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FAT METABOLISM AND THE SPRUE SYNDROME*

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The sprue syndrome is characterized by a defect of fat absorption, commonly associated with diarrhoea, wasting, abdominal distension, the radiographic segmentation pattern of the small intestine, absence of the normal post-absorptive systemic hyperlipaemia, a flattened oral glucose-tolerance curve, anaemia, and certain vitamin deficiencies. Defective fat absorption may be regarded as an essential part of the sprue system by definition. The sprue syndrome may be taken to include non-tropical sprue (idiopathic steatorrhoea) (Thaysen, 1932), tropical sprue (Fairley, 1936), and the coeliac syndrome in children (Parsons, 1932). To these may perhaps be added some cases of gastro-colic fistula. Other cases of defective fat absorption (such as the post-gastrectomy syndrome, regional

Tropical sprue can occur in epidemic outbreaks involving groups of people living under similar environmental conditions—this was often observed during the last war in South-east Asia—non-tropical sprue and the coeliac syndrome, however, occur more or less sporadically, although several cases may occur in one family. With tropical sprue recovery is the rule; with non-tropical sprue and the coeliac syndrome complete recovery is relatively rare. The syndrome in its more chronic form can be divided into two main parts—a more or less constant group of signs and symptoms, including the fat-absorption defect, and a more variable element, subject to exacerbations from time to time, including severe diarrhoea with bulky fermenting stools, vitamin-B deficiencies, and haematological changes.

TABLE I.—Features of the Sprue Syndrome

	Coeliac Syndrome	Non-tropical Sprue	Tropical Sprue	Gastro-colic Fistula	Post-gastrectomy Syndrome	Regional Ileitis	Obstructive Jaundice	Chronic Pancreatitis
Fat-absorption defect	+++	+++	+++	+	++	++	+++	+++
Proportionate defect	+++	+++	+++	?	—	—	—	?
Flat chylomicrograph	+++	+++	+++	++	—	—	(+++)	(+++)
Fine intraluminal emulsification	+++	+++	+++	+++	?	+++	—	?
Radiographic "deficiency pattern"	+++	+++	+++	++	—	—	?	—
Flat oral glucose curve	++	+	+	—	—	—	—	—
Macrocytic anaemia	+++	+++	+++	+++	+	+	+	+
Microcytic anaemia	+++	+++	+++	—	—	—	—	—
Iron deficiency	+++	+++	+++	?	—	—	?	—
Tetany: Low serum calcium	++	++	++	—	—	—	—	—
Low serum phospholipid	++	++	++	?	—	—	++	++
Low serum cholesterol	++	++	++	?	—	—	++	++
Signs of vitamin-B deficiencies	+++	++	++	++	++	+	—	+

+++ Usually present. ++ Commonly present. + May be present. — Usually not present.

ileitis, chronic pancreatitis, or obstructive jaundice) are not usually associated with a sufficient number of the characteristic features of the sprue syndrome to warrant their inclusion in this group (see Table I).

Certain differences can be observed between non-tropical and tropical sprue and the coeliac syndrome. The anaemia in the coeliac syndrome is usually microcytic, probably due to iron deficiency; an iron-deficient component is also commonly observed in the adult macrocytic anaemia. There may be several primary aetiological factors which can give rise to the sprue syndrome, and it is probable that different factors are operative in the three varieties of the syndrome under consideration.

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The Fat-absorption Defect in the Sprue Syndrome

1. Normal Fat Absorption in Man

Absorption from the intestine is conveniently considered in three phases: an intraluminal, a cellular, and a distributive phase. The absorption of fat must be studied both from a general point of view and in detail (Frazer, 1947a).

General Aspects of Fat Absorption.—The quantity of fat absorbed must be determined by the use of a fat-balance technique (Cooke *et al.*, 1946). More recently the method of de Kamer, Huinick, and Weyers (1949) has been successfully used. The criticisms of Annegers, Boutwell, and Ivy (1948) are not valid with regard to the use of these balance techniques for studies of defective fat absorption. The amount of fat ingested may be increased from 50 to 100 g. and the effect of this fat-loading of the diet determined quantitatively. The effect of different types of dietary fat can also be studied. In

addition to quantitative measurements, the characteristics of the faecal fat and the quantity of volatile short-chain fatty acids can also be determined. The results of observations made by these various methods in normal subjects are shown in Table II.

TABLE II.—*General Study of Fat Absorption*

	Normal	Sprue Syndrome
Fat-balance technique 5–12 day balance Daily fatty acid (de Kamer, 1949) ..	> 95%	50–80%
Fat-loading tests 50 to 100 g. ..	Proportionate, 48–95 g. Natural fats absorbed	Proportionate, 35–70 g. Intolerance of saturated fats
Fat-assimilation test ..	< 3 g. in 24 hr.	Neutral fat and fatty acid + + +; 10–50 g. in 24 hr. High M.Wt. and M.P., low I.V.
Faecal fats ..	< 2 g. per 100 g. dried faeces	Volatile fatty acid + + + up to 8 g. per 100 g. dried faeces

Detailed Study of Fat Absorption.—The intraluminal phase of fat absorption can be studied by an intestinal intubation technique (Thompson, 1949). A Miller–Abbott tube is passed into the small intestine and samples of intestinal contents taken before and after the administration of fat. The material recovered is examined for the presence or absence of enzymes and other substances and the changes which the fat has undergone. The action of enzymes, the effect of added bile, and the presence of bacteria can also be investigated. The cellular phase can be studied only indirectly in man, and at present interpretation is difficult. Investigation of the distributive phase is confined to blood-fat studies. The results in normal subjects are shown in Table III.

TABLE III.—*Detailed Study of Fat Absorption*

	Normal	Sprue Syndrome
Intraluminal phase: intuba- tion technique		
Hydrolysis ..	10% or more	10% or more
Emulsification ..	Particle diameter < 0.5 μ	Apparently normal
Bile addition ..	Enhances lipolysis only in resting samples	Enhances lipolysis in all samples
Enzymes ..	Lipase, trypsin, amyl- ase, and lysozyme present. Lecithinase absent	Lipase, trypsin, and amylase present. Lysozyme? and lec- ithinase absent
Bacteria ..	Absent, or small num- bers only	Present in upper in- testine in large num- bers
Cellular phase:		
Blood biochemistry		
Phospholipid ..	About 250 mg./100 ml.	Low. 40–200 mg. (aver- age 142 mg. in 60 estimations)
Cholesterol ..	About 250 mg./100 ml.	Low < 150 mg./100 ml.
Particulate absorption ..	Present	No systemic hyper- lipaemia
Other absorption tests ..	Normal tolerance curve	Oral glucose-tolerance curve flattened
Effect of therapy ..	Nothing conclusive	
Distributive phase:		
Chylomicrographs ..	Normal peak 150 par- ticles per field	Flat
Blood-fat curves ..	Normal peak 200 mg./ 100 ml. blood	..

2. Fat Absorption in the Sprue Syndrome

The changes observed when using these methods for the study of fat absorption in the sprue syndrome are shown in Tables II and III.

General Aspects.—In the general study of fat absorption the characteristic changes in the sprue syndrome consisted of a fat-absorption defect, only 50–70% being absorbed. The fat-loading tests show that the defect was proportionate to the amount ingested. Thus, if 50 g. were administered and 35 g. absorbed, the administration of 100 g. resulted in the absorption of 70 g. or more. With regard to fat assimilation, fats containing a large quantity of long-chain saturated fatty acids were less well tolerated by sprue patients than by normal individuals. Patients suffering from the sprue syndrome tolerated milk and

milk products better than mutton fat or beef fat. The faeces contained abnormal amounts of long-chain fatty acids up to 30 g. or more in 24 hours. The neutral fat was usually about 80% hydrolysed, and the fatty acids were often present as crystals and can be shown to have a high melting point, high molecular weight, and low iodine value (Parsons, 1932; de Kamer, 1949). Volatile short-chain fatty acids were often present in large quantities.

Detailed Study.—The detailed study of fat absorption showed differences from normal. Hydrolysis and initial emulsification in the upper part of the small intestine seemed to be within normal limits. Small but significant changes in emulsification may not be detected by this method; clear differences were found in cases of obstructive jaundice or chronic pancreatitis, in which emulsification was grossly defective. The addition of bile caused enhancement of lipolysis in all samples. The reason for this difference from normal is obscure. All the usual enzymes were present in approximately normal concentration, with the possible exception of lysozyme. Bacteria were present in large numbers in the upper intestine, especially in achlorhydric patients. The bacteria found were intestinal flora, which are normally confined to the lower part of the intestine.

With regard to the cellular and distributive phases, low blood phospholipid and cholesterol were usual. The oral glucose-tolerance curve was commonly depressed. There was no post-absorptive systemic hyperlipaemia following fat absorption, as shown by chylomicrographs and blood-fat curves.

Discussion

It is difficult to study the cellular phase of fat absorption in the human subject except by indirect methods. It is agreed by all workers that long-chain triglycerides can be observed as particles in the intestinal cell during absorption, and that these particles pass from the cell through the corium of the villus to the lacteal, and thence by the lymphatic route into the blood stream, giving rise to the normal post-absorptive systemic hyperlipaemia. There is evidence to support the view that these particles pass unhydrolysed, or partly hydrolysed, into the cell from the intestinal lumen, and that adequate emulsification, normal electrolyte absorption, and possibly phospholipid synthesis may influence this stage of particulate absorption (Frazer, 1948).

Alternatively, the triglycerides are resynthesized from fatty acids and glycerol inside the intestinal cell. The post-absorptive systemic hyperlipaemia is dependent upon normal particulate absorption. Absence of the normal hyperlipaemia might be due to interference either in the intraluminal or in the cellular phase, according to the partition theory (Frazer, 1946), but according to the lipolytic hypothesis (Verzar and McDougall, 1936) it must be due to faulty resynthesis in the cell. The effect of added lipase on the post-absorptive hyperlipaemia and the normal intestinal radiographic pattern during fat absorption in human subjects support the experimental evidence in animals upon which the partition theory is based. From either point of view, however, the absence of the post-absorptive systemic hyperlipaemia must be interpreted as evidence of defective absorption of triglycerides in particulate form.

It is concluded from the evidence presented that there is interference with particulate absorption in the sprue syndrome, and that larger quantities than normal of fatty acid are both absorbed and excreted. It is not possible at present to determine with certainty whether the interference with particulate absorption occurs in the intraluminal or in the cellular phase. The more unsaturated long-chain fatty acids appear to be absorbed, while the more saturated are excreted. This would account for the proportionate nature of the defect and for a number of secondary changes which will now be considered in detail.

The Effects of the Fat-absorption Defect in the Sprue Syndrome

Intestinal Mucin.—As a result of faulty particulate absorption, greater quantities of long-chain fatty acids occur in the intestinal lumen. Administration of long-chain fatty acids resulted in an increase of mucus in the intestinal lumen in normal human subjects and experimental animals, unsaturated fatty acids being more effective than saturated fatty acids. Mucus is an activator of lipolysis in the presence of bile salts. The administration of long-chain or short-chain fatty acids or hypertonic solutions induced the so-called radiographic "deficiency pattern" in normal human subjects. The changes observed were radiographically indistinguishable from those found in the sprue syndrome. The segmentation of the barium sulphate suspension was shown to be due to flocculation in the presence of mucus. The relative proportions of mucus to barium sulphate suspension were important (Frazer, French, and Thompson, 1949). There is little doubt that more mucin is present in the small intestine in a case of sprue than in a normal individual. Whether this is due to oversecretion, or whether lack of destruction of mucin may also be concerned, has not yet been determined. An increased quantity of long-chain fatty acids is at least partly responsible for the presence of excessive quantities of mucus.

Faecal Fat.—The amount of faecal fat was increased and the output of long-chain saturated fatty acids seemed to be selective and sometimes closely associated with mucin. Long-chain saturated fatty acids are not well absorbed by normal animals. The failure to absorb these fatty acids in sprue would account for the fact that the defect is proportionate and for the observation that sprue patients do not tolerate triglycerides containing much saturated fatty acid. The more unsaturated fatty acids are presumably absorbed, and, in accordance with observations in animals, they must be transported by an alternative route to the thoracic duct and thus do not give rise to a systemic hyperlipaemia. Long-chain fatty acids may cause irritation and diarrhoea, which can be controlled by the administration of calcium salts, which precipitate the long-chain fatty acids as insoluble soap. Excessive fatty acid formation might under certain circumstances be responsible for inadequate absorption of calcium and iron. The absorption of both calcium and iron is a complex question, however, and it is unlikely that any single factor accounts for their poor assimilation in the sprue syndrome.

Hypochlorhydria.—Administration of long-chain fatty acids will cause a decrease in gastric motility and gastric secretion, particularly certain long-chain unsaturated fatty acids. In the sprue syndrome decrease of gastric motility and acidity is marked. Hypochlorhydria is usual; achlorhydria may occur. The hypochlorhydria observed in sprue may be due to the absorption of abnormal quantities of long-chain fatty acids. Hypochlorhydria and large quantities of mucin in the intestinal lumen cause a relative fixation of pH, which, with decreased gastric and intestinal motility and interference with absorption, help to provide suitable conditions for increased growth of bacteria. Many intestinal bacteria can split triglycerides and may help in the hydrolysis of neutral fat to fatty acid, and they may also ferment starch. Starch fermentation may be pronounced in the sprue syndrome, giving rise to volatile short-chain fatty acids (acetic, propionic, and butyric) in large quantities in the faeces. These acids may be irritant to the intestine, giving rise to diarrhoea, which is not readily stopped by the administration of calcium salts.

Blood Biochemistry.—Certain changes in blood biochemistry were usually seen, particularly a decrease of phospholipid and of cholesterol in the blood. These changes might be due either to faulty absorption or to faulty synthesis. Particulate absorption may be closely related to absorption of phospholipid and to its synthesis in the intestinal cell. Cholesterol was also found to be associated with particulate fat in the chyle. However, the quantities involved were small and no close relation between blood phospholipid, cholesterol, and triglyceride was demonstrable during fat absorption (Frazer and Stewart, 1937). It seems likely, therefore, that the changes in blood phospholipid and cholesterol in sprue may also be related to decreased synthesis of these substances in the liver or elsewhere. There is no clear evidence at present to determine whether interference with synthesis or faulty absorption is the more important factor. Large quantities of long-chain fatty acids passing direct to the liver might modify liver function.

Discussion

The probable interrelationship of these various effects of abnormal fat absorption in the sprue syndrome is indicated in Fig. 1. Faulty particulate absorption of unhydrolysed

FIG. 1.—Fat-absorption defect in sprue syndrome. Continuous lines indicate points which have been demonstrated experimentally.

fat results in increased hydrolysis; the long-chain fatty acids formed are partly absorbed, causing increased mucus in the intestinal lumen; it is suggested that the excess mucus in the intestinal lumen may interfere with particulate absorption. The long-chain saturated fatty acids are not absorbed and passed out in the faeces. By taking this as the basic fault in the fat-absorption mechanism the main features of the sprue syndrome are readily explained. Thus the composition of dietary triglyceride, especially with regard to its saturated fatty acid content, will affect the sprue patient.

The absence of the systemic hyperlipaemia, although 70% of the fat is absorbed, the proportionate nature of the defect, and the occurrence of hypochlorhydria are explained on the basis of fatty acid absorption (Frazer, 1943). The failure to absorb the more saturated fatty acids is clearly shown by their appearance in the faeces. The existence of diarrhoea, which is only sometimes controlled by calcium, is due to the fact that it can be caused by long-chain fatty acids derived from fat breakdown or by short-chain fatty acids arising from starch fermentation.

The radiographic "deficiency pattern" has been shown to be due to flocculation of the barium sulphate suspension

with mucus. The changes in cholesterol and phospholipids may follow from failure of particulate absorption, or, alternatively, may be due to the effect of excessive amounts of long-chain fatty acids on liver function. Changes in steroid hormones and bile phospholipid may be secondary to the changes in blood cholesterol and phospholipid respectively. Symptoms can be aggravated in many cases of the coeliac syndrome by increasing the dietary starch (Parsons, 1932).

Relation of Fat-absorption Defect in the Sprue Syndrome to Multiple Aetiological Factors

The relation of the fat-absorption defect in the sprue syndrome to possible aetiological factors is shown in Fig. 2.

FIG. 2.—Fat-absorption defect in sprue syndrome in relation to aetiological factors.

Eight main causative factors of the sprue syndrome have been suggested, each of which will be considered briefly.

1. **Dietary Factors.**—The more saturated fats aggravate the fat-absorption defect. Special characteristics of the dietary fat, such as oxidative rancidity, may play some part in the aetiology of tropical sprue, especially when it occurs in groups of individuals under similar environmental conditions. Stannus (1942) suggested that dietary factors might have some causative role in tropical sprue. The inclusion of rancid fats in the diet causes diarrhoea, anaemia, and destruction of dietary vitamins (Whipple, 1932; Burr and Barnes, 1943; Györgi *et al.*, 1942). The possible significance of rancid dietary fats in the onset of tropical sprue in India was noted by J. M. French. It is unlikely that rancidity is a major aetiological factor in non-tropical sprue or in the coeliac syndrome in this country. Diarrhoea has been recently observed in infants in temperate climates receiving rancid cod-liver oil (Whipple, 1936). Rancid fats are readily hydrolysed, and the fatty acids liberated are irritant and are effective stimulants of mucus secretion. The effects of dietary fats and the products of rancidity on the fat-absorption mechanism are being investigated. Dietary factors may have some importance in the aetiology of tropical sprue.

2. **Structural Defect of the Intestinal Cell.**—It was suggested by Hurst (1941) that structural defects of the intestinal muscularis mucosa might be responsible for the fat-absorption defect in the sprue syndrome. Atrophic changes of the intestinal wall are not uncommon at necropsy. It is improbable that these changes are present in the many cases of tropical sprue which make a complete recovery. Secondary structural changes might perpetuate faulty particulate absorption and represent an irreversible stage of defective fat absorption in sprue cases of long standing.

3. **Disturbances of Electrolyte Metabolism (Adrenal Cortical Insufficiency).**—Adrenal cortical deficiency has been suggested

as a primary aetiological factor in sprue (Verzar and Laszt, 1935), since it was thought to be necessary for phosphorylation and resynthesis of triglycerides. It has been established subsequently that the adrenal cortex does not affect phosphorylation in the intestine (Stillman, Entenman, Anderson, and Chaikoff, 1942). Low blood sodium and hypotension are not uncommon in sprue, although usually observed in severe rather than early cases (Black, 1946). Changes in electrolyte metabolism and absorption might interfere with the particulate absorption of triglycerides (Frazer, 1949). In the sprue syndrome, however, treatment with adrenal cortical hormone, corticotropin, and other measures which brought the blood sodium back to normal levels did not markedly affect the fat-absorption defect. Cases of Addison's disease may show a defect of fat absorption, but they do not develop the sprue syndrome. A low level of free cholesterol in the blood may possibly result in a generalized steroid starvation, resulting in secondary hormone deficiencies, such as adrenal cortical insufficiency and delayed sexual development. Water and electrolyte changes may contribute to the fatal termination in severe cases of sprue, but they probably are not materially concerned in the primary aetiology of the sprue syndrome.

4. **Defective Phosphorylation (Adrenal Cortical Insufficiency—Verzar).**—There is little evidence of any direct relation between phosphorylation in the intestinal cell and triglyceride absorption. Simultaneous absorption of lecithin facilitates the absorption of long-chain triglyceride (Sagrott, 1949). The amount of phospholipid formed during fat absorption may be small, and for this reason phospholipid cannot be regarded as an obligatory intermediate in fat absorption (Zilversmit, Entenman, and Chaikoff, 1948). Faulty phosphorylation of fat in the sprue syndrome has been largely assumed on the basis of flat oral glucose-tolerance curves which have been attributed to failure in the phosphorylation of carbohydrate (Verzar and McDougall, 1936; Maegraith *et al.*, 1945). Other experimental studies have not supported this interpretation of the sugar curves (Emery, 1947; Fourman, 1947). Apart from the low blood phospholipid commonly observed, there seems to be little evidence of faulty phosphorylation in the sprue syndrome. If it did occur, it might affect particulate absorption as indicated.

5. **Emotional Factors.**—These cannot be disregarded in a gastro-enterological syndrome. Movement and secretion may be affected: certain other psychosomatic disorders are associated with excessive mucous secretion. Such changes might precipitate the sprue syndrome; there is no direct evidence of the mechanism at the present time.

6. **Starch Fermentation.**—In cases of the coeliac syndrome the fat-absorption defect may be aggravated by the administration of starch. Carbohydrate intolerance in the coeliac syndrome is well known (Parsons, 1932). The primary defect seems to be faulty digestion of starch granules and consequent starch fermentation, giving rise to short-chain fatty acids. Intolerance of starch also occurs in many cases of adult sprue. An extensive investigation into the mechanism of starch granule digestion and its relation to mucinases and lysozyme is being undertaken. It is possible that starch fermentation may have an aetiological significance in some cases of the coeliac syndrome.

7. **Intestinal Flora.**—Changes in intestinal flora occur in the sprue syndrome, more affecting the site of growth than the type of organism present. The predominating bacteria may vary, however, owing to alteration in environmental conditions consequent upon faulty absorption or other changes. The higher level of intestinal flora, which may reach the upper small intestine in sprue, may give rise to successful competition of the bacteria with the host. This competition hypothesis of the common vitamin deficiencies in sprue will be more fully discussed in another communication. Changes in intestinal flora are probably secondary in tropical and non-tropical sprue and the coeliac syndrome. Intestinal bacteria can hydrolyse triglycerides and ferment starch. They could therefore initiate changes which might lead to the sprue syndrome. Such a mechanism might possibly be involved in some cases of gastrocolic fistula.

8. **Vitamin Deficiencies.**—Deficiencies of riboflavin, nicotinic acid, and folic acid are fairly common in sprue—other vitamin

deficiencies are rather rare. It has been suggested that these vitamin deficiencies constitute a primary aetiological factor in the sprue syndrome (Verzar and McDougall, 1936; Castle, Rhoads, Lawson, and Payne, 1935). There is no satisfactory evidence of a direct relation between these vitamins and the fat-absorption mechanism (Frazer, 1947b). The signs of these deficiencies can be dramatically relieved without any effect on the fat-absorption defect (Cooke *et al.*, 1946). Classical cases of deficiency of these vitamins may occur with normal fat absorption. These deficiencies, which come and go during the course of the sprue syndrome, are probably secondary changes attributable to successful competition with the host for common essential nutrients on the part of intestinal bacteria.

Conclusions

It is concluded that the underlying fat-absorption fault is a defect in particulate absorption. The consequent absorption and excretion of fatty acids account for most of the major features of the sprue syndrome. Certain intermittent characteristics may be attributed to high growth of intestinal bacteria. The primary cause of faulty particulate absorption probably varies in different cases—many cases of tropical sprue may be primarily due to dietary faults, whereas some underlying defect, possibly an enzyme deficiency, may be a major factor in most cases of non-tropical sprue and the coeliac syndrome. Intestinal flora changes occur secondarily in most cases of sprue, but they may have a more important aetiological role in some cases of gastro-colic fistula. The final picture of the aetiology of the sprue syndrome will be achieved only as a result of further detailed study of the fat-absorption defect and experimental investigations designed to differentiate primary and secondary changes.

Much of the original work referred to in this paper is still in progress as part of the programme being undertaken in the Department of Pharmacology, University of Birmingham, by a team which includes Dr. J. M. French, Dr. M. D. Thompson, Dr. H. G. Sammons, Dr. R. Schneider, Dr. P. E. Sagrott, Mr. W. R. Pover, Mr. W. D. Brown, Mr. G. A. Rowe, and Mr. B. G. Taylor. While acknowledgments are made in the text to individual members with regard to points with which they have been especially concerned, the progress of the work is essentially dependent upon the combined efforts of the whole team. I am most grateful to many colleagues on the staff of the Birmingham United Hospital, especially to Professor T. L. Hardy, Dr. W. T. Cooke, Dr. A. L. Peeney, Dr. C. F. Hawkins, and Dr. Garfield Thomas, whose close collaboration and help have been invaluable. I am indebted to the Medical Research Council and the Sir Halley Stewart Trust for financial assistance in this work.

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THE TREATMENT OF MALIGNANT TERTIAN MALARIA*

BY

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The early diagnosis of malignant tertian malaria is a matter of the first importance, so that specific therapy may be started with the least possible delay. In recent years the development of modern methods of rapid transport has made it all the more imperative that medical men in all parts of the world should be familiar with the many diverse clinical manifestations of this disease.

My first experience of the difficulties which may be encountered in the diagnosis of *Plasmodium falciparum* infections occurred at an early stage of the 1914–18 war, when I was in charge of a wing of a military hospital in Nairobi. One morning about 80 British soldiers who had been evacuated from the vicinity of Lake Victoria Nyanza and sent down the line by hospital train were admitted under my care. A preliminary examination of these men disclosed a great variety of clinical symptoms, as the result of which I made a number of provisional diagnoses.

Many of the patients were obviously the victims of malaria, but there were others whose symptoms were unlike any which are usually associated with this disease. Several seemed to be suffering from some acute abdominal condition, such as appendicitis, pancreatitis, or biliary colic. Some were passing blood and mucus per rectum, and these I diagnosed as dysentery. Two or three had the clinical appearance of typhoid fever, and there were several with cerebral symptoms which I thought were probably due to heat-stroke. In one case I suspected amoebic hepatitis and in others bronchitis or bronchopneumonia. A blood smear was taken from each patient as a routine procedure and sent to the laboratory for examination; the presence of malignant tertian malaria parasites was reported in every single instance. The administration of quinine, at that time the only antimalarial drug available, was followed in all cases by prompt alleviation of symptoms and ultimate recovery.

My object in recounting this incident is to impress on those who are about to practise in malarious regions or to sail in ships which may touch at ports where the disease is endemic that malignant tertian infections often fail to conform to the popular conception of malarial fever. They may simulate a great variety of other diseases, and failure to recognize this fact has resulted in the loss of many lives which could have been saved by the prompt application of

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