ileum. Tributyrin, on the other hand, will be rapidly hydrolysed and absorbed as fatty acid. In this connexion it may be significant that the absorption of tributyrin is not affected by adrenalectomy (Bavetta and Deuel, 1942), and tributyrin is not found in the chyle (Hughes and Wimmer, 1935) or in the fat depots (Davis, 1930). The behaviour of triglycerides containing fatty acids of chain length intermediate between these two extremes is not yet known. It is of some interest, however, that the tolerance of patients with fat-absorption defects to different dietary fats appears to vary considerably.

If the pH in the upper part of the small intestine can be altered towards the alkaline side, more extensive hydrolysis might occur, with a corresponding decrease of particulate and increase of fatty acid absorption. The effect of such a change on the total efficiency of the fat-absorption mechanism is not known, but it seems unreasonable to suppose that the absorption of fatty acid from the intestine is already maximal under normal circumstances. Thus the sequelae associated with particulate absorption would be suppressed, but the total quantity of fat absorbed might not be greatly altered. Such a change might be a primary factor in the alteration of the fat-absorption pattern, or it might be secondary to a defect in particulate absorption. It is known that changes in the intestinal environment occur in a number of cases of defective fat absorption, but whether these are primary or secondary, or to what extent they are significant, has not yet been established. It may, however, be concluded that fat can be absorbed by at least two distinct mechanisms, each of which uses a different distributive pathway. The proportion of fat which is absorbed in particulate form may be reduced, with a corresponding increase in fatty acid absorption. Such a mechanism would provide the flexibility which is apparent in cases of defective absorption. The main factors which seem to be concerned in changes in the distributive phase, apart from obstruction to the lymphatic pathway, are the pH in the intestinal lumen and the composition of the dietary triglyceride.

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SOME PROBLEMS OF TROPICAL
SPRUE*

BY

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Before describing some of our observations in early tropical sprue it will be well to make two introductory digressions—the first on current views of fat digestion and absorption, the second on the type of patient with whom we were dealing.

Fat Digestion and Absorption

The classical view, of which a full statement is given by Bloor (1943), maintains that any absorption of dietary fat is preceded by splitting of the fat into glycerol and fatty acid. The glycerol is absorbed as a simple water-soluble substance and the fatty acid is absorbed as a water-soluble complex with bile salts, as cholesterol ester, or as phospholipid. The importance of phosphorylation in the absorption of fatty substances has been emphasized by Verzar, but not all of his supporting data have been confirmed.

Over the past ten years or so Frazer (1946) and his co-workers have collected a substantial body of evidence in favour of his "partition hypothesis" of fat absorption. In his view some of the fat is absorbed without preliminary splitting, so that there are two virtually independent channels of fat absorption. Neutral fat is absorbed as a very fine emulsion, and Frazer has described an emulsifying system of bile-salt-monoglyceride-fatty-acid which is adequate to produce an emulsion of the required fineness. Moreover, absorbed neutral fat enters the lacteals, and ultimately the systemic blood stream, where it may be visible as finely divided fatty particles known as chylomicrons; split fat, on the other hand, enters the portal blood stream and may therefore be absorbed without necessarily increasing the chylomicrons in the systemic blood. In support of his view Frazer has shown that liquid paraffin, which cannot be "split," can yet be absorbed if it is emulsified sufficiently. If rats are given a fatty meal with added lipase, so that splitting is practically complete, fatty particles are demonstrable in the portal blood; if, on the other hand, the fatty meal is treated with sodium cetyl sulphate, which inhibits lipolysis, fatty particles are found in the thoracic lymph and not in the portal blood stream.

Our own limited experience in this field has convinced us of the correctness of Frazer's views, with two minor reservations on quantitative grounds. The possibility of neutral fat absorption seems to be proved, but what proportion of the dietary fat is absorbed in this way is still uncertain; secondly, we found the chylomicron count was of very limited value as a measure of fat absorption, in view of the great variation in the size of the particles seen, which meant that identical "counts" might represent very different amounts of "chylomicron-fat."

Clinical Features of Early Sprue.—This is not the place for a clinical description of the textbook type, but it may be said that all the patients investigated showed loss of weight, abdominal distension, and fatty stools. Tongue changes were less constant, and anaemia of any severe degree was uncommon, nor was it necessarily macrocytic in those patients who showed it. Tetany and bone changes

* Based on a lecture given by one of us (D. A. K. B.) at the British Postgraduate Medical School.

were not seen, perhaps because alimentary absorption of vitamin D is not as essential in a tropical as in a temperate climate. About one patient in ten had profuse watery diarrhoea in place of the more usual bulky formed stools; such patients tended to go downhill rapidly, with low blood pressure, asthenia, and dehydration—a type of the disease which may be referred to shortly as “severe sprue.”

Objects of the Investigation.—Although much work has been done on the clinical and haematological aspects of sprue, notably by Castle *et al.* (1935) in Porto Rico, there is surprisingly little information on the quantitative aspects of fat absorption. Since the steatorrhoea is one of the outstanding features of sprue, it was decided that our main aim should be to collect data on fat absorption in early cases and see how the absorption might be affected by different forms of treatment. Some data were also obtained on the absorption of non-fatty substances, and an attack was made on the problem of “severe sprue,” already referred to.

Fat-absorption Studies

Three methods of studying fat absorption were used—chylomicron counts, serum lipid curves (Black and Simpson, 1947), and fat-balance experiments (Black, Bound, and Fourman, 1947). As experience with these various methods grew we found ourselves relying more and more on the fat-balance technique, but the results of the other methods may be briefly described. Chylomicron curves turned out to be fairly normal in most cases of early sprue. In some patients the chylomicron curve was below the rather wide normal range; but this type of curve was constantly present only in those patients who had profuse watery diarrhoea. Serum lipid curves were obtained by giving a standard meal of tinned milk containing 18 g. of fat, and analysing samples of serum taken off fasting, and 2½, 3, 3½, and 4 hours after the meal. The total fatty acid, cholesterol, and lipid phosphorus were directly determined, and from these data values were calculated for cholesterol-ester fatty acid, phospholipid fatty acid, and, by difference, neutral-fat fatty acid.

There was a significant difference between the fasting values in nine normal subjects and 16 patients with sprue; the total fat in the sprue patients was only slightly lower than in the normal subjects, but the cholesterol and phospholipid fatty acid was markedly lower, while the neutral fat was actually higher in the sprue patients. After the meal the increment in total fatty acid in the sprue patients was only about half that in normal subjects; neutral fat increment was much less affected than phospholipid fatty acid increment, while cholesterol fatty acid showed an actual fall in the sprue patients after a fatty meal. Unfortunately the normal range of fat curve was very wide, so that in the individual patient with sprue the curve might well fall within the normal range. This impairs the value of fat curves both in diagnosis and in investigation.

Fat-balance Experiments

Two diets of known fat content were available to us—one containing 65 g. of fat a day, the other 95 g. We measured the total output of fat in the stools and by subtraction from the dietary fat arrived at the total amount of fat absorbed; this, when expressed as a percentage of the dietary fat, may be termed the percentage fat absorption. Questions of interpretation arose very early in the course of this work.

1. It was found that the variation between successive four-day stool collections was very great, and in order to reduce error from this cause we have considered all our results in terms of twelve-day periods.

2. Any true intestinal excretion of fat will introduce error into this assessment of fat absorption. It was found, however, that sprue patients on a low-fat diet excreted no more fat than

normal people, so true excretion of fat can introduce only a small systematic error.

3. As patients originally on a 65-g. fat diet improved under treatment it often became necessary to increase their diet to 95 g. of fat a day. In five patients in whom this was done the percentage fat absorption was found not to change significantly. Apart from its practical bearing on the validity of percentage fat-absorption measurements on different diets, this result has some theoretical significance. It suggests that the impairment in absorption is not a fixed mechanical deficiency, as added fat would in that case be excreted quantitatively and the percentage fat absorption would decrease in the higher diet. On the other hand, an alteration in one of the enzyme systems connected with fat absorption would be expected to give this type of result. It is also possible, of course, that on the higher fat diet the increase in the gastric emptying time is great enough to ensure that the amount of fat actually presented to the intestine for absorption in unit time is not increased. From a more practical point of view it is to be noted that the increase in the fat content of the diet in these patients was a very moderate one, and our results do not conflict with the general experience that it is inadvisable to give large amounts of fat to patients with active sprue. Normal people taking a mixed diet containing 50 to 100 g. of fat a day will absorb over 90% of the dietary fat. In 28 patients with early tropical sprue we found that the fat absorption ranged from 50 to 85%. There was, therefore, with this method of assessment a clear-cut distinction between normal people and sprue patients, a distinction which was conspicuously lacking with the other methods which we tried as measures of fat absorption.

It is to be noted that Cooke *et al.* (1946), using a fat-balance method, also found a different range of fat absorption in normal subjects and in patients with idiopathic steatorrhoea. Results of this type commend the fat-balance technique, in spite of its tedium, as a means of assessing the severity of steatorrhoea and following progress under treatment.

In therapeutic trials with nicotinic acid and riboflavin in large doses the patients showed no improvement either in their clinical state or in fat absorption. With large doses of a crude liver extract given parenterally there was rapid clinical improvement, with gain in weight and well-being and improvement in the character of the stools. In spite of this the percentage of fat absorption showed no detectable change in several weeks of liver therapy and thereafter improved only slowly as the patient's general state approached the normal. When yeast extract in a dose of 15–20 g. daily was given to patients while on their liver treatment there was some improvement in fat absorption within the first twelve-day period. We had not the opportunity ourselves to observe the effect of folic acid in tropical sprue, but results reported by Davidson *et al.* (1947) suggest that it has an action rather like that of crude liver extract and inferior to yeast extract, at least as regards fat absorption.

Absorption of Non-fatty Substances

Apart from glucose, the absorption of non-fatty substances in sprue has been little studied; yet it would seem important in considering the aetiology of the disease to know whether the impairment of absorption is general or whether it is limited to a few substances—such as fat—absorption of which may present some special difficulty, or perhaps even whose failure to be absorbed is more readily apparent from secondary effects on the stools. If unabsorbed carbohydrate were as easily recognized in the stools as unabsorbed fat the demonstration of impaired carbohydrate absorption in sprue might not have to be based on the equivocal evidence of blood-sugar curves, so easily modified by non-absorptive factors. The evidence which we obtained on the question of non-fatty absorption in tropical sprue is mostly indirect, for the balance technique of studying absorption cannot

be applied to substances such as glucose or amino-acids. Some general impairment of absorption was suggested by our finding that in the active stages of sprue the dry weight of the stools was increased to a greater extent than could be accounted for by their increased fat content. Using indirect methods, we confirmed that glucose absorption is often impaired, and we also found some evidence of faulty absorption of iron, sodium, and chloride in certain cases. On the other hand, iodide and amino-acids were abnormally absorbed. Iodine is absorbed from the stomach and so is rather a special case.

The satisfactory absorption of amino-acids does show, however, that the intestinal absorption defect is not universal; the exact process involved in amino-acid absorption is not known, but absorption is more rapid than can be accounted for by simple diffusion (Höber, 1945). Fourman (1947) has found evidence of impaired xylose absorption in sprue: this may imply a more fundamental absorption defect than that shown by flat glucose curves, since xylose absorption, unlike that of glucose, is not inhibited by phloridzin and may therefore be produced by a different and simpler mechanism.

In summary, the evidence suggests that there is in fact a fairly general impaired absorption in sprue, and that fat malabsorption has been first observed only because its effects on the stools are more obvious.

Salt Deficiency

In preliminary work on the syndrome described above as "severe sprue" it was found that the serum sodium and chloride were both low. A balance experiment showed that large amounts of sodium and chloride were being lost in the watery stools, and that sodium was practically absent from the urine although chloride was still present in about half the normal amount. This is the biochemical pattern of salt deficiency (Black, 1946) accompanied by some acidosis; the absence of sodium from the urine is very much against supranal insufficiency being the cause of the hypotension—a suggestion made by Thaysen (1932). The persistence of some chloride in the urine may be misleading if reliance is placed on the urinary chloride alone in detecting salt deficiency in this type of patient.

Conclusion

We would emphasize the two findings which seem to us of practical therapeutic significance. The first is that yeast extract in large doses has a favourable effect on fat absorption: we have seen clinical benefit from yeast treatment in patients with chronic sprue in this country, and it is more convenient for the patient than frequent injections of crude liver extract. Secondly, a number of patients with sprue became acutely ill, with salt-deficiency dehydration associated with watery diarrhoea; in such patients the diarrhoea must be controlled with sulphaguanidine and parenteral liver, and their diet should also be supplemented with moderate amounts of salt.

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SHOCK IN OBSTETRICS

BY

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The essential mechanism of surgical shock is yet to be definitely established. It is understandable, therefore, that the physiologists and experimental surgeons desire to keep surgical shock in a special category until the mechanism of its inception may be discovered. As regards this subject I am neither a physiologist nor an experimental surgeon, and I speak, therefore, simply as a clinician. To the clinician there is a group of cases characterized by circulatory deficiency, with low blood pressure, decreased blood volume, decreased cardiac output, and increased concentration of blood that present a common clinical picture irrespective of the primary cause. These patients present a group of symptoms and not a disease. The prevention and treatment of these are of primary importance, and whether there is a special kind of shock called "obstetric shock" occurring in normal women after normal labour is of little importance. At one time it was customary to attribute a certain number of sudden deaths during or after labour to primary shock; but Sheehan, as well as other observers, has made it quite clear that in the great majority, if not all, of these cases necropsy will reveal some condition sufficient to account for the fatality.

In all urban centres the number of maternal deaths certified as due to "shock" is a great deal less than it was twenty-five years ago. Of 122 maternal deaths during a two-year period from May, 1938, carefully evaluated by the Department of Health and Welfare of the Province of Manitoba, five were originally attributed to "strain and shock." Two of these, on review of the clinical history, were obviously due to internal haemorrhage, and the other three, on review, could not easily be attributed to shock. All five of these patients were delivered at home, remote from hospitals, and necropsies were not done.

Table I is an analysis of the maternal deaths with clinical evidences of shock in the Province of Ontario for 1943, the last year for which complete data were available.

TABLE I.—*Maternal Deaths Accompanied by Shock: Province of Ontario, 1943*

Total live births	..	81,173
Maternal deaths—exclusive of ectopic gestation (14)	..	189
Maternal deaths with clinical evidence of shock	..	82
Pulmonary embolism	..	33
Haemorrhage	..	31
Failed forceps and version	..	5
Difficult forceps	..	5
Rupture of the uterus	..	5
Acute dilatation of the stomach (necropsy)	..	1
Normal delivery with severe hypertension	..	1
Normal delivery with no apparent haemorrhage (no necropsy)	..	1

It will be seen that at the most only 11 of these did not have definite lesions accounting for the shock, and of the 11 there were 5 versions after failed forceps and 5 difficult forceps cases, in most, if not all, of which there was probably severe injury to the birth canal, with haemorrhage.

It is my opinion that, from the clinical point of view, the great majority of cases of obstetric shock can be evaluated in terms of haemorrhage. That is not to say that other causes of shock do not occur in the parturient patient: it is to say that they are relatively infrequent.

Table II summarizes the cases of shock on the public ward service of the Toronto General Hospital for the period 1931–43.

In the third group, with a blood loss of more than 1,000 ml., it will be noted that there were 6 deaths. Two of these were cases of placenta praevia; both had severe haemorrhages before admission and were bleeding when