KEELE in his handling of cases of sprue and, basing his opinion on the findings of RHOADES and MILLER (1934) and CASTLE et. al. (1945) that the anaemia and other symptoms of sprue all respond to liver when given a crude extract parenterally, states "This observation has been proved beyond any doubt and should be the basis of all modern treatment of this syndrome." He goes on to state that it is his practice to allow all patients with sprue a full ward diet and to get up when they wish and to give them crude liver parenterally (Plexan 4 ccs. daily) for one week and then twice weekly with nicotinic acid 50 mg. t.d.s.

orally.

WINGFIELD is justified in his observation that his cases did better on liver extract than on dietary measures because he was seeing a far more chronic type of case in this country than KEELE was in India where many of the patients had landed from the United Kingdom as healthy soldiers only a few months previously.

Liver therapy has proved to be of such great value in the treatment of sprue that it should be given in all cases seen under peace conditions.

The early and acute case which responds to dietary measures alone was seen under conditions of war and is not likely to be met with in normal times.

RHOADES and MILLER (1934) and CASTLE et. al. (1935) first showed the marked effects of Liver on the tropical cases of sprue although it does not produce such good effects in the non tropical forms of the syndrome, and these findings have been confirmed by clinical experience of so many physicians that Liver therapy must be given pride of place in any discussion of the treatment of sprue.

The treatment of Sprue will be discussed under the following headings:

1. General Management
2. Dietary Treatment
3. Vitamin Therapy
4. Liver Therapy
5. Treatment with Folic Acid

The objects to be aimed at in treating sprue are:

(a) To remove any painful or harmful features of the disease which are impeding the patient's recovery.

Under this heading will fall the relief of the glossitis, which makes it difficult for the patient to eat, the relief of vaginitis and proctitis which disturb the patient's rest and the treatment of dehydration and low blood sodium with its attendant asthenia which constitute a menace to the very life of the patient.

(b) To relieve the distension, the diarrhoea and the steatorrhoea.

The distension is due largely to the presence of digested but unabsorbed food in the small intestine and the diarrhoea is probably due to the presence of irritant soaps in the large bowel (HURST). The steatorrhoea is the essential feature of the disease and can be obviated by dietary restriction of the fat intake and liver or Folic Acid therapy.

(c) The treatment of the anaemia by liver extract or folic acid.

This feature of the disease is often one of the most resistant to therapy and is, in many cases one of the last signs to disappear.

(d) The replacement of deficiencies such as Vitamins, and Minerals.

Cases of sprue should be treated in bed, especially the acuter type of case with marked relapses

and remissions.

If these cases are allowed to get out of bed too early they often relapse although liver therapy has curtailed the period of absolute rest considerably.

Before a case is allowed out of bed he should have begun to put on weight and should be taking a number 4 diet (see Appendix 3). His diarrhoea should be controlled and he should have completely recovered from any asthenia and he should have recovered sufficiently to want to get out of bed himself.

The nursing of sprue cases requires a great deal of patience: when they are in the advanced stages of the disease they are apt to be difficult and querulous, their appetite is uncertain and particular attention must be paid to the condition of the mouth.

Where the mouth is very sore two hourly feeds of skimmed milk may be all that can be given.

There is no doubt that nicotinic acid and riboflavine will accelerate the recovery of the glossitis and angular stomatitis and, as this recovery takes place solids can be added to the diet.

Where gastric acidity is low dilute hydrochloric acid should be given in orange or lemon juice at meals.

DEHYDRATION must be suspected in cases where the blood pressure is low and there is asthenia.

This feature of the disease was not appreciated in its proper importance until BLACK (1946) drew

attention to it.

In tropical climates a fluid intake and output chart must be kept in all cases of sprue and the blood pressure should be taken daily. Should the output of fluid fall appreciably and a corresponding fall be noted in the blood pressure active treatment should be taken to restore fluid and salt.

It must be remembered that patients with diarrhoea in hot and humid climates can lose a great deal of fluid and BLACK has shown excessive sodium chloride excretion in the stools.

Up to ten pints of liquid may be given daily and up to 10 grams of sodium chloride may be needed daily to restore this balance.

Oral administration of fluids and salt will usually suffice and it is rare to have to recourse to intravenous saline.

If dehydration is detected early and treated at once a patient may be restored from a condition which is apparently hopeless to one in which he can benefit from therapy.

Once dehydration is well established the prognosis is not so good and LEISHMAN (1946) has noted that these patients do not respond so well to hydration.

Dehydration, by concentrating the blood, may mask an anaemia which will become apparent as the dehydration is relieved.

## 2. DIETARY MEASURES.

Many and varied diets have been tried for

tropical cases of sprue, the most useful of which were MANSON'S skimmed milk regime and later FAIRLEY'S high protein, low fat and carbohydrate diet.

As many cases were not able to tolerate milk well FAIRLEY advocated the use of "Sprulac" a dried milk with a low fat and carbohydrate and a high protein content as this preparation is often better tolerated than milk.

Strawberries, bananas, apples and the juice of oranges lemons and tomatoes are well tolerated in sprue and MAEGRAITH (1946), as a result of his studies of fructose absorption in cases of sprue, stated that these fruits were well tolerated because they contain no glucose, which is badly absorbed, but fructose which is well absorbed.

The malabsorption of carbohydrates and starches may be as great as that of fats and the presence of imperfectly digested starch may increase the diarrhoea.

In the Army the sprue dietary consists of six diets ranging from the Number 1 diet of only 721 calories to the number 6 diet of 3,120 calories.

The number 1 diet contains only 5 Gms. of fat and 119 Gms. of carbohydrate and this is increased by stages until the number 6 diet contains 115 Gms. of fat and 343 Gms. of carbohydrate.

These diets are given in detail in Appendix No.3.

A case of average severity can start with solid food and can be begun at the number 3 diet and with liver therapy can usually be increased up through

the No.4 and No.5 diets to a number 6 diet in three or four weeks.

More severe cases require a number 2 or even a number 1 diet to begin with.

If the tongue is very sore it is wise to give a number 1 diet and, in addition nicotinic acid 50 to 100 mgs. three times daily until the glossitis and cheilosis is relieved.

Raw minced liver can be added to the diet but, as the therapeutic effect is more certain if liver is given parenterally this should not replace the intramuscular route.

Nicotinic acid, riboflavine, thiamin, yeast and marmite can all be added to reinforce the diet and undoubtedly seem to have speeded recovery in some cases but the rôle of vitamin preparations in the treatment of sprue will be discussed later.

Many cases, especially those seen in the early stages of sprue, will eventually be able to return to a normal diet but there is always a proportion, especially in those cases where treatment is begun late who will always be intolerant of fat and will have to restrict it, and possibly carbohydrates also, for the rest of their lives.

KEELE (1946), who was largely dealing with acute and early cases in men who had landed in India in perfect health only a few weeks previously found that dietary measures alone sufficed in 67% of cases and that liver was useful in only 33%.

It was not uncommon to see cases during the last

war who became emaciated rapidly and cleared up quickly on dietary measures alone but in the type of case seen in peace conditions, which is slower of development and evades detection for a longer time, it is always sound policy to reinforce dietary measures with parenteral liver therapy.

WINTROBE (1942) has found that vegetable oil such as Olive Oil may be well tolerated when animal fats cause diarrhoea and he quotes one of his severely ill patients who could not take polysaccharides or animal fats without getting diarrhoea but who could take seven ounces of glucose and one ounce of Olive Oil daily without ill effects.

### 3. SPECIFIC THERAPY WITH KNOWN VITAMINS.

For many years vitamin therapy has been advocated in sprue. Liver contains the vitamin B<sub>2</sub> complex and in 1934 RHOADS and MILLER described the beneficial effects of therapy with crude liver extracts in cases of sprue.

MANSON-BAHR in 1940 claimed good results with nicotinic acid and riboflavine but most cases were treated with liver extract in addition to these vitamins.

WINGFIELD in 1946 advocates the treatment of sprue with Liver, nicotinic acid and riboflavine.

Following SPIES' original investigations in 1945 other workers have used folic acid and there is no doubt that it produces dramatic results, though the steatorrhoea, the anaemia and the hypochlorhydria

are not improved *pari passu* with the general improvement of the patient.

It is considered that therapy with liver extract and with folic acid is of established benefit to the patient and that folic acid may well produce improvement in cases who are stationary under liver therapy.

The replacement of other vitamin deficiencies is not on such firm ground.

Nicotinic acid and riboflavine given alone (that is to say without liver extract as well) do not produce improvement in the patient's general condition or in the fat absorption.

BLACK, BOUND and FOURMAN (1947) found no clinical improvement in cases treated with nicotinic acid and riboflavine by injection and no improvement in the fat absorption. They claimed that yeast extract would improve fat absorption and that cases could be maintained on it and that it was preferable, under these conditions, to give yeast extract by mouth than liver extract by injection.

As cases can be maintained on 5 mgs. folic acid by mouth daily the advantage of giving yeast extract is not so apparent. Commercial yeast products vary in their content and it is felt that folic acid is a more scientific method of maintaining a patient than is the use of yeast preparations.

Apart from this there seems no reasonable indication for any vitamin therapy unless a patient with sprue shows signs of a specific vitamin deficiency, such as scorbutic signs complicating the picture of

sprue.

If the diet is adequate in vitamins it should not be necessary to reinforce it with vitamin pills or injections apart from the therapeutic administration of folic acid.

#### 4. LIVER THERAPY.

RHOADS and MILLER (1934) and CASTLE et. al. (1935) described the very successful results of treating cases of sprue with crude liver extracts parenterally.

They pointed out that adequate doses of liver extract would, in most cases benefit the steatorrhoea, the glossitis, and the diarrhoea, flatulence and anorexia.

When a severe case of sprue is on dietary treatment and is given liver therapy it is surprising how quickly he gains weight in view of the restriction of his fat and carbohydrate intake.

As the steatorrhoea decreases the X-ray appearances of the intestine return to normal and the case enters the convalescent stage much more quickly than did cases treated on dietary measures alone.

The absorption of fat has been shown to be improved in some cases but it is not an invariable finding and in many cases improvement in the general condition occurs without any appreciable increase in fat absorption.

Where macrocytic anaemia is a feature the blood regeneration is not as a rule as rapid as in perni-

scious anaemia and it is a fairly common occurrence to find a blood count slightly lower than normal and a degree of macrocytosis for some weeks after the patient has returned to full health in every other way.

WINTROBE (1942) states that liver may be beneficial even when the anaemia is not macrocytic.

The more refined liver extracts do not do nearly as much good as the cruder extracts, so that it seems that more than the haemopoietic factor alone is concerned in the improvement following its administration.

Plexan Compolon and Hapatex are widely used in this country and 4 ccs. daily for 10-14 days is the dosage used for a case of average severity.

After 10-14 daily injections a dose of 4 ccs. twice weekly for two or three weeks will usually suffice, though, as stated before, the anaemia may lag behind the general clinical improvement.

Where there is marked emaciation even larger amounts of liver may be necessary (up to 8 ccs.daily) and, if emaciation is extreme, it is often wise to give the liver extract intravenously.

Some physicians, who have treated cases after they have been invalided home from the endemic areas, tend to treat dietary measures and rest in bed as of little importance but they are certainly very necessary adjuncts to liver therapy in the acute cases seen in the tropics.

In any case it seems rather futile to give a

patient fat which he cannot absorb and, in view of the hypothesis put forward earlier in this thesis that the absence of fat from the intestine will inhibit sprue it seems only rational to combine liver therapy with dietary measures.

It is of interest to note that native physicians in Ceylon have treated sprue with a liver soup for many centuries and MANSON found Chinese physicians treating cases of sprue with success using pills of dried crow's livers.

#### 5. FOLIC ACID THERAPY.

The name "Folic Acid" was first applied in 1941 by MITCHELL, SNELL and WILLIAMS to a substance which they concentrated from the leaves of spinach.

This substance had previously been referred to as Vitamin M (DAY et. al., 1938), factor U (STOKSTAD, 1938), factors R and S (SCHUMACHER et. al. 1940), Vitamin Bc (HOGAN and PARROTT 1940), norite eluate factor (SNELL and PETERSON, 1939) and Lactobacillus casei Factor (HUTCHINGS et. al., 1944).

It is acidic in nature, contains nitrogen, has a molecular weight of 500, and it was first isolated in crystalline form in 1943 by PFIFFNER et. al.

In October 1943 DAFT and SEBRELL treated granulocytopenia and leucopenia, previously produced in rats by adding 1% sulphaguanidine or sulphasuccidine to their diet which contained thiamin, pyridoxin, riboflavine, calcium pantothenate, nicotinic acid and biotin. They found that four days administration of folic acid augmented the

white blood count from an average of 2,700 to 14,400 and the percentage of granulocytes from 1 to 39.

This work was the result of observations that leucopenia in rats was cured by concentrated extracts of liver, the preparation of which suggested that the substance which stimulated leucocyte production might be the growth factor for lactobacillus casei (SNELL and PETERSON, 1940).

Its crystallisation led to its identification with the anti anaemic factor of the chicken which is also known as vitamin Bc. (PFIFFNER, BINKLEY et. al. 1943).

In very small quantities folic acid is a powerful factor in growth stimulation of normal cells and is a growth factor for chickens, rats, dogs, pigs and certain bacteria among which is the lactobacillus casei.

A three months old chicken which has been deprived of folic acid is only one sixth the size of a chicken from the same brood that has been given adequate folic acid.

In 1945 LEUCHTENBERGER et. al. reported complete regression of breast cancer in 43% of mice affected by the tumour which were treated with 5  $\mu$ .g. of folic acid daily, no regression of the tumour occurring in controlled mice which were not given folic acid.

In certain animals such as the rat it has been shown that synthesis of folic acid takes place in

the intestine and, as this biosynthesis is inhibited by sulphaguanidine and sulphathiazole, it is thought that this biosynthesis probably occurs due to the agency of coliform bacilli (WELCH and WRIGHT, 1943). It has also been shown that when these sulpha derivatives are given the level of folic acid in the liver falls considerably (DAFT and SEBRELL, 1943).

The human excretion of folic acid is very low - about 10  $\mu$ .g. daily - compared with the average intake of 1.4 mg.

DAVIDSON and GIRDWOOD (1947) found grounds to believe that the daily requirement of folic acid in human beings lies between 0.5 and 1 mgm.

The identification of folic acid with the anti anaemic factor in the chick naturally suggested that it was concerned not only with the production of white blood cells, as had been hitherto supposed, but that it might also be a factor in the production of red blood cells.

The extraction of folic acid from liver and yeast yields such small quantities of the substance that clinical trial had to be postponed until it could be synthesised in adequate quantities.

In August 1945 ANGIER et. al. succeeded in synthesising the substance and the following month SPIES et. al. published the results of the first clinical trial of synthetic folic acid (Lactobacillus casei factor) in 42 cases of macrocytic anaemia of which 8 were cases of sprue. They found in the cases of sprue that the anaemia recovered and that the liquid fatty stools were also affected and

reverted to solid brown faeces.

DARBY et. al. (1946) described three cases of sprue treated with intramuscular injection of 15 mgm. daily in which complete haematological response occurred and, in addition, the glossitis and diarrhoea also disappeared and the patients put on weight rapidly. In all three cases however the blood count did not completely return to normal the figures being, in the first patient a rise from 2.2 to 3.6 millions, in the second patient from 1.8 to 3.2 millions and in the third patient from 2 to 3 millions. These authors concluded that the response to the L. casei factor resembled in all respects that which follows the administration of an active liver preparation and they stated that improvement in the general condition was noticeable after three days. They suggested that vitamin M deficiency in monkeys was an experimental analogue of sprue in man and proposed that the group of substances related to the L. casei factor and folic acid, and which exhibit haemopoietic activity for primates, be termed the "Vitamin M group."

SPIES et. al. (1946) described five cases of sprue treated with folic acid.

In all five patients the macrocytic anaemia was determined by the Wintrobe indices, the bone marrow showed the typical megaloblastic arrest seen in macrocytic anaemia and the red blood cell counts were below 2,500,000.

All were untreated, had persistently low

reticulocyte counts during the period of observation, and each patient had glossitis and diarrhoea characterised by fatty stools. Following the oral administration of 29 mgs. of folic acid daily, the clinical improvement of the patients was striking and an increase in the sense of well being, strength, vigour and appetite was noted by all the patients.

Remission was characterised by a reticulocytosis beginning on the fourth day and reaching a peak about the sixth and this was followed by a typical haemopoietic response and an increase in the number of red blood cells and haemoglobin.

MANSON-BAHR and CLARKE (1946) describe the rapid and dramatic recovery of health when a long-standing and serious case of sprue, which had resisted liver extract and nicotinic acid, was put on 10 mgms. of folic acid a day for five days.

Their supply of folic acid was limited and therefore the dose had to be restricted to this amount.

On the fourth day the patient felt fitter than for many months, his appetite returned and he was soon allowed full normal hospital diet. Three days later the soreness of the tongue had ceased and the abdomen was not distended. Fourteen days after the completion of therapy a fractional test meal, which the day after the completion of the course of folic acid showed no free hydrochloric acid in the gastric juice, was within normal limits. The haemopoietic response was pronounced but not dramatic, probably

because of the previous long continued liver therapy.

SPIES et. al. (1946) describe a similar dramatic improvement in a Cuban lady who was one of their series of patients.

MORRISON and JOHNSTON (1947) described four cases treated with folic acid. Two cases, previously untreated, showed a dramatic improvement both in their blood and intestinal absorption. Two cases of long standing with much previous liver therapy were improved subjectively, but little or no effect on the blood was observed.

DAVIDSON, GIRDWOOD and INNES (1947) described ten cases, chiefly from the haematological point of view, treated with folic acid.

Of their cases four only were tropical sprue, three being cases of idiopathic steatorrhoea and three being cases of coeliac disease. One of the cases of tropical sprue occurred in a woman 26 years after she had left India and the authors question whether this was a case of tropical sprue or idiopathic steatorrhoea.

During the past year these authors have investigated 33 adults with the sprue syndrome, of which 13 were cases of tropical sprue and 20 cases of idiopathic steatorrhoea.

The anaemia was usually only moderate (mean red blood cell count about 4,000,000 per c.mm.), the blood picture was usually macrocytic as judged by the stained film, the high colour index and the high M.C.V., and the bone marrow was usually normoblastic.

These patients had received treatment with high protein low fat diets, supplemented with liver injections and vitamins for months or years before coming under observation. They state that they have found the anaemia associated with the sprue syndrome to be particularly resistant to all forms of treatment, including the injection of both purified and crude liver extracts and the administration of iron and vitamins.

Their hope that folic acid might supply the answer to this therapeutic problem did not seem to have been fulfilled, judged by the unsatisfactory haematological responses obtained in 9 out of 10 patients reported by them.

They therefore suggested that, since neither parenteral liver extract nor folic acid may be effective in restoring the blood picture to normal, some other haematinic factor, as yet unidentified, may be required.

They point out that SPIES et. al. (1946) and GARCIA LOPEZ et. al. (1946), who were dealing with cases of tropical sprue in Cuba, laid down definite criteria for the selection of their patients, one of which was that the bone marrow should be megaloblastic, and only one of their cases had a classical megaloblastic marrow at the start of folic acid therapy and it was this one case that produced the most dramatic initial haematological response.

They further point out that owing to previous liver therapy their cases had an average red blood

count at the commencement of folic acid therapy which was about the same as that recorded by GARCIA LOPEZ et. al. (1946) at the end of folic acid therapy.

As regards the general condition of the 7 patients suffering from tropical sprue or idiopathic steatorrhoea, they found that the diarrhoea was controlled and clinical improvement resulted, but fat absorption was not improved in 5 out of 6 cases of the sprue syndrome.

Tentatively the authors submit the hypothesis that in idiopathic steatorrhoea and coeliac disease in Britain, the steatorrhoea is not primarily due to dietary deficiency or infection but results from a constitutional abnormality of the bowel and they cite the familial history of steatorrhoea in some patients to support this hypothesis and they stipulate certain modifying genes and special environmental factors which determine the onset of the disease in infancy or adult life.

"There are reasons for believing that folic acid will give dramatic results in the treatment of megaloblastic anaemia of the sprue syndrome, but there is little evidence that it will restore the red cells qualitatively and quantitatively to complete normality." (MANSON-BAHR (1947) ).

DAVIDSON and GIRDWOOD (1947) studied folic acid as a therapeutic agent in 48 patients suffering from a variety of disorders of the blood and alimentary tract. Their observations reinforce those of other workers - namely that a haematological response to

folic acid will be obtained only when the bone marrow shows megaloblastic reaction.

It appears that free folic acid is the essential factor for the continuation of normoblastic blood formation and a deficiency causes reversion of the bone marrow to the megaloblastic state.

When free folic acid (pteroyl - glutamic acid) is given in pernicious anaemia a transformation of the megaloblastic marrow occurs.

When purified liver extract is given parentally in pernicious anaemia the classical haemopoietic response occurs with marked excretion of free folic acid and hence they **assume** that purified liver extracts contain a factor, which enables the conversion of conjugated folic acid to free folic acid, to take place.

This liberating factor is the product of the interaction of Castle's intrinsic and extrinsic factors in the alimentary tract and is absorbed from the intestine and stored in the liver. They refer to this liberating factor as L.F.

Folic acid is a vitamin of the B2 complex and therefore should conform to the general principles of vitamin therapy which are :-

- (1) A beneficial result will occur only if the body is deficient in the vitamin.
- (2) When a person has a sufficiency of a vitamin the giving of excessive amounts is valueless and wasteful.
- (3) In a vitamin deficiency disease replacement therapy produces a therapeutic result rapidly.

It is believed that the daily requirement of folic acid lies between 0.5 and 2 mgm.

There is evidence for the belief that for the treatment of any megaloblastic anaemia, quantities of folic acid in excess of 10 mgm. daily are unnecessary and wasteful and, if haematological and clinical improvement does not occur within 2 weeks, it can be assumed that the disorder is not due to deficiency of folic acid and that continued administration is contraindicated.

SPIES, LOPEZ, MILANES and ARAMBURU (1947) describe the following 5 substances which have been isolated in crystalline form:

- (1) Vitamin Bc: (2) Lactobacillus casei factor from liver: (3) Lt. casei factor from yeast:
- (4) Another L. casei factor from a fermentation residue and: (5) Vitamin Bc conjugate.

Vitamin Bc factors from liver and yeast are identical with synthetic folic acid (pteroyl-glutamic acid) which contains one molecule of glutamic acid. The special L. casei factor from the fermentation residue yields 3 molecules of glutamic acid and the vitamin Bc conjugate yields 7 molecules. These last two substances are called pteroyl diglutamyl-glutamic acid and pteroylhexa glutamyl-glutamic acid respectively.

The authors report on the synthetic analogue of the pteroyl diglutamyl-glutamic acid, or L. casei factor from the fermentation residue, in the treatment of sprue, pernicious anaemia and nutritional

macrocytic anaemia. This substance differs from folic acid in that it has two more molecules of glutamic acid and is not excreted so promptly in the urine of subjects with macrocytic anaemia as is the L. casei factor.

It seems probable that the response to synthetic L. casei factor is greater than to the conjugated form, but under natural conditions, much of the folic acid occurs in the latter form, and many patients with macrocytic anaemia are unable to convert Vitamin Bc (a conjugated form) to free folic acid.

In Appendix 1 nine cases of tropical sprue treated with folic acid are recorded.

Unfortunately folic acid did not become available until the number of cases of sprue invalided home had fallen and cases were not so plentiful as they had been previously.

When possible, fat balance estimations were performed, but, when conditions precluded this, the percentage of fat in the dried faeces was estimated and, when this was done the patient was given a diet containing 70 G. of fat for 2 days before estimating the faecal fat and two days stools were pooled, isolated stools not being used for fat estimation.

The effects of folic acid on the signs and symptoms displayed by these cases is given in tabulated form in Fig. 4.

The ninth case had been treated with liver and had responded well to this therapy before he was seen and therefore the response to folic acid was not so

dramatic or as easy to assess as in the other cases.

The remaining eight cases will now be discussed briefly.

CASE 1. Showed remarkable improvement in his sense of well being and this improvement was noted by the patient within 48 hours of the commencement of his treatment. His appetite began to improve at the same time and had completely recovered by the 6th day of treatment. His stools got fewer in number and more solid after 48 hours therapy but the fat content of his stools diminished only very gradually and was still abnormally high at the end of his convalescence. (3 months after commencement of treatment). His body weight increased from 7st. 9 lbs., at which weight he was emaciated, to 9st. 11 lbs. in 2 months. In spite of this very slow and incomplete response as far as fat absorption is concerned the flat glucose tolerance curve became normal in 14 days. His hypochlorhydria was not improved by the treatment.

The blood response was quite good when compared with that of other cases but even after 73 days therapy with folic acid the red cell count was only 3,900,000 and the cells were macrocytic. Before treatment the marrow showed erythroblastic hyperplasia with 2% megaloblasts, after 12 days therapy there was a marked shift towards maturity. The maximum reticulocyte response was 4.4% in the eleventh day of treatment.

In this case improvement in the blood picture

and in fat absorption lagged behind the striking and rapid improvement in general health and vigour and he required a maintenance dose of 5 mgms. of folic acid every other day until the 74th day after the commencement of treatment.

CASE 2. The onset of this patient's illness began with indefinite diarrhoea between 1942 and 1943.

She was diagnosed "Hill Diarrhoea" in 1943 and it seems from her story that she was then in the early stages of sprue. The repeated attacks of diarrhoea that occurred during the next two years illustrate the remissions and relapses of the disease as the patient went down hill. It is noteworthy that although these attacks of diarrhoea were diagnosed bacillary dysentery no record of any organism having been isolated appears in her documents.

Within 7 days of the commencement of folic acid therapy the glossitis, which was present on admission, disappeared.

She had a transient attack of angular stomatitis 6 months later. Her general condition and sense of well being improved after 7 days therapy but she appeared to be subject to remissions and did not put on weight as she should have done.

The diarrhoea responded inside the first week of therapy and the stools diminished in weight due to loss of fluid from them.

Her steatorrhoea improved and 2 months after

the folic acid therapy her stools only contained 9.6% total faecal fat instead of 40% which was the average finding on admission.

Her blood picture showed no appreciable change after 2 months of therapy and did not respond to a massive dose of 100 mgm. of folic acid. Her maximum reticulocyte count was 2.5% and at this stage the case was thought to be, if not a failure, a very poor response to the treatment.

She had had previous liver, yeast and vitamin therapy and this had improved her blood count from 2,500,000 to 4,000,000 before folic acid therapy was started so that it was perhaps not reasonable to expect any further or dramatic improvement in the blood count.

She was given very large doses of folic acid and the lack of any further response to the massive dosage and the continued presentation of Folic Acid bears out the observations of DAVIDSON and GIRWOOD (1947) that benefit from this drug can only be expected if the body is deficient in vitamin, and that excessively high doses are unnecessary and wasteful.

This case had been treated with Liver and with Vitamins for some time before folic acid was administered so that a dramatic response was not to be expected. It does seem however that at the end of her folic acid therapy her response to treatment was actually better than was appreciated at the time. Her weight had improved by 6 lbs. and, had

the fact that she was not eating fats been appreciated at its true significance, the reason for this would not have been attributed to failure of therapy.

The fact that her amenorrhoea responded and her menses commenced again is a good indication of recovery.

It appears that this case was successfully treated for sprue but during her prolonged illness she had developed a phobia for fats amounting almost to an anorexia nervosa and, although she was given an ordinary diet, she was not eating the fat content of it. This fact was not properly appreciated until she was persuaded to eat fat as a therapeutic test and then the true nature of her trouble was revealed.

She is still continuing under observation but she was doing so well when she last left hospital that there seems little reason to doubt that the last phase of her illness was due to lack of dietary intake rather than to any pathology.

CASE 3, displayed an excellent response to treatment with folic acid.

He had not been diagnosed sprue until seen at Millbank and in consequence he had not received previous liver therapy.

The glossitis and cheilosis improved after 48 hours administration of the drug as did his feeling of well being, appetite and diarrhoea, the number of stools passed daily falling from 4-6 to 2. The weight of stools passed daily showed striking improvement (50 ozs. daily became 10 ozs. daily in a week) and the consistence of the stool became firmer

and more solid owing to loss of fluid from the stool.

The amount of fat passed in the stool did not improve so quickly as his other symptoms although faecal fat dropped from 41% to 25% after 4 weeks treatment.

Before treatment his bone marrow showed 7.5% megaloblasts on a differential count and his blood picture was 57% Hb. (Sahli) with a red cell count of 3,300,000.

His reticulocytes showed a maximum response of 7% on the 7th day of treatment and the megaloblasts in the marrow dropped to 1.5% and his blood picture improved to 95% (Sahli) Hb. and a red cell count of 4,200,000 after 3 weeks treatment.

His achlorhydria was not improved by the treatment. His sugar tolerance was within normal limits when the treatment was started.

This case left England to return to duty in India six months after the commencement of treatment. his body weight had increased to 138 lbs. from 110 lbs. at the beginning of treatment and he was symptom free.

CASE 4. In this case there was pronounced improvement in her sense of well being, in the glossitis, and in the appetite after 4 days therapy.

At the end of 7 days treatment she had put on 5 lbs. in weight, the number of stools passed daily had dropped from 2-6 to 1-2 motions daily and they had diminished in weight and were more solid. Her appetite began to improve on the 3rd day and was

voracious by the 7th day of treatment.

The faecal fat was 55% by weight of dried stools when the treatment was instituted. This fell to 25% after 12 days therapy and 18% one month later. At the end of 2 months a fat tolerance test showed that 12% of ingested fat was being excreted.

The flattish glucose tolerance curve came back to within normal limits. This case was suffering from achlorhydria when treatment was instituted and at the end of treatment which lasted 14 days, the curve was within normal limits.

Her blood responded well to therapy. Before treatment was instituted the Hb. was 7.4G/100 ccs., the red cell count was 2,500,000 and the bone marrow showed megaloblastic arrest.

By the end of her convalescence the Hb. was 10.5 G/100 ccs. and the red cell count was 4,400,000. The maximum reticulocyte response occurred on the 9th day and was 5%.

She put on 44 lbs. in weight in ten weeks and was fit to return to her duties as a nursing sister three months after the commencement of treatment.

CASE 5, was a long standing case dating from 11 or 12 years previously, and he had had a serious relapse 7 years ago from which he had never completely recovered in spite of liver therapy. His energy had gradually become more and more impaired and his weight remained constant at a level 21 lbs. below his usual weight before this relapse.

When he was given folic acid his cheilosis

cleared up in ten days and the daily number of his stools diminished and the daily weight of stools fell in 5 days from 40 to 65 ozs. to 15-20 ozs.

The faecal fat had fallen from 40% to 22% by the 16th day of treatment and the intramuscular injection of 15 mgms. of folic acid was discontinued and he was kept on 10 mgs. orally.

His weight did not improve appreciably and his blood showed no response at all, although marrow puncture revealed megaloblastic arrest.

When folic acid was withdrawn he began to deteriorate and it was necessary to keep him on 5 mgms. daily as from one month after the commencement of therapy and he continues to take this as a maintenance dose.

In this case folic acid improved the patient's general condition and controlled his diarrhoea but it had little effect on the intestinal absorption as is evidenced by the fact that the flat glucose tolerance curve never improved and a fat balance test at the end of 2 months showed excretion of 20% ingested fat.

The blood, when the patient was first seen was 11.5 G. Hb/100 ccs. and 3,500,000 red cells and this was not affected by therapy; the bone marrow was predominantly normoblastic in character but showed 5.5% megaloblasts. The achlorhydria was not improved.

This case appears to be one in which irreversible changes have occurred and no permanent cure is to be expected but a daily maintenance dose of

folic acid does control his diarrhoea, keeps his motions solid, and increases his sense of general well being and his appetite.

The cessation of folic acid was followed by retrogression in his sense of well being and in his appetite and he is probably a case who will have to continue taking 5 mgms. folic acid daily as a maintenance dose for life.

CASE 6. This patient developed sprue about eight months before his admission to Millbank.

He was treated with Liver extract parenterally and vitamins in the Military Hospital, York, before being transferred to Millbank and, although this had improved him he was still far from well.

He responded well to folic acid therapy. The slight glossitis, which had survived liver therapy, cleared up in 3 days under folic acid and his appetite and sense of well being also began to improve about this time.

His appetite was described as "ravenous" on the tenth day of his treatment. After 12 days the daily number of his stools had dropped to one or two well formed stools a day and the total weight of his daily stools had come down to 8-12 ozs. owing to their becoming less liquid.

He put on 24 lbs. weight in 5 weeks and at this time it was found that his glucose tolerance curve, which was flat at the beginning of treatment, had reverted to normal.

He had a hypochlorhydria when he arrived at

hospital but this gradually reverted to within normal limits under treatment.

His fat absorption too came back to within normal limits and at the end of 5 weeks he was only excreting 8% of his fat intake.

His blood responded well: on admission his Hb. was 9.8 G/100 ccs. and the red cell count was 3,080,000. The marrow showed megaloblastic arrest. At the end of 5 weeks his Hb. was 13 G/100 ccs. and the red blood count was 4,000,000 though there was still macrocytosis and a C.I. of 1.1.

This case had been improved by liver therapy but had reached a stationary stage in which his diarrhoea was not controlled and he was not well.

Folic acid had a very beneficial result and, although the blood count could not be pushed up higher than 4,000,000 he felt perfectly well when he left hospital to be demobilized.

CASE 7. This patient complained of diarrhoea and loss of appetite during his first month of service in the Far East. He was diagnosed as sprue, after repeated attacks of diarrhoea, six months later, when he developed glossitis for the first time, and was sent home to this country having had a course of liver extract parenterally.

He was still far from well on his arrival home and was still some 40 lbs. below his normal weight when he left England.

The absorption from his intestine was gravely impaired and he was excreting 40% of the fat intake

and his glucose tolerance curve was flat and so low as to constitute a hypoglycaemia.

He felt better himself after 5 days therapy with folic acid and his appetite recovered in 5 days.

He was only passing one or two stools daily on admission but they were very liquid and, under folic acid they diminished markedly in weight, due to diminution of fluid in the stool after 5 days therapy.

After 1 months his fat absorption had improved so that he was only excreting 22% of the fat ingested and his glucose tolerance curve was practically normal.

He was achlorhydric on admission and after two months only a trace of free H.Cl. (up to 4 ccs. N/10 NaOH at 60 minutes) was apparent in the test meal.

His blood on admission showed an anaemia of 11.8 G. Hb/100 ccs. a red cell count of 2,800,000, and one month after completion of treatment was Hb. 10.5 G/100 ccs. and red cell count 3,100,000.

CASE 8, was a soldier who complained of diarrhoea eleven months after arriving in Burma which was diagnosed "clinical dysentery." Although he was discharged from hospital he did not feel well and his appetite was poor and he went gradually downhill until he was diagnosed sprue 8 months later when he was admitted to hospital.

He was invalided home in January 1947 and was seriously ill on arrival, being 21 lbs. under his average weight, (11 stone before sailing for Burma), and suffering from an anaemia of 1,200,000 R.B.C.

and 22% Hb. (Sahli). He was treated with blood transfusions, low fat, high protein diet and liver injections (Plexan 4 ccs.) every other day and folic acid 5 mgms. b.d. by mouth.

Within 10 days his tongue and mouth were normal and his appetite was fair but it was still thought that he was unlikely to recover in anything under one year.

When treatment commenced he was so weak that he could not feed himself but after ten days he was sitting up in bed. His diarrhoea had improved and he was passing only one formed stool daily.

His steatorrhoea had improved from 55% by weight of dried stools to 26.25% after 14 days therapy. His oedema had also disappeared.

He continued to do well and was transferred to Millbank a fortnight later.

On arrival at Millbank his weight had increased by 17 lbs. and he was symptom free.

He was only passing one formed stool daily and a fat tolerance test showed that he was only excreting 8% of the ingested fat.

His sugar tolerance showed a curve within normal limits.

The blood picture showed 84% Hb. (Sahli), a red blood count of 3,860,000 and a C.I. of 1.1. The film showed that macrocytosis was still present.

After 5 weeks sick leave his Hb. was 100% and the red count was 4,500,000 but the C.I. was still 1.1 and macrocytosis was still apparent.

He was discharged to duty weighing 11 st. 3 lb.

This patient made an excellent recovery on liver extract and folic acid given together.

He was in such good condition on arrival at Millbank that the folic acid and liver extract were discontinued. He continued to improve for the next 5 or 6 weeks and did not relapse on cessation of treatment.

CASE 9. Was an example of a patient who, though seriously ill with sprue, showed a blood count which was substantially within normal limits as far as the red cell picture was concerned.

The raised white count raised the question of pancreatitis and this suspicion was strengthened by the passage of undigested meat fibres in the stools.

He had however been in an endemic area and had a history of glossitis and ulcers in his mouth and his history suggested sprue rather than pancreatitis and the urinary diastase was not raised.

He was treated with liver extract and a low fat diet and made very good progress.

His stools were reduced to one or two firm stools daily and he had put on 18 lbs. in weight in 4 weeks.

On admission to Millbank he weighed 8 st. 2 lbs. and a fat tolerance test showed that he was excreting 20% of the fat intake in his diet.

He was treated with folic acid, 10 mgms. daily by mouth, and showed great improvement in his sense of well being and appetite. His body weight in-

creased by 21 lbs. during the month during which he was under treatment.

His blood picture was not appreciably affected when therapy commenced and therefore showed no change at the end of his course of folic acid.

The improvement was seen in the patient's subjective feeling of well being and in the absorption from his intestine - at the end of the month's treatment he was only excreting 14% of his intake of fat and the sugar tolerance curve was in normal limits.

From the summaries of the nine cases, given above, the following responses to folic acid treatment can be stated.

5 cases showed glossitis and five showed cheilosis.

This invariably cleared up in a period varying between 4 days and 12 days.

The patients' general feeling of good health and well being was improved in every case within 2 to 12 days. In one case a maintenance dose of 5 mgs. of folic acid had to be taken in order to hold this improvement.

Seven of the cases were suffering from diarrhoea when they came under observation - the other two had had their diarrhoea controlled by liver therapy before coming under observation. This diarrhoea ceased in all seven cases in periods varying from five days to 14 days.

In all these cases the weight of the stools diminished to within normal limits in a similar

period and this loss of weight of the faeces was accompanied by a diminution of the fluid in the faeces.

The cessation of excretion of fluid from the bowel is not understood, but it seems that folic acid may have an effect on the absorption of fluid from the large intestine when it is given in adequate doses. X-ray observations show that the speed of passage through the intestine is, if anything, impaired in sprue and it is known that inflammation is not a feature. Thus defective absorption of fluid must be accepted as the cause of the liquid stools. PRUNTY and MACOUN (1943) have suggested that absorption, even of fluid, from the bowel is probably more than a mere diffusion of fluids across a cell membrane and it may be that folic acid is necessary to this activity of the intestinal cells.

All nine cases were underweight and eight of them showed material increases in body weight.

All the cases suffered from steatorrhoea and, although all showed a decrease in the amount of fat excreted, only two were excreting normal amounts of fat in the stools after 3 months from the commencement of therapy.

The improvement in fat absorption takes longer to become apparent than the general improvement and the disappearance of the patient's diarrhoea and glossitis.

The blood picture was improved in five cases only and in no case could the red cell count be

pushed up beyond 4,500,000. In two cases which did not respond the marrow was megaloblastic - in one of them the megaloblasts were 19% before the beginning of therapy.

In two cases which did respond the marrow showed a megaloblastic arrest before therapy, which disappeared after therapy.

Five cases showed a flat glucose tolerance curve and four of them became normal within periods varying between 14 days and two months. This improvement preceded the finding that fat absorption had improved in two cases.

Four cases were hypochlorhydric and these showed no improvement: in one case the free hydrochloric acid returned gradually to within normal limits as the case improved.

Four cases were achlorhydric and in two of these there was no change at the end of therapy. One case returned to normal limits gradually within 2 months and one case showed a trace of free H.Cl. after two months.

Four cases had been treated with liver extract parenterally before being treated with folic acid and one case was treated with liver extract and folic acid given together. This last case was cured and required no further therapy when seen.

It appears from this limited number of cases that/

that more than 10 mgms. of folic acid daily for 10 days is necessary to obtain full clinical improvement as a result of the therapy.

Most cases appear to require 20 mgms. daily for at least 7 days and in two cases of this series a maintenance dose of 5 mgms. daily had to be given. In one of these the folic acid was discontinued after 4 months maintenance but in the other case it may have to be continued for life. When folic acid was given intramuscularly this was due to shortage of tablets for oral use and not because of any clinical indication.

CASE NUMBER	GLOSSITIS & CHEILOSIOSIS	GENERAL CONDITION & WELL-BEING	ANOREXIA	DIARRHOEA & WEIGHT OF STOOLS	STEATORRHOEA	BODY WEIGHT	ACHLORHYDRIA & HYPOCHLORHYDRIA	GLUCOSE TOLERANCE	BLOOD AND BONE MARROW FINDINGS	PREVIOUS THERAPY
1.	NIL	Improvement within 48 hrs.	Improved on 2nd day. Voracious on 6th day.	No. of stools less on 3rd day. Stools firmer on 5th day.	50% ingested fat excreted before treatment. 15% after 3 months.	increased from 107 lbs. to 143 lbs. in 4 months.	Hypochlorhydria did not improve	Flat curve changed to normal after 14 days.	Hb. 9.4 G% R.B.C. 2,900,000 Marrow normoblastic After 20 days treatment Hb. 11.6 G. R.B.C. 3,600,000	NIL
2.	Glossitis cleared up in 7 days. Angular stomatitis 6 months later	Improved after 7 days but remissions occurred	Anorexia nervosa was present.	6 stools daily reduced to 1-3 daily and stools firmer in 7 days	40% faecal fat reduced to 8.6% faecal fat.	Did not improve till anorexia improved.	Hypochlorhydria did not improve	--	Hb. 85% R.B.C. 4,000,000 before treatment. No response to Folic acid	Low fat diet Liver Vitamins.
3.	Glossitis and cheilosis responded in 2 days	Improved in 2 days. Vigorous in 10 days	Appetite voracious in 3 days	4-6 daily → 2 well formed stools in 3 days.	Faecal fat 41% became 25% after 4 weeks	108 lbs. → 138 lbs 4 weeks.	Achlorhydria - unchanged. No achylia	Normal.	Hb. 51% R.B.C. 3,800,000. Blood film macrocytic → Hb. 95% R.B.C. 4,200,000. Reticulocytes 7%.	NIL.
4.	Glossitis better after 4 days and cheilosis improved.	Improvement after 4 days.	Appetite better on 3rd day and voracious in 7 days	2-6 stools daily → 1-2 firm stools daily in 7 days.	55% ingested fat excreted → 25% in 12 days. 12% in 2 months.	Rapid increase. 5 lbs. increase in first week.	Achlorhydria became normal in 2 months. No Achylia	Flat curve became normal.	Hb. 7.40% R.B.C. 2,500,000. Marrow was megaloblastic. (7.5%) After 2 months. Hb. 10.50% R.B.C. 4,400,000	
5.	Slight cheilosis cleared up in 10 days.	Noticeable improvement	Improved but relapsed when Folic acid stopped.	2-6 frothy stools daily - became firmer	40% faecal fat became 22%. 20% by F.T.T.	Only 4 lbs. increase in 6 weeks.	Achlorhydria - no change. No Achylia	Flat curve did not improve	11.5G. Hb.%: 3,500,000. Normoblastic Marrow: No improvement.	Liver therapy and diet.
6.	Glossitis disappeared in 3 days.	Improvement noted in 3 days.	Improved in 3 days	3-4 stools → 1 formed stool in 12 days.	50% faecal fats → 8% in 5 weeks.	Put on 24 lbs. in 5 weeks.	Hypochlorhydria became normal.	Flat curve → normal in 5 weeks.	Hb. 9.80% R.B.C. 3,080,000. Marrow megaloblastic. In 5 weeks Hb. 13.00% R.B.C. 4,000,000	Diet. Liver. Riboflavine and nicotinic acid.
7.	No glossitis or cheilosis had it 5 months previously	Marked improvement in 5 days.	Appetite recovered in 5 days	Stools firmer in 3 days.	40% ingested fat excreted → 22%.	Rapid increase. 23 lbs. in 1 month.	Achlorhydria. Trace of free H.Cl. in 2 months. No Achylia	Flat curve → normal in 2 months	11.8G. Hb. R.B.C. 2,800,000. Marrow megaloblastic. Anaemia not much improved. R.B.C. 3,000,000.	Previous liver therapy and low fat diet
8.	Glossitis and cheilosis cleared up after 12 days.	Improvement in 10 days. Much better in 1 month	Improved after 10 days.	1 well formed stool after 14 days.	55% faecal fat → 8% F.T.T. after 6 weeks.	Put on 17 lbs. after 1 month on Folic acid	--	Normal curve	Hb. 84% R.B.C. 3,860,000 → Hb. 100% R.B.C. 4,500,000 in 2 months.	Previous low fat diet, liver and vitamin therapy.
9.	No glossitis but tongue smooth.	Improved in 4 days	Improved in 4 days	Stools solid in 4 days but he was only passing 2 stools daily on admission.	F.T.T. 17% fat excreted. After 16 days treatment 12%.	Put on 9 lbs. in weight in 16 days.	NIL.	Normal.	Hb. 98% and R.B.C. 5,000,000 on admission. Films were macrocytic. No change.	Treated with liver and low fat diet and pre-digested protein.

SUMMARY AND CONCLUSIONS.

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## SUMMARY AND CONCLUSIONS.

The problems presented by sprue have been discussed and the conclusions arrived at are set down under the headings of the various sections of this thesis.

### 1. THE PHYSIOLOGY OF NORMAL FAT ABSORPTION.

(a) VERZAR and McDOUGALL'S partition theory of fat absorption is discussed in the light of FRAZER'S investigations, which show that the partition theory will not account for certain observations made by himself and his fellow workers, chief of which is the fact that fat can be demonstrated to be absorbed by the intestinal cell in particulate and non hydrolysed form.

(b) FRAZER'S work has been extensively quoted and described in full. His findings point to the conclusion that the failure to absorb fat in sprue is dependant on a breakdown of the process in the intra cellular phase and that the fault probably is to be found in the process of phosphorylation.

(c) FRAZER'S findings suggest that absorption of triglycerides and of fatty acids occurs by different routes, the triglyceride being absorbed by the lacteals into the systemic circulation whereas the fatty acids appear to be absorbed into the portal circulation and thence pass to the liver.

### 2. THE BIOCHEMICAL CHANGES IN SPRUE.

(a) Absorption defects occur in sprue which affect many dietary constituents and are not limited to fat alone.

(b) The fallacy of assessing fat excretion by determining the faecal fat in a single stool specimen is stated: the importance of putting the patient on a known fat intake for at least two days before doing a fat tolerance test and then estimating the amount of fat excreted in the collected stools of 2 to 5 days, in order to determine the percentage of ingested fat which is excreted, is described. Excretion of more than 10% of the ingested fat is regarded as evidence of deficient absorption.

(c) The stools of cases of sprue are not always of the typical bulky and frothy character: they may be normal on cursory examination and, only when examined by laboratory methods will steatorrhoea be discovered. The watery diarrhoea which may occur in cases of sprue is described: it responds to sulphaguanidine and therefore may be mistaken for dysentery.

(d) The carbohydrate metabolism is discussed and MAEGRAITH'S findings regarding the difference between the absorption of glucose by mouth and intravenously are given and also the difference between the absorption of glucose and of fructose. The typical "flat" glucose tolerance curve found in sprue is described.

(e) The dehydration and changes in the blood sodium chloride described by BLACK are noted, and also the fact that sprue diets, which contain only a normal salt content, require augmentation.

### 3. THE AETIOLOGY OF SPRUE.

(a) The tendency to couple sprue with other diseases such as pellagra and pernicious anaemia is criticized and reasons for not regarding these diseases as being a series of overlapping clinical conditions due to the same basic aetiological factors are given.

(b) The theory that tropical sprue, coeliac disease, idiopathic steatorrhoea and non tropical sprue are essentially the same is discussed and it is concluded that, in our present state of knowledge, there is insufficient evidence for regarding these conditions as having the same aetiology and, although it is admitted that they all show biochemical similarities, the term "sprue" in this thesis is used to refer to tropical sprue only.

(c) Certain facts regarding geographical distribution, race, age and preceding infection are stated as they appear to have a bearing on the incidence of sprue.

(d) The condition of "Hill Diarrhoea" is discussed. It is concluded that this condition is often one of the modes of onset of sprue: if it is not the precursor of recognisable sprue it is concluded that proper investigation of the cases will reveal the cause of the diarrhoea. "Hill Diarrhoea" is not admitted to be a disease entity.

(e) The work done during the past fifteen years and the theories propounded are stated and criticized.

STANNUS'S theory that phosphorylation is dependent on catalysation by co-enzymes which catalyse the phosphorylation of fats and polysaccharides, and that these co-enzymes are identical for both, is discussed.

It is concluded that, as cases of sprue often show defective fat absorption but a normal glucose tolerance curve, there is a difference between the factors which affect the phosphorylation of fats and sugars respectively.

(f) It is concluded that no evidence has been established for regarding deficiency of the adrenal cortex as an aetiological factor in sprue.

(g) The rôle of vitamin deficiency in the causation of sprue is discussed.

MANSON-BAHR'S theory that nicotinic acid and riboflavine deficiency is responsible for the incidence of sprue is criticized. LEISHMAN'S theory concerning interference with the biosynthesis of vitamins in the intestine is discussed.

It is concluded that there is not sufficient evidence to support the theory that deficiency of the vitamin B2 complex is a fundamental factor in the aetiology of sprue, with the exception of folic acid, which, judged by the results of its administration, appears to replace a deficiency.

(h) DAVIDSON and GIRDWOOD'S conception of a liberating factor in the liver, deficiency of which is responsible for the production of pernicious anaemia, is described.

It is concluded that, in view of the inconstant blood picture in untreated sprue and its variable response to treatment, that deficiency of folic acid or "liberating factor" is not an aetiological factor in sprue, although it may play a part in the production of the blood picture in some cases.

(i) The enormous increase in the incidence of sprue among our troops in India and the Far East during the last war is contrasted with its virtual non-occurrence among the prisoners-of-war in Japanese hands.

These were living under identical or even greater hardship. It is emphasized that these prisoners did not develop signs of sprue when they were repatriated and were taking a diet which contained a normal fat content.

The difference in the incidence of sprue between these two groups is attributed to the difference between the dietary fat intake of the two groups and it is concluded that a certain intake of fat is essential to the development of sprue and that this is an essential aetiological factor.

(j) The type of fats in the diets of different races is considered and it is concluded that the type of fat ingested in the diet may be an aetiological factor of importance in sprue.

It is suggested that diets in which fats occur mainly as vegetable oils may react differently to the circumstances which produce sprue from diets in which the fats are predominatingly of animal origin.

#### 4. THE DIAGNOSIS OF SPRUE.

(a) An effort has been made to confine the condition of sprue within certain limits so that it may be possible to define it clinically.

Therefore the clinical picture and differential diagnosis have been set down. The finding of steatorrhoea, which cannot be explained as being secondary to any other pathological process, is considered an essential which must be present at some phase in the course of the disease to warrant the diagnosis being made.

(b) The X-ray findings in the intestine are described and it is noted that these findings are not confined to sprue but are seen in other deficiency syndromes. It is not considered justifiable to ascribe the dilatation of the colon to bulkiness of the stools because this finding occurs in cases which are in a state of clinical recovery and whose stools are not bulky: it is suggested that this dilatation of the colon must be due to atony of the large intestine.

(c) The glucose tolerance curve, if flat in character, is of value in confirming the diagnosis of sprue but it is not exhibited in all cases.

(d) Loss of weight is an important sign of active sprue: when the patient regains weight it is considered to be a sign of remission and re-establishment of absorption from the gut, although a degree of steatorrhoea and anaemia may persist after the body weight has returned to normal.

(e) The blood picture is described and it is noted that in some cases the blood changes are normal or slight in degree.

(f) The differential diagnosis of sprue is discussed.

## 5. THE TREATMENT OF SPRUE.

(a) The treatment is described under sections dealing with the general management, dietary treatment, vitamin therapy, liver therapy and treatment with folic acid.

(b) The general principles of treatment are stated and the importance of rest in bed and the treatment of dehydration is stated.

(c) Graduated diets used in the Army are given in Appendix No. 3.

(d) The use of vitamins other than Folic Acid is not considered to be so important in the treatment of sprue as many workers believe. The main indication for their use is to treat concomitant vitamin deficiencies, such as scorbutic symptoms, which may complicate sprue.

Other than this it is not considered necessary to give vitamins, provided the diet is adequate in them.

The fact that cases of sprue can be maintained on yeast as described by BLACK and FOURMAN is noted but it is considered that this therapy has no advantage over a daily maintenance dose of 5 mgms. of folic acid by mouth.

(e) The results of liver therapy are discussed: crude extracts seem to be more beneficial in sprue than are more refined extracts: it is also noted that steatorrhoea may persist after general clinical improvement and that the response of the blood to liver therapy, even in cases which exhibit macrocytic anaemia, is usually not so complete as is the response in pernicious anaemia.

(f) The early work on folic acid and the results of the first clinical trials by SPIES, DARBY et. al. are described. DAVIDSON and GIRDWOOD'S conception of a "liberating factor" (L.F.) in the liver which enables the liberation of free folic acid from conjugated folic acid is discussed.

(g) Nine cases of sprue treated with folic acid are tabulated and summarised.

It is noted that folic acid may produce clinical improvement in cases which have failed or ceased to respond to liver therapy.

Folic acid causes rapid improvement in the general condition but in some cases the steatorrhoea does not revert to normal, though it may be improved, and often the blood picture cannot be restored to normal completely.

(h) It is considered that larger doses of folic acid are necessary for the treatment of sprue than for the treatment of pernicious anaemia and

that maintenance therapy may be required for some time in order to retain the health recovered.

(i) The action of folic acid in reducing the fluid in the stool is not understood. It is concluded that it must perform this by affecting the absorption of fluid from the large intestine.

(j) It is considered that the use of folic acid represents an important advance in the treatment of sprue and that it should be used in all cases if available.

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APPENDIX 1

The Clinical Reports of 9 cases  
treated with Folic Acid.

CASE NO.1

A Lieut. Colonel of the Indian Army aged 64 who in 1939 had a perforation of a duodenal ulcer.

He recovered from this and remained in good health until 1943 when he was stationed at Madras and began to complain of nausea and vomiting after meals (usually about 3 hours after).

He was given a barium meal and a Gastric ulcer was diagnosed and since that time he has always suffered from "indigestion" which used to affect him badly about one day in every three and he frequently complained of nausea about 1-3 hours after meals which was relieved by vomiting. There was no distension or flatulence at this time.

In January 1946 he suffered from diarrhoea alternating with periods during which he passed firm stools and by this time he had lost about 10 lbs. in weight. His normal weight was between 10 st. 7 lbs. and 11 stone and he went down to 9 st. 10 lbs.

He was given a barium enema and was told that he had a "stoppage in his colon" and he was invalided home in March 1946. He was told that he might require a "short circuiting operation" if he got worse. After he arrived home his health did not improve, his appetite remained poor and he continued to lose weight and he reported sick to Millbank Hospital on January 27th 1947.

For 3 days before admission he had been suffering from 3-5 watery stools a day following a self administered dose of alophen and this was, for him, an

unusual reaction to this drug.

On questioning about his previous health in India he stated he had suffered from occasional transient attacks of diarrhoea during the past 10 years of his service but he had never suffered from dysentery, amoebic or bacillary, as far as he knew. During the past 2 months he had been suffering from Waterbrash.

On Examination. - 27.1.47. Weight 7 stone 9 lbs. 27.1.47. - He was strikingly thin and looked almost cachectic and his complexion was very pale as were his mucous membranes.

No lymph glands palpable in neck, axillae or groins. Tongue clean, smooth and pale, and the normal fissures had disappeared.

Abdomen was slightly distended and hyper resonant. The abdominal wall was thin. No tenderness in abdomen and no tumour mass palpable. Liver not palpable. There was gurgling on palpation over the caecum. The colon was not palpable anywhere from the caecum to the L.I.F.

Chest. - Nil abnormal discovered. Bases clear.

C.V.S. - Within normal limits for his age. Arteries slightly thickened.

B.P. 120/90

28.1.47. Blood Examination. Hb. 9.8 Gm. (67% sahli): R.B.C. 3,000,000: C.I. 1.10: M.C.V. 106  $\mu$ : M.C. H.C. 31%: E.S.R. (corrected) 34/hour.

The red cells showed considerable anisocytosis and poikilocytosis and the average cell diameter appeared large suggesting a macrocytic anaemia.

Daily stool examinations were performed for 6 days and revealed no amoebae histolytica but large numbers of Trichomonas hominis were present. The stools were liquid (although it is now 10 days since he took Alophen) and contained no blood, microscopic or macroscopic, or pus. There was some mucous in the stools.

30.2.47. Barium meal revealed a very irregular duodenal cap and thick mucosal pattern. No apparent active ulceration present. No dilatation of the stomach. Normal transit of the meal through the small intestine.

No signs of neoplasm in stomach or pylorus.

3.2.47. Diarrhoea still continued.

F.T.M. (alcohol meal) Fasting juice 5 cc. Curve is hypochlorhydric.

4.2.47. Repeat of blood examination. Hb. 9.4 G (64% sahli): R.B.C. 2,900,000 C.I. 1.11: M.C.V. 103  $\mu$ . M.C.H.C. 31%. P.C.V. 32%: E.S.R.(corrected) 32 mm./hour. W.B.C. 6,300.

Polys 64%: Lymphocytes 29%. Monocytes 3%. Eosinophils 4%.

The anaemia is severe and macrocytic in type.

6.2.47. Barium Enema. On filling, the rectum, sigmoid and descending colons were observed to be smooth and regular in outline with no filling defects, but a very large diameter. 5½ pints of barium were given and the head of the enema reached only half way across the transverse colon. No more could be given, (? spasm of colon).

After evacuation the remaining barium was seen to have been distributed throughout the whole large intestine and caecum but the intestine is not adequately filled and therefore no comment can be made as to the possibility or otherwise of a filling defect in the caecum and ascending colon.

On closer questioning the patient stated that before he left India he noticed that for some weeks his stools were loose, pale, bulky and offensive and that during this time he suffered from urgency of defaecation especially in the mornings and that this passed off about the middle of the morning.

10.2.47. A faecal fat estimation on an isolated stool having given a result of 34% of dry faeces (91% split and 9% unsplit) a fat tolerance test was performed and he was put on a diet containing 50 G fat and 70 G protein and 70 G carbohydrate daily. At the end of 2 days his faeces were collected for 3 days and it was found that he had excreted 80 G of fat during this time - i.e. 50% of the fat ingested.

Sternal Puncture. - The marrow showed marked myeloid and erythroblastic hyperphasia -

10.2.47 - Laboratory Report.

	Neutrophil	Eosinophil	Basophil
Segmented Polys	6.6%	0.4%	
Non-segmented Polys.	21.4%	0.8%	0.2%
Metamyelocytes	11.8%	0.8%	
Myelocytes	12.8%	0.2%	
Premyelocytes	0.6%		
Monocytes		6.0%	
Lymphocytes		16.6%	
Plasma cells		0.2%	
	Normoblasts	Megaloblasts	
Type C (Israel's)	5.4%	0.8%	
Type B	7.0%	0.6%	
Type A	4.6%	0.2%	
Proerythrocytes	1.2%	Haemocyto blasts	3.0%
Myeloid/Erythroblastic Ratio = 3/1			
Total nucleated count = 47,000 per c.mm.			
Megakaryocytes = 60/cu.mm.			

Glucose Tolerance Test showed a flat blood sugar curve, the fasting sugar being 86 mgms.% and the figures estimated at half hour intervals were 92 mgms%, 98 mgms%, 100 mgms%, 108 mgms%, and 104 mgms%.

He was put on a course of 30 mgms Folic Acid (FOLVITE), intramuscularly daily.

12.2.47. After two days folic acid he feels very much better and his stools are fewer in number: instead of 3-5 daily he is passing 1-3 and the stool is now semisolid though it still contains some mucous. His appetite is definitely better and he is beginning to eat more today and not leave food on his plate.

16.2.47. The clinical response to folic acid therapy have been excellent. The patient looks and feels vastly better. He has regained his appetite and states he now looks forward to meal times and is eating better than he has done for 10 years. He is passing 1 or 2 solid motions daily but the faecal fat still varies between 25% and 40% by weight. His reticulocyte response is up to 4.4%.

Blood Picture. - Hb. 9.2 Gms/ 100 ml. R.B.C.

2,800,000. C.I. 1.14.

M.C.H.C. 29.5%. M.C.H. 32.877. M.C.V. 106 c.u.

His weight today was 8 stone.

21.2.47. Improvement has been maintained. His weight is 8 st. 3 lbs. and he is ravenous for food.

Blood Picture. - Hb. 11.8 Gms/100 ml. R.B.C.3,600,000.

C.I. 1.12.

The reticulocyte response is 4.8%.

Glucose Tolerance Test. Fasting sugar level 94 mgms% and the half hourly figures being 142 mgms%, 142 mgms%, 132 mgms%, 131 mgms%, 108 mgms%.

23.2.47. Barium Enema - the barium passed easily and filled the whole large intestine which was large in diameter, especially the descending and sigmoid colons, but presented no filling defect or other abnormality.

4.3.47. Progress has been excellent. Weight now 8 st. 12 lbs.

Blood Picture. Hb. 11.8 Gms/100 ml. R.B.C. 3,600,000.

C.I. 1.12.

He is now symptom free but his stools are still containing 30% fat in some specimens.

He is to go to Osborne House for a month's convalescence and then to return to Hospital for fat tolerance test and review of his condition. He is given a maintenance dose of Folic Acid gr V orally twice weekly.

24.4.47. Patient has returned for review following convalescence at Osborne where he was from 17.3.47 until 23.4.47.

During this time his Folic Acid was at first given as one 5 mgm. tablet twice weekly but as he did not feel so well on this reduced dosage he was given 1 tablet of 5 mgms three times weekly.

Convalescence was interrupted by a cold followed by bronchitis.

His weight increased from 9 st.  $4\frac{1}{2}$  lbs. on arrival at Osborne to 9 st. 11 lbs. but he lost 1 pound during last week.

His stools have improved now and are of normal consistency - one or two per day.

He still gets easily tired.

25.4.47. Hb. 12.4 Gms. per 100 ml. R.B.C.  
3,900,000 per cu. mm. C.I. 1.1. W.B.Cs. 10,200.  
Polys 65%. Lymphocytes 30%. Macrocytes 3%.  
Eosinophils 1%. Basophils 1%.

Sternal Puncture - There is a marked shift towards maturity of both myeloid and erythroblast series.

Laboratory Report.

	Neutrophil	Eosinophil	Basophil
Segmented Polys.	11.8%	-	-
Non-segmented Polys.	39.4%	0.2%	-
Metamyelocytes	8.4%	-	0.2%
Myelocytes	6.2%	-	-
Premyelocytes	0.4%	-	-
Monocytes		5.6%	
Lymphocytes		14.6%	
Plasma cells		0.2%	
	Normoblasts	Megaloblasts	
Type C	6.8%	-	
Type B	4.8%	-	
Type A	0.6%	-	
Proerythrocytes =	0.2%	Haemocyto blasts =	0.6%
Total nucleated count = 39,000/cu:mm.			
Megakaryocytes = 20/cu:mm.			

6.5.47. Fat tolerance test revealed that he was excreting 15% of his fat intake. The barium enema was repeated and, apart from a large diameter of the lower colon, no filling defect or other abnormality was found.

X-ray chest: N.A.D.

His weight now is 10 st. 3 lbs. and he feels better than he has done for the past two years. He is now symptom free and has stopped taking folic acid since he returned from Osborne on 24.4.47.

Discharged from Hospital. To report to Out Patients' Department in three months time for observation.

CASE NO.2

A nursing sister aged 32 who was invalided home from India in Sept 1945. She gave a history of illness beginning with some dysentery in 1942 in Poona. This cleared up but in January 1943 she developed symptoms suggestive of sprue in Bangalore. A diagnosis of Hill Diarrhoea was made and she returned to work after slight improvement had occurred. For the next two years she had repeated attacks of diarrhoea which was always diagnosed as bacillary dysentery. On return to this country she was admitted to Hospital suffering from soreness of the lips and tongue, lassitude, recurrent diarrhoea with pale loose stools, loss of 35 lbs. in weight and abdominal distension. She weighed only 88 lbs., her general condition was very poor and she was suffering from angular stomatitis.

A blood count showed Hb. 58% (Sahli) and R.B.C. 2,500,000.

Faecal fat was 26% by weight of dried faeces. No entamoebae or parasites were found in the stools on 7 consecutive daily examinations.

She was treated with a high protein and low fat diet, liver extract and vitamins, and made slow progress.

She went out on sick leave but her condition deteriorated again and in February 1946 she was readmitted.

She weighed 96 lbs. and was still passing loose stools with a fat content of 40% by weight. Her tongue was red and indented.

The Hb. was 85% and the R.B.C. 4,100,000.

The high protein diet, liver injections and vitamins were continued until June 1946 when all previous treatment was stopped and she was put on a low protein and carbohydrate diet and folic acid 15 mgms. daily by mouth (Folvite) was commenced as she had made practically no progress on previous treatment.

Her weight was steady at 97 lbs. and the faecal fat was 9.6% by weight but she had abdominal discomfort and diarrhoea, soreness of the tongue and marked hypochlorhydria. The haematological response was negligible, a daily reticulocyte count showing a maximum rise to 2.5% only on the 8th day of treatment and on the 15th day of treatment the Hb. was 88% and the R.B.C. was 3,700,000.

It was noted however that there was definite improvement subjectively and in the diarrhoea, the number of stools decreasing from 6 daily to 1 to 3 daily by the 7th day, and the abdominal discomfort was lessened. The sore tongue disappeared in 7 days.

In view of the poor response in her blood picture it was decided to give a large single dose of 100 mgms. of folic acid on the 16th day, and subsequently 20 mgms. daily, and to put her on an ordinary diet.

This failed to produce a reticulocyte peak or any change in the Hb. or the total red cell count.

She continued on folic acid, rising to 30 mgms. daily for another 3 weeks when it was withdrawn owing to the static condition of her blood counts.

She was put back on the high protein, low fat diet with vitamins and proteolysed liver by mouth and continued reasonably well for four months.

Folic acid was tried again in 20 mgms. daily doses with no effect on the reticulocyte or red cell count but with some improvement in her abdominal discomfort.

It was considered that, owing to the failure of the blood to respond and the failure to put on weight, that folic acid had not succeeded and she was sent out on 3 months' sick leave in November 1946.

She attended the Out Patients at intervals for review and on the whole she remained fairly well. She had occasional attacks of abdominal pain with distension but her stools were formed, of normal colour and inoffensive.

She had to take great care with her diet and omitted all forms of fat.

She first attended the Out Patients at Millbank in February 1947 and it was thought that some other condition than sprue must be present to account for her condition and she was therefore admitted for reassessment on 24th February 1947.

On clinical examination she was found to be extremely thin, her weight having fallen again to 94 lbs.; angular stomatitis was present and there was marked tenderness over the caecum.

The stools for 3 days were pooled and a fat analysis showed only 8.6% fat in the faeces by weight (57% split fat and 44.2% unsplit fat).

Blood count showed 90% Hb. (Sahli) and R.B.C. 4,000,000. M.C.V. 100. M.C. Hb. 34%.

Stools were examined for entamoebae histolytica repeatedly and found negative and sigmoidoscopy was negative.

No conclusive signs of Tuberculosis could be found but a faint opacity of doubtful pathology was found in the left infraclavicular zone.

She was discharged from hospital in April to attend the Out Patients at intervals for assessment but up till October 1947 showed little change in her condition. Her weight has not gone up, she has in fact lost 4 lbs., but she feels well, and her only symptoms are that if she eats fatty foods, indigestion results.

She was admitted to Hospital again on October 3rd to be given a Fat Tolerance test in order to find out whether any defect of fat absorption was still present and, if not, whether any other disease was responsible for her symptoms.

On examination she was still very thin but she is not clinically anaemic and has no soreness of the mouth or lips.

Blood Picture - Hb. 80%. R.B.C. 3,800,000. B.S.R. 19 mm/hr.

Repeated X-rays of the chest have revealed no change in the faint opacity in the left infraclavicular zone discovered in April.

Fat Tolerance Test. It was with some difficulty that the patient was persuaded to eat a diet containing 100 G fat as she was afraid of subsequent indigestion. The rationale of the test was explained to her and she ate the diet and tolerated it well.

In a 3 day specimen only 35 G was excreted.

The fat content in the diet was maintained and the patient rapidly put on weight and at the end of 3 weeks on this diet she had gained 15 lbs. and weighed 105 lbs. She was discharged on sick leave at the end of November to report again to hospital at monthly intervals for assessment of progress.

When she left hospital she was eating well and gaining weight.

CASE NO.3

A Colonel of the Indian Army, aged 47, who had served over 20 years in the country reported sick to Millbank on October 17th 1946 as an out patient with the following history.

He developed ill defined epigastric pain in 1944 in Assam which recurred at intervals until July 1945 when he developed a sore mouth, asthenia, thinning and greying of the hair and anorexia. In May 1946 he noticed he had lost weight appreciably and his symptoms were gradually getting worse. In September 1946 he began to pass pale, soft, offensive and bulky stools which numbered up to 4 or 5 motions daily. The epigastric discomfort and anorexia became more severe and he noticed that his abdomen was distended. His tongue became sore and he noted numbness of the soles of his feet and of his legs in September 1946.

Past History. 1935. Inactive pulmonary tuberculosis was detected for which he has continued under voluntary observation.

His last X-ray on August 6th showed no signs of activity in the lesion and his E.S.R. was 5 mm/hour.

1944. Developed ill localised epigastric pain lasting all day for which he was X-rayed with negative results. Symptoms were relieved in hospital but recurred after discharge at intervals up to July 1945.

November 1945. After 8 years continuous service in the Far East he returned to England feeling far from well.

May 1946. Had right ulnar nerve transplantation performed at the Military Hospital, Horley, on account

of progressive wasting of the hand muscles and deadness of the 4th and 5th fingers dating from an injury to the inner aspect of the elbow ten years previously. June 1946. Onset of lassitude and a feeling of exhaustion and tiredness.

He developed a bad taste in the mouth, thinning and greying of the hair, loss of one stone in weight, anorexia and looseness of his motions.

Present Condition. In addition to the above symptoms he is complaining of numbness of the soles of the feet but no paraesthesiae and abdominal distension in the evenings. His bowels open 3 or 4 times a day and his motions are loose, pale and offensive but contain no blood.

His appetite is better than it has been.

Past Health. Over 20 years tropical service but no serious illnesses. Denies ever having had dysentery of sprue.

Appendicectomy 12 years previously.

On Examination. Grey haired and markedly wasted but colour fairly good.

Tongue abnormally smooth and red but not sore. There was a small ulcer on the fraenum.

No abnormal signs in cardiovascular system, chest, central nervous system.

B.P. 110/70.

Abdomen somewhat distended.

Blood Count. R.B.C. 3,500,000 per cu.mm.

Hb. 14.5 grams%. M.C.V. 111 c.u. W.B.C. 4,800. - normal differential count.

The case was admitted to the Military Hospital, Horley, for investigation of the cause of the macrocytic anaemia.

18.10.46. On admission. - he was feeling very exhausted: even the effort of walking about his room made him feel tired.

He was very wasted and thin: the abdomen was distended and tympanitic, the abdominal musculature was atonic and poorly developed and the subcutaneous fat had largely disappeared.

His bowels were moving 4 to 6 times daily and the stools were bulky, liquid and offensive.

On standing in a glass jar yellow liquid pools of fat separated out from the stool.

26.10.46. Blood count. Hb. (Sahli) 57%. R.B.C. 3,300,000. Reticulocytes 0.25%.

Sternal Puncture. Polymorphs 38%. Basophils 0%. B. myelocytes 0.5%. Lymphocytes 22%. Megakaryocytes 0%. Myeloblasts 6.5%. Monocytes 3%. Normoblasts 11.5%. E. Myelocytes 1.5%. Megaloblasts 7.5%.

Fractional Test Meal revealed complete absence of free hydrochloric acid. No Achylia when histamine given (5 ccs  $\frac{N}{10}$  NaOH).

Fat Analysis of Stools. (48 hour specimen), gave 41% of the dried faeces.

Barium Meal did not reveal any abnormal pattern in the small intestine.

Glucose tolerance test after 50 G. glucose by mouth:

Fasting 88 mgs. %:

after  $\frac{1}{2}$  hour 150 mgs. %: after 1 hour 130 mgs. %:

after  $1\frac{1}{2}$  hours 124 mgms.%; after 2 hours 118 mgms.%;  
after  $2\frac{1}{2}$  hours 90 mgms.%.

7th November 1946. Patient put on treatment with folic acid 20 mgms. daily by mouth and a low fat diet - 25 G. daily.

10th November. A very definite improvement was noted within 48 hours. Appetite has returned appreciably: dyspepsia has ceased and he feels appreciably stronger physically. Diarrhoea has ceased and stools have diminished in numbers to two daily and were of the consistency of clay.

15th November. Appetite has become voracious and he has been eating a full ward diet for the past 3 days. The daily weight of faeces has diminished from 50 ozs. daily at the outset of treatment to 10 ozs. daily (see fig.)

A daily reticulocyte count showed a maximum rise of 7% on the 7th day of treatment.

A gain of 13 lbs. in weight has occurred after 8 days treatment.

2nd December. Sternal Puncture.

Polymorphs. 46%. Basophils. 1.5%. B.Myelocytes 0%.  
Lymphocytes. 16%. Megakaryocytes. 0%. Myeloblasts 1.5%.  
Monocytes. 2.5%. N.Myelocytes. 8%. Normoblasts 21.5%.  
Eosinophils. 0%. E.Myelocytes. 1.5%. Megaloblasts 1.5%.

Blood Count. Hb. 95%(Sahli). R.B.C. 4,200,000

F.T.M. Still showed achlorhydria.

Faecal fat. A 48 hour specimen showed 25% by weight of dried faeces.

On the 37th day of treatment the folic acid was

reduced to 10 mgms. daily and on the 60th day it was reduced to 5 mgms. daily, on which dose patient was discharged from hospital on December 18th 1947.

January 20th. Patient has been at home, eating a normal diet and walking 8 miles a day and feels perfectly fit.

His weight has increased to 138 lbs. - (see attached weight chart).

He has discontinued his folic acid.

March 1st. Improvement has been maintained. He feels perfectly fit and is returning to India in 14 days time.

CASE NO.4

A nursing sister aged 29 who went overseas in April 1943 and served in India, Burma and Singapore until September 1946 when she was posted home.

In May 1945 she complained of abdominal distension soreness of the mouth, persistent diarrhoea and loss of weight. She noticed that in the mornings her belt was tight and that as the day progressed it would become looser. She was treated with sulphaguanidine for the diarrhoea and she improved but she had a recurrence of the same symptoms in February 1946 and again was treated with sulphaguanidine, which again produced improvement. She was posted home to England and arrived in this country in September 1946 and after 6 weeks in England she again complained of diarrhoea and soreness of the mouth and tongue. She also complained of loss of appetite and lassitude and she felt completely incapable of working.

She reported sick and a blood count showed that she was suffering from a hyperchromic anaemia and she was sent to Millbank for investigation and treatment on November 4th 1946. She had also experienced irregularity of her periods which for the last 3 occasions had been overdue and when they did appear only lasted 24 hours or a little longer. She is normally a 3/28 day type.

On examination (4.11.46).

She was pale and very thin. She weighed only 6 stone - her normal weight is in the region of 9 st. 7 lbs.

She had marked cheilosis and her tongue was red and glazed and fissured with small papillae.

The mucous membranes of her mouth and conjunctivae were pale.

The abdomen was markedly distended and doughy on palpation and was dull on percussion.

The liver was palpable two fingers below the costal margin.

Spleen not palpable.

B.P. 115/60. Nil else abnormal found clinically.

#### Investigations.

1. Blood Picture. Hb. 7.4 Gms. R.B.C. 2,470,000.  
C.I. 1.2. M.C.H.C. 38. P.C.V. 32%.  
Reticulocytes 0.25%. W.B.C. 5,400.
2. Marrow Puncture. Polymorphs (band forms) 28%:  
Lymphocytes 12.5%: Monocytes 3%:  
Eosinophils 2.5%: Basophils 0. Megakaryocytes  
0.5%: Myelocytes (neutrophils) 7.5%: Myelocytes (Eosinophils) 2%: Myeloblasts 5.5%:  
Normoblasts 31%: Megaloblasts 7.5%.
3. Glucose Tolerance Test. - A flattish curve -  
fasting 125 mgms%;  $\frac{1}{2}$  hour 150 mgms: 1 hour  
131 mgms:  $1\frac{1}{2}$  hours 130 mgms: 2 hours 126 mgms:  
 $2\frac{1}{2}$  hours 111 mgms.
4. X-ray examination. - Barium Meal showed that the  
stomach was distorted by the colon which was  
markedly distended with gas.

There was loss of mucosal pattern and the typical "moulage" appearance in some coils of the small intestine and "pooling" of the meal in others.

5. Faeces. - number of stools varied between 2 and 6 daily and the 24 hour specimen weighed between 30 and 60 ozs. daily.

The stools were of porridgy consistence and were pale, offensive and frothy.

6. Fat Tolerance Test. (Only 50 G fat daily could be tolerated in the diet) showed that 55% of fat ingested was being excreted.

16.11.46. A diagnosis of sprue was made and the patient was put on a low fat, high protein diet and given 20 mgs. Folic Acid daily by mouth in 2 doses of 10 mgms. each.

7. F.T.M. showed no free H.Cl (alcohol meal).

Histamine produced a trace of free HCl.

19.11.46. She feels better. The abdominal distension is less and the stools less offensive though they still vary between 2 and 4 daily. The soreness of the tongue has disappeared and the cheilosis is improved. She can eat more and she has today been put on 50 G fat in the diet daily.

24.11.46. Is very much improved. Her weight is now 6 stone 5 lbs. (an increase of 5 lbs. in 7 days).

The number of stools daily has fallen to one or two, the weight of the 24 hour specimen is 8-12 ozs. The stools are now solid. The abdominal distension has disappeared and her appetite is enormous.

She has been put on the ordinary Ward diet today.

1.12.46. The improvement continues and patient now weighs 6 st. 11 lbs.

The number of stools is maintained at 1-3 daily and the weight varies between 5-8 ozs. for the 24

hour specimen.

Daily reticulocyte counts have shown a rise to 2.5% on the third day and reached their highest on the 9th day when the reticulocyte response reached 5%.

Blood Count. - Hb. 8.8 G. R.B.C. 3,800,000.

Faecal Fat. - 48 hour specimen was 26% by weight of dried faeces.

Marrow Puncture. Polymorphs 37%. Lymphocytes 7%.  
Monocytes 2.5%. Eosinophils 2.5%. Basophils 0.  
Megakaryocytes 0. Myelocytes (neutrophils) 12%.  
Myelocytes (eosinophils) 3%. Myeloblasts 1.5%.  
Normoblasts 30%. Megaloblasts 4.5%.

She is feeling much better and her appetite is voracious and she is able to eat fats and tolerate them well.

Folic acid reduced to 10 mgms. daily.

1.1.47. Weight is now 7 st. 10 lbs.

Hb. 10.5 G/100 ml. R.B.C. 4,500,000.

Faecal fat (48 hour stools) 18% by weight of dried faeces.

Folic acid discontinued.

14.1.47. Patient discharged on one month's sick leave.

17.2.47. Patient has returned after leading an active life in the country. Feels quite well and now weighs 9 stone 2 lbs.

Hb. 10.5 G/100 ml. R.B.C. 4,400,000.

M.C.H.C. 27.

F.T.M. shows return of free acid to gastric contents and the curve lies within normal limits.

Fat Tolerance Test shows 12% of ingested fat is being excreted.

24.2.47. Discharged to duty.

CASE NO.5

A major who had served many years in the Far East reported sick in August 1946 with a history of sprue dating back eleven or twelve years. He was 55 years old and stated that a diagnosis of sprue was first made about 10 years ago but that he had been complaining of diarrhoea, loss of weight and sore tongue for at least 12 months before then. He was treated by dietary measures and improved but never regained perfect health and had periods of abdominal discomfort and flatulent dyspepsia, during which he could not tolerate fatty foods.

He had a serious relapse in India in 1940 which necessitated blood transfusions and treatment with liver injections. These improved him but he never completely recovered from his lassitude and his blood counts had never been above 4,000,000 since then.

He returned to England in 1941 and enjoyed fairly good health but for the 6 months before admission he had been passing pale bulky stools and his energy was decreasing. He had been treated with liver injections but these had not improved him and his blood counts had varied between 3 and 4 million during the past six months.

On examination. He was pale and thin; he weighed 9 st. 2 lbs. which he states is about what he has weighed for the past 5 or 6 years but before his relapse in 1940 he weighed about 10 st. 7 lbs.

His skin was loose and wrinkled and the subcutaneous fat was scanty. His skin felt dry and there was some pigmentation on the backs of the

hands, forearms, axillae and neck.

Conjunctivae and oral mucous membranes pale but no pigmentation in the mouth.

Some cheilosis present.

Tongue smooth and the papillae had been lost but the tongue was not sore.

Abdomen. - distended in the mid line and duller on percussion than one would expect with the amount of distension present.

Liver and spleen not palpable.

Stools - were the large, offensive and frothy pale stools which are typical of sprue. He was passing 2 to 6 stools daily.

The following investigations were carried out:

1. Oral Glucose Tolerance Test. - showed a flattish curve. Fasting level 82 mgs.‰:  $\frac{1}{2}$  hour 93 mgs.‰: 1 hour 115 mgs.‰:  $1\frac{1}{2}$  hours 118 mgs.‰: 2 hours 112 mgs.‰:  $2\frac{1}{2}$  hours 108 mgs.‰.

2. Blood Picture. Hb. 11.5 Gms./100 ml. R.B.C.

3,500,000. C.I. 1.12. M.C.V. 108 c.u.

M.C. Hb. 30%. Reticulocytes 0.5%.

W.B.C. 5,000. Normal Differential Count.

3. Sternal Puncture.

Polymorphs. 40.5%. Basophils. 0%. B.Nyelocytes. 0%.

Lymphocytes. 22.5%. Megakaryocytes. 0%. Myeloblasts. 4%.

Monocytes. 2.5%. N.Myelocytes. 11%. Normoblasts. 11%.

Eosinophils. 1%. E.Myelocytes. 2%. Megaloblasts. 5.5%

4. Barium Meal follow-through: showed coils of intestine distended with gas and collections of pools of barium in other coils.

The barium was visible in pools in the small intestine 36 hours after the meal.

5. Fractional Test Meal (Alcohol) showed no free hydrochloric acid in the gastric contents. Histamine produced a trace of free hydrochloric acid.

6. Faecal fat: (48 hour stools tested) showed 40% by weight of dried faeces. On Sept 17th 1946 he was put on Folic Acid 20 mgms. orally daily. Daily reticulocyte counts revealed no response so he was given 10 mgm. by mouth and 15 mgm. intramuscularly as from Sept 28th.

Oct 1st. The patient was feeling better and the number of stools had diminished from 40 to 65 ozs. daily before treatment to 15-20 ozs. daily. His appetite was better and he did not get tired so easily. His faecal fat, with the patient on a daily intake of 75 Gms. of fat daily, was 22% by weight of the dried stool (2 days stools tested).

In spite of his improvement he had only put on 4 lbs. in weight and on October 14th the intramuscular folic acid was discontinued and he was kept on 10 mgms. by mouth daily.

October 30th. Folic Acid stopped. No change in patient's condition.

November 8th. Patient does not feel so well without folic acid. He is beginning to feel tired again and states that his abdomen does not feel comfortable. There is no distension - but in view of the return

of his abdominal discomfort he has been put back on 5 mgms. daily by mouth.

28th November. Patient feels reasonably well with 5 mgms. of Folic Acid daily. His blood picture and bone marrow have shown no response at all and a reticulocytosis of 2.5% on the 9th day of treatment is all that has been achieved. There is however a marked improvement in his feeling of "well being" and the diarrhoea has stopped. To be discharged hospital and return in 1 month for follow up.

Jan 3rd 1947. Is still much the same but is not happy without his folic acid. He requires 5 mgms. a day to maintain a fairly good state of health. He omitted to take it for 5 days owing to his having run out of supplies and his condition deteriorated.

To continue with 5 mgs. Folic acid daily and to come up for follow up every 3 months.

Fat Tolerance Test - showed 20% of ingested fat was still being excreted.

CASE No. 6.

A Major of the British Army aged 51 returned to Great Britain in June 1946 after a 7 year stay in Ceylon without taking any leave out of the island.

He first complained of looseness of the stools in January 1946 i.e. 6 months before his return to this country. In February and March he noticed that his stools were frothy, large in amount, offensive and yellow in colour. The number of stools passed in the day increased gradually until he was passing 9 stools daily during the latter half of May, and at about this time his appetite deteriorated. Soreness of the mouth began in June 1946. He began to suffer from lethargy and disinclination for work about April and this increased until June when he felt completely unable to undertake his daily work.

Flatulence was first noticed in June-July 1946.

He began to lose weight: his normal weight is about 12 stone (checked in February 1946) but by August 1946 he only weighed 9 stone 5 lbs.

He was admitted to York Military Hospital in August 1946 and was found to have a sore tongue, a lax abdomen which was greatly distended, his liver was palpable 1" below the costal margin and he was suffering from anaemia (figures not available).

He was treated with injections of liver (amount given not available), a high protein low fat diet, riboflavine and nicotinic acid.

On this regime he improved slowly but steadily but no figures or results of tests are obtainable.

He was transferred to the Military Hospital, Millbank on December 6th 1946. He was still passing 4-7 stools daily and had a slightly sore tongue at this time and, although he stated his general condition had improved he was still far from well.

Past Illnesses. Amoebic dysentery treated with a full course of Emetine, E.B.1. and Yatren retention enemata in 1941. He states that after treatment he had no more trouble.

Had several attacks of mild diarrhoea during his stay in Ceylon but this never lasted more than 2 or 3 days and occurred mainly in the hot weather.

He is not teetotal - states he is a moderate drinker - 2-4 whiskies a night.

Has suffered from attacks of arthritis in the hands and feet for the past 10-12 years.

These attacks have always been treated with Sodium Salicylate.

7.12.46. On Examination: Weight 10 stone. He has obviously lost weight and his subcutaneous fat appears to have decreased so that his skin "hangs loosely."

Looks pale and ill. No angular stomatitis but tongue is red and glazed in appearance and is indented by the teeth.

Chest. Nothing abnormal discovered. Bases clear.

Cardiovascular system. Nil abnormal. B.P. 135/95.

Abdomen. Distended and dull on percussion. No tenderness on palpation but abdomen feels doughy in consistency. Palpation caused a desire to de-

faecate.

When examined after this the distension was not so pronounced and the abdomen was more resonant on percussion. No tumours felt and no thickening of the colon detected. Liver and spleen not palpable.

The stool passed was very bulky and was frothy and offensive and of a porridgy consistency. It was a pale yellow colour.

Blood Picture: Hb. 9.8 G per 100 ml. (67% sahli).  
R.B.C. 3,080,000. C.I. 1.12. M.C.V. 109. P.C.V. 34%. E.S.R. 10 mm/hour.

W.B.C. 5,600. Polymorphs 70%, lymphocytes 25%.  
Monocytes 3%. Eosinophils 2%.

Marrow puncture showed a megaloblastic reaction (for myelogram see Fig.)

Fractional Test Meal (Histamine). Low total acid and free H.Cl. Hypochlorhydria.

Glucose Tolerance Test. A flattish blood sugar curve followed the ingestion of 50 G. Glucose, the figures being : 84 mgms.% (fasting), 92 mgms%, 96 mgms.%, 106 mgms%, 118 mgms%.

He was put on 100 G fat daily and a 48 hour specimen of stools was pooled and dried faeces contained 50% fat of which 60% was split and 40% unsplit, the total weight of fat excreted being 65 G.

13.12.46. Patient feels worse owing to the fact that he has had to ingest 100 G. fat which he was very unwilling to do.

He was put on folic acid (Folvite) 15 mg.

daily intramuscularly.

16.12.46. States he feels better. The soreness of the tongue has disappeared and the tongue looks normal in colour but still looks large and the fissures are not as apparent as in the normal tongue.

His appetite is better but he is still passing 3-4 stools a day - he has passed 3 by 12.00 hours today. His "well being" is improved and he is not so lethargic - in fact he is somewhat euphoric today and states he has not felt so well for many years.

20.12.46. There is considerable clinical improvement. He has completely lost his tiredness and lassitude and his appetite is ravenous. He is passing one or two well formed stools daily for the past 3 days, though they still contain 25%-50% faecal fat.

His diet has been increased for the past 48 hours to include 70 G fat daily and he is eating this without discomfort.

Fractional Test Meal. (Histamine). - shows a return of free H.Cl. though the curve is still hypochlorhydric.

Blood Picture. Hb. 12 Gms/100 ml. R.B.C. 3,800,000.  
C.I. 1.09. M.C.V. 103. M.C.H.C. 32.5.

24.12.46. F.T.M. (Histamine) shows a definite increase in the total acid and free H.Cl.

Weight 10 stone 8 lbs.

He is feeling very much better and his appetite remains good but so far the reticulocyte response has only reached 2.5.

30.12.46. Improvement is maintained. He now only passes 1 or 2 well formed stools daily. He is feeling very well and is eating enormously. He is still passing 30% by weight fat in his stools.

Blood Picture. Hb. 12.2 Gm/100 ml. R.B.C. 3,800,000. M.C.V. 104. M.C.H.C. 31.2. P.C.V. 39. C.I. 1.1.

2.1.47. Patient has developed a painful left foot, the upper surface of the instep being particularly painful and the toes are also tender.

There is swelling of the toes and over the instep. Treated by radiant heat and salicylates - he states he has had a similar condition twice before which subsided with local therapy and salicylates.

For X-ray of Lt. foot.

7.1.47. The Lt. foot has subsided with local treatment but was immediately followed by a similar condition of the Lt. wrist which became red, swollen and tender - the swelling affecting the peri-articular tissues especially. His temperature has varied between 98.4° and 100° and in questioning he gives a history of two former attacks of arthritis affecting the wrists, knees and big toes and accompanied by pyrexia in 1937 and again in 1941. Since 1941 he has had one or two attacks of arthritis every year affecting only 1 joint at a time, usually the left wrist, and lasting 3 or 4 days. The big toes have been affected on 2-3 occasions but by no means invariably and previous attacks have been

treated with Sod. Salicyl with success.

X-ray examination revealed "punched out" areas of osteoporosis very suggestive of gout but no tophi could be discovered and no significant urate excretory changes could be found. He was treated with Vin Colchicum and the condition cleared up.

F.T.M. shows an increase in the total acidity and free H.Cl. and the curve is now within normal limits. (4.1.47).

There is a trace of mucous in all specimens.

Blood Picture. (6.1.47).

Hb. 13 Gm/100 ml. R.B.C. 4,000,000. C.I. 1.1.

Marrow Puncture, shows a shift towards normality (for myelogram see fig.)

Weight 10 st. 12 lbs.

12.1.47. Patient is now fit for discharge. He is eating well and feels very fit. His weight is now 11 st. 10 lbs. He is passing 1 well formed stool a day as a general rule though he still occasionally passes a second, rather loose stool, after breakfast.

Fat Tolerance Test - ingesting 100 G. fat daily - shows that he is excreting 8% of the ingested fat.

Glucose Tolerance Test (10.1.47) - shows a normal curve - figures being 90 mgms% (fasting) and thereafter 120 mgms%, 145 mgms%, 138 mgms%, 110 mgms%, 87 mgms%.

He is discharged from Hospital and is due for demobilization and he intends to get a job in Sheffield as a salesman.

8.3.47. Follow up not available. No letters answered.

CASE NO. 7.

A driver in the R.A.S.C. aged 20 was admitted to Hospital on arrival from Hong Kong on January 17th 1947 with the following history.

He went overseas in April 1945 and served in Burma, India and Hong Kong until he was invalided home in December 1946.

He remained in good health until May 1945 when he began to complain of looseness of the bowels and loss of appetite. In July 1945 he was admitted to hospital complaining of vomiting, diarrhoea, and loss of weight (his normal weight was 10 st. 8 lbs.)

He was in hospital for one month.

Between May 1946 and September 1946 he was again in hospital for 10 weeks with a similar condition.

In September 1946 he was again in hospital suffering from diarrhoea, lassitude and anorexia. His blood picture was Hb. 13 Gms/100 ml. R.B.C. 3,700,000.

His chest was X-rayed and he also was given a barium meal but both of these investigations proved negative.

His general condition improved but his tongue became sore and he developed ulcers in his mouth.

The total fats in his stool were 57% (dried weight).

He was treated with liver injections and was invalided home, arriving in this country in January 1947.

He gives no history of dysentery or malaria or any other illness during his tour of duty abroad. On Admission he was passing one or two stools daily which were pale and offensive but not bulky. He weighed 7 st. 8 lbs. and states he has been gaining weight lately. While he was in the Far East he had been down to 7 stone.

On examination. - He looked pale and was very thin. No glossitis or cheilosis.

Abdomen was distended and tympanitic. Skin dry and inelastic. Liver and spleen not palpable.

B.P. 120/65. Nil else abnormal found.

Investigations.

1. F.T.M. - Achlorhydria (alcohol meal).
2. Glucose Tolerance Test. - Fasting 53 mgms%:  
 $\frac{1}{2}$  hour 51 mgms%: 1 hour 57 mgms%:  
 $1\frac{1}{2}$  hours 58 mgms%: 2 hours 62 mgms%:  
 $2\frac{1}{2}$  hours 66 mgms%.
3. Blood Picture. - Hb. 11.8 Gms/100 ml.  
R.B.C. 2,840,000. M.C.H. 46. M.C.V. 125.  
P.C.V. 35%.  
W.B.C. 5,250. Polymorphs 57%.  
Lymphocytes 36%. Monocytes 6%.  
Eosinophils 1%.  
D.C. normal.

4. Sternal Puncture.

<u>Mature.</u>		<u>Immature.</u>	
Polymorphs.	31%.	Neuter-myelocytes	8%
Lymphocytes.	16½%.	Eosin-myelocytes.	-
Monocytes	1½%.	Myeloblasts.	5%
Eosinophils.	1½%.	Normoblasts.	18½%
Basophils.	-	Megaloblasts.	19%

5. Fat Tolerance Test. - 100 Gm. fat given daily in diet and three days stools tested showed excretion of 120 Gm. fat - i.e. 40%.
6. Barium Meal. - showed typical loss of mucosal pattern in small intestine and pooling of the barium in loops of the small intestine.

During the two weeks that the above investigations were being carried out the patient was treated on normal diet with no improvement. Weight 7 st. 8 lbs.

20.2.47. Folic acid 5 mgm. b.d. orally.

A rapid decrease in the number and weight of stools occurred although they still remained loose (see stool chart "D"). His appetite improved within 5 days and his flatulence decreased.

His weight increased very rapidly and one month after the commencement of treatment was 9 st. 3 lbs. i.e. an increase of 23 lbs. (See attached weight chart "C").

23.3.47. Repeat F.T.M. - Trace of free H. Cl., up to 4 ccs. n/10 NaOH at 60 minutes.

26.3.47. Repeat Glucose Tolerance Test: Fasting  
 87 mgms%:  $\frac{1}{2}$  hour 121 mgms%: 1 hour 113 mgm%:  
 1 $\frac{1}{2}$  hours 106 mgms%: 2 hours 90 mgms%. 2 $\frac{1}{2}$  hours  
 97 mgms%.

27.3.47. Sternal Puncture. No megaloblasts seen:  
 normoblastic reaction.

Marrow count. - Normoblasts 23%. Megaloblasts 0.

W.B.C. Neutrophils 16 $\frac{1}{2}$ %. Eos. 1 $\frac{1}{2}$ %. Baso. 0.

Lymphs. 8 $\frac{1}{2}$ %. Monos. 0.

Juveniles. 19 $\frac{1}{2}$ %. Myelocytes :- Neuts 23 $\frac{1}{2}$ %. Eos. 2%.

Basophils  $\frac{1}{2}$ %.

Myeloblasts 4 $\frac{1}{2}$ %. Megakaryocytes 0.

R.B.C. 23%)

) Ratio 3 : 1.

W.B.C. 77%)

Reticulocytes rose to 3% but his previous anaemia has been little affected by Folic Acid (see attached reticulocyte chart "B").

Fat Tolerance test showed that he was excreting 22% of the fat ingested in the diet.

Conclusion. 30 April 1947. The folic acid has had a marked effect on the absorptive powers of the small intestine and consequently on his general condition but there has been little response on the part of the haemopoietic system.

Discharged hospital on one month's sick leave and to report again on expiry of this leave.

CASE NO. 8.

A soldier aged 29 was admitted to Hospital with the following history:

He went overseas in July 1945 and remained in good health until May 1946 when he had a prolonged attack of diarrhoea which was diagnosed "clinical dysentery." This cleared up and he was discharged from hospital but he did not feel well, his main complaints being loss of energy and appetite. He thinks he had lost weight but he cannot be sure about this. His normal weight in the U.K. was 11 stone and he noticed that his clothes were very loose on him after his discharge from hospital.

In November 1946 he weighed himself and found that he only weighed 9 st. 8 lbs. and at this time he had a recurrence of diarrhoea and noticed that his stools were very bulky like "an elephant's stool." His appetite was poor but he attributed this to the monotony of the rations as he was in an out station in Burma and living mainly on tinned food. He got steadily worse and was admitted to Hospital in Burma on 13.2.47.

He was found to be ill and anaemic and to have fatty stools.

His Blood Picture showed Hb. 55% (sahli) and R.B.C. 2,500,000. C.I. 1.1.

Faecal fats were 48% total - Fatty acids 14.6%, soaps 2%, neutral fats 7.28%. Ratio soaps, fatty acids and neutral fats 3 : 2 : 1. (no other

figures or findings available).

Sigmoidoscopy showed pallor, no ulceration of mucosa.

Faeces never contained *Entamoebae histolytica*.

He was diagnosed as Sprue and given a high protein diet plus milk, liver and marmite and liver extract (dose not stated) intramuscularly on alternate days. Multivite tablets and iron were also given.

On 1.3.47 he was invalided to U.K. and admitted to Lincoln Military Hospital on 8.6.47.

On arrival he was dangerously ill with cheilosis, glossitis, diarrhoea and occasional vomiting and oedema of the legs and sacrum. He weighed only 7 st. 6 lbs. and the records of his blood count show an anaemia 1.200.000 and 22% Hb. (Sahli).

He was treated with blood transfusions and diet and made gradual improvement.

26.6.47. Stool fat analysis showed total fat 55% of dried faeces. Split fat 16% of dried faeces (i.e. 29% of total fat), and 39% unsplit (i.e. 71% of total fat).

He was still ill and pale and thin and only weighed 8 stone 2 lbs. He was still suffering from intermittent fatty diarrhoea but was beginning to gain weight and could sit up in bed and do handiwork. His weight was 9 st. 7 lbs.

4.7.47. He was put on a regime of "sprulac" with a little toast and occasional lean meat, marmite and multivite, and liver injections (Plexan 4 ccs.)

every other day and folic acid 5 mgms. b.d. by mouth.

On 17.7.47 his appetite was fair and the tongue and mouth were normal and there was no cheilosis. Nails were normal but hair was thin and lustreless.

No changes in the nervous system. Chest normal. Abdomen not distended and liver and spleen not palpable. No fever.

His weight is now 10 st. 4 lbs.

Faecal fat analysis showed total fat 26.25%. Split fat 9.2% and unsplit fat 17.0% - all of total dried faeces.

The medical specialist's opinion at this time was "this man is seriously ill, suffering from tropical sprue. He is unlikely to recover for a period of about one year and he needs constant hospital treatment."

5.8.47. He has been kept on the above regime and has made rapid progress and today has been transferred to Queen Alexandra's Military Hospital, Millbank.

His weight is 10 st. 10 lbs. and he is symptom free.

He is passing one well formed stool daily as a general rule and has been doing this for the past two weeks.

His appetite has improved enormously and he states he has recovered his feeling of "well being."

He has not been allowed out of bed yet but is anxious to become convalescent.

He can eat anything without subsequent dis-

comfort.

Blood Count. Hb. 84%. (Sahli) R.B.C. 3,860,000.

C.I. 1.1.

Fat Tolerance Test showed that 8% of ingested fat was being excreted.

Sugar Tolerance Test. - curve within normal limits.

On examination he appeared reasonably well nourished and nothing outside the range of normal findings was discovered.

The folic acid has been discontinued since his admission to Millbank.

28.8.47. Discharged on 5 weeks' sick leave and at this time his Hb. was 100%.

2.10.47. Readmitted for review. He feels in perfect health.

The Blood Picture is Hb. 100%. R.B.C. 4,500,000.  
C.I. 1.1.

Nil abnormal found on examination.

Fat Tolerance test showed that only 6% of ingested fat was being excreted.

Weight 11 st. 3 lbs.

14.10.47. Discharged.

To report for follow up in 3 months' time.

CASE NO.9

A soldier, aged 20, enlisted in July 1945 and, after a brief period of training in the Middle East, he was sent to Poona in Feb 1946, to Madras in April, to Rangoon in May and to Tonngoo in Burma in Jan 1947

He had his first attack of diarrhoea in March 1946; this lasted only 4 days and appeared to respond to sulphaguanidine. In April 1946 he had recurrent attacks of diarrhoea but did not feel really ill till June 1946 when he lost interest in life, lost his appetite, decreased in weight and suffered from intermittent diarrhoea. He had recurrent ulcers in his mouth and probably the tip of his tongue was sore for a time, but he does not remember this with certainty.

Throughout his service in India and Burma he used deep trench latrines so that he never observed the character of his motions.

His symptoms cannot have been very obvious because he had an attack of gonorrhoea in August 1946 but was only retained in hospital for a few days. He gradually got worse as time went on.

In May 1947 he was given leave to England and entered a transit camp to await a ship home. In this transit camp and in the ship until it had made its last call before England he managed to conceal his symptoms.

He then reported sick and the M.O. records that his gait was unsteady, he was markedly anaemic, his tongue was smooth, temperature and pulse was normal,

and he had lost about 30 lbs. in weight. On arrival in England he was sent to a Military Hospital and, on arrival there, he was so weak he could not stand up unsupported. He was having 3-4 motions daily, which his M.O. reports were putty coloured, bulky, but not frothy. There was no glossitis.

The red blood count was substantially normal but the white count suggested a septic condition.

10.7.47. Hb. 92% (Sahli); R.B.C. 4,910,000.

C.I. 0.94. E.S.R. 92mm/Hr. W.B.C. 18,400;

Polys. 86%; lymphocytes 12%; monocytes 2%.

2.8.47. Hb. 84% (Sahli); R.B.C. 4,100,000.

C.I. 1.0. W.B.C. 12,500. Polys. 84%, lymphs 9%;  
monos. 3%; eosins. 4%.

#### Stool Analysis.

23.7.47. A pale, semi-solid stool containing no blood or mucous. No amoebae seen. Undigested meat fibres with ragged ends and transverse striation present. No neutral fat globules (but there is a history that these were plentiful on 29.7.47.)

Total faecal fat by weight of dried stool 43.5%.

Split fats 90%. Unsplit fats 10% of the total fat content.

31.7.47. Total faecal fat 32.5% by weight of dried stool. Split fats 85%. Unsplit fats 15%.

The urinary diastole - 4.0 units per c.cm.

25.7.47. He was put on a low fat diet, injections of crude liver extract and pre-digested protein capsules and made very good progress. His stools were reduced to 1 or 2 daily and though still pale were of more normal appearance. He put on 18 lbs. in weight

in 4 weeks.

On 28.8.47 he was transferred to Millbank. On admission he appeared to be reasonably well.

His weight was 10 st. 10 lbs. - i.e. about 11 lbs. below his normal weight before he went abroad.

His tongue was smooth but not sore: no cheilosis.

No abdominal distension or tenderness.

States he feels fairly well but still not "up to the mark."

12.9.47. He passes 1-3 stools of porridgy consistence daily - is prone to periods of bulky stools lasting for 3-7 days.

Investigations. - Fat Tolerance showed 17% of ingested fat is excreted. Glucose Tolerance curve - within normal limits.

It was thought that this patient had responded well to liver therapy but, in view of his lack of energy and the fact that he was still 11 lbs. below his normal weight and was excreting 17% of ingested fat that he should be put on folic acid 10 mgs. daily.

15.9.47. Folic acid therapy commenced.

19.9.47. Feels very much better. His appetite is very keen and he is eating enormously. His stools are solid and have come down to XII yesterday.

30.9.47. After 16 days treatment he has put on 9 lbs. in weight and is passing one well formed stool daily. He feels fit and wants to go out of Hospital on leave.

Fat Tolerance test shows 12% of ingested fat is excreted.

Blood picture - no change.

5.10.47. Folic acid stopped. He now weighs 11 st.  
7 lbs.

Barium meal shows normal mucosal pattern but  
some dilatation of colon.

8.10.47. Discharged on 6 weeks sick leave.

APPENDIX 2.

1. EMERGENCY RATIONS USED BY BRITISH TROOPS.
  - (a) The 10-in-1 Ration Pack
  - (b) The "K" Ration
  
2. RATIONS ISSUED IN NO.1 PRISONER OF WAR CAMP, TAIWAN.

## 10-in-1 RATION PACK (ORIGIN U.S.A.) (after "Operational Feeding Use of Special Ration Packs 1945")

	MENU I		MENU II		MENU III		MENU IV		MENU V	
	Item	Scale oz.	Item	Scale oz.	Item	Scale oz.	Item	Scale oz.	Item	Scale oz.
Items common to more than one meal	Biscuit Coffee Army spread Milk Sugar Cocoa Salt	5.3/5 1/5 3/4 1.1/5 1.1/5 2 1/5	Biscuit Coffee Army spread Milk Sugar Salt	6.2/5 2/5 3/4 1.1/5 2.2/5 1/5	Biscuit Coffee Army spread Milk Sugar Cocoa Salt	5.3/5 1/5 3/4 1.1/5 1.1/5 2 1/5	Biscuit Coffee Army spread Milk Sugar Salt	6.2/5 2/5 3/4 1.1/5 2.2/5 1/5	Biscuit Coffee Army spread Milk Sugar Cocoa Salt	5.3/5 1/5 3/4 1.1/5 1.1/5 2 1/5
Break-fast	Cereal Ham & Eggs Jam	2 6.4/5 2.1/5	Cereal Bacon Jam	2 4.4/5 2.1/5	Cereal Pork sausage meat Jam	2 6.4/5 2.1/5	Cereal Bacon Jam	2 4.4/5 2.1/5	Cereal Sausages Jam	2 6.2/5 2.1/5
Partial dinner unit	Biscuit Starch jelly bar Chewing gum Beverage crystals (grape) Sugar	3 2 1 stick 1 pkt 1 1/4	Biscuit Caramels Chewing gum Caramel nugget bar Sugar	3 1 pkt 1 stick 2 1 1/4	Biscuit Chocolate (sweet) Chewing gum Beverage crystals (orange) Sugar	3 2 1 stick 1 pkt 1 1/4	Biscuit Chocolate (coconut) Chewing gum Beverage crystals (lemon) Sugar	3 2 1 stick 1 pkt 1 1/4	Biscuit Vanilla fudge Chewing gum Beverage crystals (orange) Sugar	3 2 1 stick 1 pkt 1 1/4
Other Meals	Hamburgers, canned Corned beef hash, dehydrated Tomatoes Fruit Pudding Caramel nougat bar	6 2.3/5 3.4/5 3 1/2 2	Pork, tender loin M & V ration (a) Canned corn Fruit cake Peanuts, canned	6 6.4/5 2.2/5 3 1/2 1 1/2	Pork & corn(a) P. meat Peas Plum pudding Fruit bar	6 4.4/5 4 3 1/2 2	Pork & apple sauce (a) Roast beef Beans, snap Fig pudding Caramel nougat bar	6 4.4/5 3.4/5 3 1/2 2	Ham & raisin sauce (a) Corned beef hash dehydrated Lima beans Pineapple rice pudding Cheese Chocolate bar (sweet)	6.4/5 4 4 4 3 1/4 2
	Cigarettes Matches Water purification tablets Soap Towels, hand, paper. Latrine paper Tin opener	10 Nos. 1 book of 20 10 tablets 1 tablet per 5 men 4 Nos. 25 pieces 2 per pack	Cigarettes Matches Water purification tablets Soap Towels, hand, paper. Latrine paper Tin opener	10 Nos. 1 book of 20 10 tablets 1 tablet per 5 men 4 Nos. 25 pieces 2 per pack	As for Menu I		As for Menu I		As for Menu I	

## NOTES.

- (a) Alternative meatstuffs may be provided.  
 (b) Packed in fibreboard case 21 1/4 x 14 1/2 x 7 3/4 ins. Gross weight 45 lb. approximately.

"K" RATION (ORIGIN-U.S.A.) (after "OPERATIONAL FEEDING USE OF SPECIAL RATION PACKS 1945")

Complete ration			Breakfast unit		Dinner unit		Supper unit		Description of Containers	Bulk packing
Item	No. of pieces	Ration (approx)	Item	Ration (approx)	Item	Ration (approx)	Item	Ration (approx)		
Biscuits	6 pkts	9 ozs	Biscuits	3 ozs.	Biscuits	3 ozs.	Biscuits	3 ozs	Separate meal packing  Each 6 <sup>3</sup> / <sub>8</sub> "x3 <sup>3</sup> / <sub>8</sub> "x1 <sup>1</sup> / <sub>2</sub> " in waxed board containers and fibreboard outers. Each 15 ozs gross	36 cartons = 12 rations to fibre- board case.
Meat items	2 tins	7 <sup>1</sup> / <sub>2</sub> ozs	(a) Meat & Egg	3 <sup>3</sup> / <sub>4</sub> ozs	--	--	(c) Meat	3 <sup>3</sup> / <sub>4</sub> ozs		
Cheese	1 tin	4 ozs	--	--	Cheese	4 ozs	--	--		
Fruit bar	1 bar	2 ozs	Fruit bar	2 ozs	--	--	--	--		
Candy	1 pkt	2 ozs	--	--	(b) Candy	2 ozs	--	--		
"D" ration (chocolate)	1 pkt	2 ozs	--	--	--	--	"D" bar (chocolate)	2 ozs		
Coffee	1 pkt	5 grammes	Coffee	5 grammes	--	--	--	--		
Lemon powder	1 pkt	7 grammes	--	--	Lemon powder	7 grammes	--	--		
Bouillon powder	1 pkt	10 grammes	--	--	--	--	Bouillon powder	10 grms		
Sugar	8 lumps	1 ozs	Sugar	1/2 oz	Sugar	1/2 oz	--	--		
Chewing gum	--	3 pieces	Chewing gum	1 piece	Chewing gum	1 piece	Chewing gum	1 piece		
Cigarettes	3 pkts	12 nos.	Cigarettes	4 nos	Cigarettes	4 nos	Cigarettes	4 nos		
Matches	1 bklt	1 no.	--	--	Matches	1 bklt	--	--		
Toilet paper	--	--	--	--	--	--	Toilet paper	--		

NOTES - (a) Tuna fish canned ... 3<sup>1</sup>/<sub>2</sub> ozs (tin) }  
 (b) Cereal .. ... .. 2 ozs (packet) } are substituted for the items stated, when the ration is provided  
 (c) Salmon .. ... .. 3<sup>1</sup>/<sub>2</sub> ozs } for Indian troops.

RATIONS ISSUED IN NO.1 PRISONER OF WAR CAMP, TAIWAN (after BENNET)  
(g. per man daily)

Year and month	Strength		Rice*	Barley	Flour	Rice Flour	Vegetables <sup>†</sup>	Meat	Fish	Dried fish	Oil	Beans	Bean paste	Bean sauce	Salt	Sugar	Tea	
	Fit	Sick																
1943 (mean)	360	160	410	135	--	--	217	0.09	--	4.8	0.6	1.3	4.16	1.5	8.2	3.85	0.4	
1944																		
1	710	75	625	40	9.2	13.2	217	17.2	1.1	12	1.8	9.0	21.6	16.3	20.0	18.0	0.34	
2	706	76	645	--	5.8	26.4		14.4	1.3	8.8	4.9	17.6	16.3	10.5	23.2	11.0	0.37	
3	702	80	645	--	9.0	22.6		9.4	1.25	0.02	3.7	19.0	21.5	14.8	15.6	11.0	0.42	
4	699	82	650	--	11.2	43.0		26.8	3.2	2.1	4.2	17.8	24.0	11.2	14.0	9.5	0.68	
5	698	82	650	--	7.7	49.0		32.2	--	2.7	4.5	10.0	20.2	16.6	18.3	11.3	0.40	
6	682	96	690	--	7.6	47.5		24.0	0.08	1.9	0.78	11.1	27.0	17.5	17.2	10.5	0.11	
7	663	113	600	--	13.7	98.0		12.2	--	2.4	0.76	9.4	24.6	15.0	12.1	8.7	0.05	
8	639	123	600	--	10.2	50.5		25.7	0.04	0.84	2.27	9.3	22.7	15.6	15.5	9.4	0.06	
9	632	133	575	--	7.6	77.5		22.6	--	0.4	1.52	9.2	21.9	13.3	16.3	9.0	0.04	
10	596	153	585	--	3.5	25.5		4.25	1.27	--	2.7	3.6	25.3	13.0	12.5	9.6	0.195	
11	546	163	585	--	2.9	54.0		32.1	--	0.22	2.45	--	15.2	13.0	15.0	10.2	0.14	
12	507	185	590	--	3.0	55.0		37.9	1.57	2.2	3.32	1.8	17.9	12.1	22.7	13.9	0.19	

\* Latterly fixed at 718 g. for a fit man; 350 g. for a sick man; 390 g. for officers

<sup>†</sup>Vegetables included cabbage, onions, yams, pumpkin, makuma, brinjal, bamboo, marrow, cucumber, potatoes, daikon, gobi and tomatoes.

AVERAGE NUTRITIVE VALUE PER HEAD DAILY (RAW FOOD) OF RATIONS IN NO. 1 PRISONER OF WAR CAMP, TAIWAN (after BENNET)

Year and month	Calo-ries	Pro-tein g.	Animal protein g.	Carbo-hydrate g.	Fat g.	Cal-cium g.	Iron mg.	NaCl g.	Vitamin A I.U.	Vitamin B.1 mg.	Ribo-flavine mg.	Nico-tinic acid mg.	As-corbic acid mg.
1943(mean)	1938	42.9	0.5	437.3	5.2	0.12	14.5	8.78	405	1.12	0.34	11.5	24
1944													
1.	2698	61.9	2.5	574.6	14.1	0.20	22.5	20.89	427	1.75	0.51	15.0	24
2.	2665	61.3	1.9	566.1	16.4	0.20	23.2	24.03	430	1.76	0.51	14.4	24
3.	2670	61.8	0.8	566.8	14.8	0.21	23.6	16.30	435	1.78	0.51	14.6	24
4.	2813	66.4	2.5	585.3	20.1	0.22	24.4	14.76	437	1.91	0.55	15.2	24
5.	2801	63.2	2.6	585.5	20.5	0.20	23.4	19.07	427	1.84	0.54	15.6	24
6.	3001	66.4	2.0	616.0	15.3	0.22	25.1	18.00	432	1.91	0.56	16.2	24
7.	2733	63.2	1.2	587.2	11.7	0.20	22.7	12.86	430	1.71	0.51	14.1	24
8.	2608	59.6	1.9	549.6	16.4	0.19	22.1	16.17	428	1.73	0.51	14.2	24
9.	2595	60.3	1.7	539.0	15.7	0.21	23.2	16.96	432	1.71	0.51	14.4	24
10.	2363	53.3	0.3	508.5	10.3	0.18	21.1	13.10	425	1.52	0.45	12.7	24
11.	2482	53.0	2.3	526.7	15.4	0.15	22.3	15.65	412	1.56	0.47	13.8	24
12.	2565	55.9	3.1	538.3	18.6	0.17	20.8	23.40	418	1.65	0.49	14.4	24
1944, 12													
Fit Man	3025	64.9	3.1	639.3	19.0	0.18	24.5	23.52	418	1.91	0.56	16.6	24
Sick Man	1733	39.1	3.1	349.3	17.7	0.14	14.0	23.20	418	1.18	0.37	10.2	24
Officer	1771	41.9	3.1	380.3	17.9	0.14	15.2	23.23	418	1.26	0.39	10.9	24

Notes on analysis.

1. All values calculated on a raw food basis less average allowance for wastage.
2. Values for all foodstuffs except soya bean taken from Field Service Hygiene Notes, India (Anonymous, 1945) Soya bean values from tables of the nutritive value of foodstuffs (War Office, 1945)
3. Rice taken as undermilled rice.  
 Flour taken as white flour, similar to Indian millings.  
 Rice Flour calculated as polished rice.  
 Meat calculated as pork, including bone.  
 Fish, fresh assumed to be cleaned, but not filleted; dried, calculated as smoked haddock.  
 Vegetables average daily intake per head assumed to be 8 oz.  
 Soya bean, bean paste, amounts added together and the result analyzed as dry soya bean.  
 Bean sauce omitted from the calculation, no values being available; mineral values might be thereby affected.

APPENDIX 3

THE DIETS USED IN THE ARMY FOR THE  
TREATMENT OF SPRUE.

THE DIETS USED FOR THE TREATMENT OF SPRUE IN THE  
ARMY (after Medical Diseases in Tropical and Sub-  
Tropical Areas 1946 - The War Office).

STAGE 1.

P.50, F.5, C.119, Ratio 1 : 0.1 : 2.3. Cals. 721.

Hour

- 0730 Skimmed Milk, 8 ounces, flavoured with tea.  
0930 Marmite, 1-2 teaspoons in hot water, 10 ounces.  
1230 Skimmed Milk, 8 ounces. One ripe banana.  
1400 Skimmed Milk, 8 ounces, with Marmite 1-2 teaspoons  
1600 Skimmed Milk, 8 ounces, flavoured with tea.  
1800 Orange Juice, 8 ounces, sweetened with 1 ounce  
of Glucose.  
2000 Skimmed Milk, 8 ounces, with Marmite 1-2  
teaspoons.  
2200 Skimmed Milk, 8 ounces.

STAGE 2.

P.110, F.17, C.160. Ratio 1 : 0.2 : 1.4. Cals. 1,233.

Hour

- 0730 Skimmed Milk, 10 ounces, flavoured with tea and  
sweetened with Glucose  $\frac{1}{2}$  ounce.  
0930 Marmite, 1-2 teaspoons in hot water, 10 ounces.  
1100 Skimmed Milk, 10 ounces - may be served as cocoa.  
1230 Liver Soup, 8 ounces. Fish minced, 4 ounces, with  
white sauce or Marmite gravy.  
One slice of twice-baked bread (one ounce).  
One ripe banana.  
1400 Skimmed Milk, 10 ounces, with 1-2 teaspoons of  
Marmite.  
1600 Skimmed Milk, 10 ounces, flavoured with tea.  
1800 Orange Juice, 8 ounces, with Glucose one ounce.  
One ripe banana.  
2000 Skimmed Milk, 10 ounces, with 1-2 teaspoons of  
Marmite.  
2200 Skimmed Milk, 10 ounces.

\*STAGE 3.

P.144, F.23, C.198. Ratio 1 : 0.2 : 1.4. Cals.1,575.

Hour

- 0730 Skimmed Milk, 10 ounces, flavoured with tea and  
 $\frac{1}{2}$  ounce sugar.
- 0930 Marmite, 1-2 teaspoons in hot water, 10 ounces.
- 1100 Skimmed Milk, 10 ounces - may be served as cocoa.
- 1230 Liver Soup, 8 ounces. Fish 4 ounces minced,  
 served with white sauce.  
 One thin slice of twice-baked bread (1 ounce).  
 One banana.
- 1400 Skimmed Milk, 10 ounces, with 1-2 teaspoons of  
 Marmite.
- 1600 Skimmed Milk, 10 ounces, flavoured with tea.  
 One banana.
- 1800 Chicken, 4 ounces or Liver, 4 ounces.  
 Twice-baked bread (1 ounce).  
 Orange Juice, 8 ounces, sweetened with sugar,  
 1 ounce.
- 2000 Skimmed Milk, 10 ounces, with 1-2 teaspoons of  
 Marmite.
- 2200 Skimmed Milk, 10 ounces.

STAGE 4.

P.168, F.69, C.235. Ratio 1 : 0.4 : 1.4. Cals.2,237.

Hour

- 0730 Whole Milk, 5 ounces, in tea with sugar. One  
 lightly-boiled egg.  
 One slice of twice-baked bread (1 ounce).  
 Butter  $\frac{1}{2}$  ounce.
- 0930 Marmite, 1-2 teaspoons in hot water, 10 ounces.
- 1100 Skimmed Milk, 10 ounces - may be served as  
 cocoa.
- 1230 Liver Soup, 8 ounces. Fish, 8 ounces, with white  
 sauce.  
 One slice of twice-baked bread (1 ounce).  
 Two bananas.  
 10 ounces of custard made with skimmed milk.

\* A case of average severity may begin with Stage 3.

STAGE 4. (Contd).

- 1400 Skimmed Milk, 10 ounces, with 1-2 teaspoons of  
Marmite.
- 1600 Whole Milk, 5 ounces, in tea with sugar.  
One banana.
- 1800 Chicken, 4 ounces, or Lean Meat, 4 ounces.  
One slice of twice-baked bread (1 ounce).  
Orange Juice, 8 ounces, sweetened with sugar,  
1 ounce.
- 2000 Skimmed Milk, 10 ounces, with 1-2 teaspoons of  
Marmite.
- 2200 Whole Milk, 10 ounces.

STAGE 5.

P.162, F.85, C.320. Ratio 1 : 0.5 : 2.0. Cals.2,693.

Hour

- 0730 One lightly-boiled egg. Twice-baked bread  
(2 ounces).  
Butter  $\frac{1}{4}$  ounce.  
Tea with 5 ounces of whole milk. Sugar  $\frac{1}{2}$  ounce.
- 0930 Marmite, 1-2 teaspoons in hot water, 10 ounces.  
Biscuits, 2 ounces.
- 1100 Skimmed Milk, 10 ounces as cocoa.
- 1230 Liver Soup, 8 ounces. Steamed Fish, 8 ounces,  
with white sauce.  
Potato, 4 ounces.  
Two bananas.  
Custard with skimmed milk, 10 ounces.
- 1400 Whole Milk, 10 ounces, with 1-2 teaspoons of  
Marmite.
- 1600 One banana. Tea with 5 ounces of whole milk.  
Sugar,  $\frac{1}{2}$  ounce.
- 1800 Lean Meat or Chicken, 4 ounces. Two slices of  
twice-baked bread  
(2 ounces).  
Butter,  $\frac{1}{4}$  ounce. Orange Juice, 8 ounces,  
sweetened.
- 2000 Whole Milk, 10 ounces, flavoured with Marmite.
- 2200 Whole Milk, 10 ounces.

STAGE 6.

P.174, F.115, C.343. Ratio 1 : 0.7 : 2.0. Cals.3,120.

## Hour

- 0730 One ounce Porridge Oats as porridge, 8 ounces, with 10 ounces of whole milk.  
Two lightly-boiled eggs.  $\frac{1}{2}$  ounce marmalade.  
 $\frac{1}{2}$  ounce butter. Two slices twice-baked bread (2 ounces).  
Tea with 5 ounces whole milk. Sugar,  $\frac{1}{2}$  ounce.
- 1000 Marmite, 1-2 teaspoons in hot water, 10 ounces.  
Biscuits, 2 ounces.
- 1230 Liver Soup, 8 ounces. Steamed Fish, 8 ounces, with white sauce. Potato, 4 ounces.  
Light Steamed Pudding - one portion. Two bananas.
- 1400 Whole Milk, 10 ounces, with 1-2 teaspoons Marmite.
- 1600 Tea with 5 ounces whole milk with sugar,  $\frac{1}{2}$  ounce.  
One slice twice-baked bread (1 ounce).  
Butter,  $\frac{1}{2}$  ounce. One banana.
- 1800 Lean Meat or Chicken, 4 ounces. Two slices twice-baked bread (2 ounces).  $\frac{1}{2}$  ounce butter.  
One tomato. 8 ounces sweetened orange juice.
- 2200 10 ounces Whole Milk. Biscuits, 2 ounces.

## NOTES.

1. Until Stage 5 is reached, the patient should remain in bed.
2. Only those items ordered on the diet sheet should be given and quantities stated should be strictly observed.
3. All cocoa and custard for sprue patients is to be made with skimmed milk. Custard is to be made with custard powder.
4. Tea in diets 1, 2, and 3 to be made with skimmed milk. Tea in diets 4, 5, and 6 to be made with whole milk.
5. When in good supply, liver may be substituted for chicken or lean meat.

6. Twice-baked bread. This is prepared by taking a slice of bread roughly  $4\frac{1}{2}$  inches square by  $\frac{1}{4}$  inch thick and placing it in a hot oven until it is light brown in colour and chippy in consistency. This should weigh one ounce after baking.

Butter. A cube of butter with sides  $\frac{3}{4}$  inch long, weighs approximately  $\frac{1}{4}$  ounce. Another method of measuring is to take a 1 lb. packet and divide it into 64 equal portions.

7. A case of average severity may begin at Stage 3.

CONSTITUENTS OF THE SPRUE DIETS.

	Stage or Sprue Diet No.					
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
Milk, skimmed, pints	2½	3	3	2	1	-
Milk, whole, pints	-	-	-	1	2	1½
Oranges, number	2	2	2	2	2	2
Bananas, number	1	2	2	3	3	3
Glucose or cane sugar, ounces	1	1	1½	2	2	2
Marmite, ounces	½	½	½	½	½	½
Bread, ounces	-	1½	3	4	6	6
Liver, as raw, ounces	-	8	8	8	8	8
Fish, as raw, ounces	-	8	8	16	16	16
Chicken, as raw, ounces	-	-	10	10	10	10
OR						
Lean Meat, as raw, ounces	-	-	8	8	8	8
Flour as white sauce, ounces	-	½	½	½	½	½
Cocoa, ounces	-	½	½	½	½	½
Tea, ounces	-	1/3	1/3	1/3	1/3	1/3
Butter, ounces	-	-	-	¼	½	1½
Eggs	-	-	-	1	1	2
Biscuits, ounces	-	-	-	-	2	4
Potato, as raw, ounces	-	-	-	-	8	8
Marmalade	-	-	-	-	-	½
Tomato	-	-	-	-	-	1
Porridge Oats, ounces	-	-	-	-	-	1
Steamed pudding as below -						
Butter, ounces	-	-	-	-	-	1/3
Flour, ounces	-	-	-	-	-	2-3
Eggs	-	-	-	-	-	1/3
Sugar, ounces	-	-	-	-	-	1/3

NOTES.

1. Sugar - in diets 1 and 2 is best given as Glucose.
2. Chicken and lean meat - in diets 3, 4, 5, and 6. To ensure variety, one or the other should be ordered, not both on the same day.
3. Diet 3 - when Liver is in good supply this should be ordered in place of lean meat, i.e., on every second day alternatively with chicken.
4. "Vegemite" may be substituted for Marmite.
5. Sprue diets must be ordered strictly in accordance with the above tables. Extras are not allowed and increase in quantity is not permitted.