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FAT ABSORPTION AND SOME OF ITS PROBLEMS*

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Some twenty years ago physiologists considered that the process of fat absorption was largely understood. Fats were supposed to be taken up by the intestinal cells only after hydrolysis to fatty acid and glycerol, and neutral fats were never absorbed as such. Furthermore, since free fatty acid, although well absorbed, is not found free in the chyle, it was assumed that reconversion of fatty acid and glycerol to neutral fat occurred in the cells of the villi, and that this neutral fat was then passed on into the lacteals. There was no suggestion then that any portion of the fatty acids which were produced by hydrolysis of the food fat escaped this process of resynthesis and gained access as such to the blood or the lymph. But there was not then, and there is not now, sufficient quantitative evidence to tell us exactly what happens to the whole of the fat absorbed after any one meal.

This picture of the mechanism of fat absorption, accepted as largely true, as I say, twenty years ago, has had considerable doubt thrown upon it in the last decade. But it was not as complete as I have suggested even before then, for the passage of fat from the cells of the villi to their central lacteals was not understood. Sharpey-Schafer had suggested from histological investigation that this transfer was carried out by amoeboid cells in the reticulum of the villus. But the difficulty of accounting for the speed at which fat absorption may take place by the unaided activity of these cells has not supported Sharpey-Schafer's view. What is more probable is the view of Verzar that the pumping action of the villi causes fat to enter the central lacteals, and that the absorption not only of fats but of other substances is promoted in this way.

Earlier Beliefs

Before dealing with recent work it will be profitable to consider on what kind of evidence these views of twenty years ago were based.

Evidence that fat is absorbed only after hydrolysis in the intestinal lumen was partly histological. Even at the height of fat absorption, fat particles could not be seen in the free border of the cells of the villi, though they were abundant in the body of these cells. It is, however, well known that fat may be present in cells and not be stainable as particles or globules, so that histological evidence by itself, which does not support the idea of fat being absorbed in a very highly emulsified state, is not conclusive. More con-

vincing evidence was that, although fat-like substances such as esters of fatty acids are well absorbed, there is no evidence that this can be done without their previous hydrolysis by the lipase of pancreatic juice. For example, fatty acid esters such as cetyl palmitate, ethyl palmitate, and a lauric acid ester of mannitol are all well absorbed, but none of them appears unchanged in the fat of the chyle. What is found there is the glyceride of palmitic or lauric acid respectively.

Other information on this question had been got by feeding oily substances which were like fats physically but not chemically and were capable of being emulsified. It was found that they were completely unabsorbed. In this category come experiments with lanolin, mixtures of petroleum jelly and lard, or petroleum oil and olive oil. With the mixtures of natural fats and petroleum hydrocarbons the natural fat was absorbed but the petroleum product was not. The non-absorption of the petroleum was demonstrated either by its complete recovery from the faeces or by its non-appearance in the fat of the chyle.

Evidence, then, that fats could be absorbed only after hydrolysis to fatty acid and glycerol seemed fairly conclusive. But the problem of how fatty acids were absorbed even after hydrolysis still remained. The higher fatty acids are as insoluble as the fats and would still have to be absorbed from the fine suspensions or emulsions which were supposed to be present in the intestinal lumen, and histological appearances did not give any evidence that this actually happened. For this reason it had been suggested that the fatty acids formed soaps which, being soluble in water, could be absorbed in solution. There were two facts against this. First, it was believed that soaps are not formed at the faintly acid reaction of the upper regions of the small intestine. Secondly, even if soaps could be formed, there is not enough alkali secreted in the pancreatic juice to produce soap from the whole of the fatty acids which might be liberated from the fat taken at a normal meal.

The fact that bile salts will dissolve fatty acids, and, furthermore, the discovery that the lecithin normally present in bile assists this action very considerably, showed that a means existed whereby fatty acids could be brought into solution in bile and thus be absorbed in the dissolved state. There is ample proof, both from clinical findings and from animal experiment, that the presence of bile in the small intestine is essential to obtain the figure of about 90 to 95% absorption of fat which is normally found.

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The effect of bile in promoting absorption might be due to its well-known adjuvant action on the hydrolysis of fat in the small intestine by pancreatic lipase. This would facilitate fat-splitting, and this was deemed a preliminary essential to absorption. But examination of the faeces in cases of biliary obstruction and consequent steatorrhoea showed that fat-splitting was not defective. Therefore, at the time I am considering, it was the solvent action of bile salts, potentiated by lecithin, which appeared to provide the explanation of the action of bile. Other possible ways in which the action of bile might be accounted for have been pointed out since; I shall deal with these later, for the mode of action of bile in promoting fat absorption is still a physiological problem. Nevertheless, at the time of which I am speaking, this solvent action of bile on fatty acids was accepted as solving the problem of how the insoluble higher fatty acids might be brought into solution and so absorbed.

Evidence that fatty acids when absorbed are resynthesized and appear as neutral fat in the lacteals was first provided by Immanuel Munk nearly 70 years ago. By collecting chyle from the thoracic duct of dogs to which fatty acids had been administered Munk found that the chyle contained not fatty acids but almost wholly neutral fat. He also showed some years later, in a human subject with a lymphatic fistula which discharged chyle, that after a meal including erucic acid the chyle contained only the glyceride erucin and not free erucic acid. Analyses of fat from the mucosa during fat absorption carried out by Moore about 50 years ago showed that this was a mixture of fat and fatty acids, and collection of chyle before it had traversed the lymphatic glands which lie along the course of the lacteals showed that the fat in these peripheral lacteals was almost wholly neutral. This indicates that resynthesis occurs in the cells of the villi.

It is interesting to recall that Munk, who had proved to his own satisfaction that free fatty acids were as well absorbed as neutral fat, believed firmly that the fatty acids were absorbed in a finely emulsified state. This was stoutly disputed by the indomitable Pflüger, but not, unfortunately, supported by any very satisfactory evidence, except the histological finding, already referred to, that fat is not detectable by staining methods in the free border of the cells of the villi. It was the discovery by Benjamin Moore of the solvent action of bile salts which to a large extent reconciled these opposite views and gave rise to what persisted as the classical view of fat absorption until a few years ago.

The Quantitative Aspect

There is one other aspect of these older experiments that I must deal with before proceeding to discuss later evidence on fat absorption, and that is the quantitative one.

The physiologist can be satisfied that what is termed the classical view of the process of fat absorption is true only if he can account satisfactorily for the whole of the fat absorbed. This has not yet been done. It would be thought to be a simple matter to collect the chyle from a thoracic-duct fistula in an animal during the whole period of the absorption of a meal containing a known amount of fat, but this has so far not been achieved. This is partly due to the inhibiting effect of general anaesthetics on fat absorption and to mechanical difficulties caused by frequent clotting of the chyle one is endeavouring to collect. Munk and Rosenstein, however, did succeed, using their patient with a lymphatic fistula in the leg, in collecting chyle for a period of 13 hours. After a meal containing 41 g. of fat, 1,134 g. of chyle were collected, and this contained

25 g. of fat—i.e., 60% of that administered. Although the chyle still contained fat, the experiment was stopped. Munk and his colleague assumed that, had the chyle been collected until fat was no longer present, an additional 6% of the fat administered might have been collected. This is the only quantitative experiment that has been recorded in which an attempt was made to give a balance-sheet accounting for the fat fed and that which passed into the thoracic duct. It has the obvious defect that the amount of fat actually absorbed was not measured. We know that olive oil is very well absorbed as a rule, and, assuming that all the chyle was being collected, for which Munk gave indirect evidence, we are left with the conclusion that about two-thirds of the fat absorbed reaches the thoracic duct via the lacteals, whereas the remaining third is unaccounted for. It has generally been assumed that it passes into the blood stream via the capillaries of the villi.

To sum up, the classical view was that fat was absorbed only after hydrolysis. The fatty acids so produced were absorbed dissolved in bile. They underwent resynthesis into neutral fat in the epithelial cells of the villi. This was then discharged into the reticular spaces of the villi and taken up by lacteals or blood capillaries. In the former case it entered the systemic blood vessels and in the latter it reached the portal blood and so passed direct to the liver.

Physiologists are perhaps more critical of classical views than are other scientists. It is not, therefore, a matter for surprise that the beliefs of twenty years ago have continually been questioned and subjected to further experimental inquiry. The result is that this classical view has been called in question and other possible mechanisms of fat absorption have been put forward.

Role of Phosphates

In 1934 Verzar and Laszt described experiments on rats which indicated that phosphates may play a part in fat absorption. Their method was to inject into the small intestine of the animals the mixtures they were testing and after six hours to withdraw them. The amount of fatty acid was estimated and compared with that introduced at the beginning, thus showing the magnitude of the absorption. There was practically no absorption when oleic acid alone was injected into the gut, but it was moderate when the fatty acid was mixed with bile acid or with bile acid and glycerol. It was nearly doubled when phosphate was added to the mixture. When glycerophosphate was used instead of phosphate then the absorption was increased still further. This suggested that esterification of glycerol by phosphoric acid may be an important factor in fat absorption.

It is known that the mucosa of the small intestine is one of the body's richest sources of the enzyme phosphatase, so that in the presence of phosphate the glycerol split off from fats in the process of digestion might undergo conversion to glycerophosphate in the cells of the villi.

Furthermore, it was shown that mono-iodoacetic acid, which inhibits the enzyme phosphatase, also inhibits the absorption of fatty acid. But this inhibition of fat absorption is still evident when the fatty acid is mixed with bile acids and glycerophosphate, so that Verzar concluded that the iodoacetic acid acts by preventing in some way the resynthesis of neutral fat in the mucosal cells rather than by preventing phosphorylation. It was shown in Verzar's laboratory that the action of lipase was not hindered by iodoacetic acid, so that a failure to hydrolyse fat did not

explain why the fat was not absorbed after administration of this substance. What seems most likely is that its action as a general cellular poison is a sufficient explanation of its prevention of fat absorption.

Verzar showed also that phlorizin prevented fat absorption in rats. This substance also inhibits the enzyme phosphatase. The doses that have to be used are very large and the complete inhibition lasts for only a few hours. Nevertheless, these experiments are more suggestive than those with iodoacetic acid that phosphorylation is an accelerating factor in fat absorption. Histological observations from Verzar's laboratory indicate that it is not the entry of fatty acids into the cells of the mucosa which is prevented, but rather the resynthesis into neutral fat and its transport away from these cells. Thus, staining methods which differentiate fat from fatty acid show that a few hours after administration of iodoacetic acid or phlorizin most of the globules or particles inside the cells of the villi consist of fatty acid, whereas normally they would be neutral fat.

If phosphorylation is an important aid to fat absorption by the villi, it probably indicates that the synthesis of lipins is an intermediate stage in the resynthesis of neutral fat.

There is, however, not much more experimental evidence on this point. Examination of the fat in the chyle has shown that it does contain a small amount of lipin, but the proportion does not exceed 10% of all the fat present.

Estimations of the lipin content of the cells of the villi during the absorption of cotton-seed oil in pigs have also been made by Reiser, but have shown no change within five hours. It has also been shown by Barnes, Miller, and Burr in rats fed with a methyl ester of the conjugated acids of corn oil, which can be estimated by spectrophotometric methods, that at a time when the absorption was maximal there was only a slight incorporation of the fatty acids administered into the lipins of the cells. This indicates that if lipin formation is essential in fat synthesis in the cell the rate of transformation of lipins into neutral fat must be very rapid.

Experiments in which phosphate containing radioactive phosphorus has been fed along with fat have shown that the isotopic phosphorus becomes incorporated in the lipins of the mucosa. But this does not provide evidence of new formation of lipins during fat absorption, because the isotope might have undergone exchange with the phosphorus of the pre-existing lipins.

We must therefore, I think, come to the conclusion that the facilitation of fat absorption by phosphate and glycerophosphate, which was demonstrated in rats by Verzar and his colleagues, has not yet led to an explanation of the mechanism by which it is brought about. The study of the lipins in the mucosa during fat absorption has certainly not given one.

The Partition Hypothesis

Other experiments which I wish to describe next have been concerned to a large extent with the fat in the blood and its relation to the processes of fat absorption. It is well known that during the absorption of fat the blood plasma has an opalescent appearance. This is due to the presence of fat in extremely fine suspension.

Under dark-ground illumination the microscopic particles of fat appear as points of light and can be counted. A method for estimating their number under standard conditions was described about ten years ago by Frazer and Stewart. The particles are called "chylomicrons," and the number present under these standard conditions we may

refer to as the chylomicron count. The graph representing the change in this count with time is spoken of as a "chylomicrograph." It is obvious that unless the chylomicrons are always of the same average size a mere estimation of their number would not give an accurate indication of their weight. If, therefore, the chylomicrograph is to be used to indicate the relative amounts of fat in the blood at different times, then it must be known whether under all conditions the fat content of the blood runs parallel to the chylomicron count.

A study of the results published from Professor Frazer's laboratory shows that the count is very low during starvation, and that it rises considerably after a meal which contains fat. There is a peak about three hours after the meal. When the fatty components of the blood are estimated and the amount is compared with the count there is a rough parallelism between the two with glycerides, but not with lipins and cholesterol esters. It must therefore be borne in mind that the chylomicrograph gives no more than a qualitative indication that the amount of fat in the blood varies under different conditions. It does not allow us to estimate either the percentage variation or the absolute amount present under those different conditions.

Nevertheless, the study of chylomicrographs in relation to fat absorption has revealed several interesting facts which require explanation.

Rats were given some olive oil or the equivalent amount of oleic acid and glycerol. After olive oil the lacteals appeared milky, and the chylomicron count in the systemic blood was high, but in the portal blood it was low. With the oleic acid and glycerol the chylomicron count in the systemic blood was low, whereas that in the portal blood was high and the lacteals were relatively free from fat.

These findings suggest that in the rat, at all events, neutral fat and fatty acid are dealt with differently in the process of absorption. Additional evidence for this view was obtained by feeding stained fat or fatty acid to rats. After a week of such feeding the fat depots were deeply stained when stained fat was fed, but were not when equivalent amounts of stained fatty acid and glycerol were given. Furthermore, if rats were fed with small quantities of stained fat or fatty acid and killed five hours later the liver showed only a small amount of stained fat after feeding with fat, but a large amount after feeding with fatty acid.

From these and other observations Frazer concludes that neutral fat is absorbed direct into the intestinal cells and is passed on without change to the lacteals. On the other hand, fatty acid is absorbed into the cell by a different mechanism. It is passed into the blood capillaries of the villi and reaches the liver in the portal vein.

According to Frazer, therefore, lipolysis is *not* an essential preliminary to absorption, and neutral fat and free fatty acid can both be taken up by the intestinal cells. When they are taken up they are treated differently.

The view that some of the absorbed fat might be taken up by blood vessels in the villi and not by the lacteals does not conflict with previous evidence. It will be remembered that in Munk's quantitative experiments with the patient who had a lymphatic fistula about one-third of the fat administered was not accounted for by passage into the lacteals, and it has therefore been assumed that the pathway of this fat was the blood vessels of the villi.

What is new about the deductions drawn by Frazer and his colleagues from the comparisons they have made between the absorption of fat and fatty acids is that an unspecified amount of the fat which is absorbed in the

rat when neutral fat is administered is absorbed without previous hydrolysis in the intestinal lumen.

Histological Picture

In addition to the evidence obtained from chylomicrographs and the appearance of the lacteals, Frazer and his colleagues have drawn attention to the different histological pictures presented in the small intestine when olive oil and oleic acid are administered. With olive-oil feeding the cells are mostly occupied by large globules of fat, whereas when oleic acid is given the cells are full of much smaller particles, presumably of the fatty acid. Frazer makes the point that if fat-splitting must precede fat absorption then administration of fatty acid should produce the same histological picture as administration of neutral fat.

It is, however, a legitimate comment on this view that one might not necessarily expect to get the same histological appearances, because the conditions are not the same. In the case of olive-oil feeding, the fatty acid is liberated gradually and therefore in small concentration; when fatty acid is fed it is presented to the cells in maximum concentration ready formed. In the latter case the cells are, so to speak, swamped with fatty acid, but in the former case they may be able to deal with it in a more leisurely manner. This is the old problem of histology. To what extent are we justified in interpreting dynamic functions from static pictures? I feel that it is unsafe to draw fundamental conclusions on fat absorption from histological evidence of this kind alone.

Frazer, however, has obtained other evidence in support of his view that in absorption fat and fatty acid are treated differently by the intestinal cells.

The rate and amount of lipolysis in the intestine can be increased by adding an active preparation of lipase to the fat which is fed. When this is done in rats, the histological picture is like that obtained when a fatty acid such as oleic acid is fed—i.e., the cells are filled with fine granules. The path of absorption is also like that observed with fatty acid feeding—namely, absence of milkiness in the lacteals—and when stained fat is given along with the lipase the liver is deeply stained but not the fat depots. In addition to these observations it is found in man as well as in the rat that addition of lipase to the diet causes a considerable change in the chylomicrograph. At the peak period the chylomicron count obtained when fat is fed greatly exceeds that which results from feeding the same amount of fat with added lipase.

The reverse of this experiment has also been carried out by Frazer. This was the inhibition of the action of lipase of pancreatic juice by giving a small amount of sodium cetyl sulphate with the oil fed. This prevents the hydrolysis of fat by lipase and, in the rat, produces a histological picture like that obtained with neutral fat alone—namely, intestinal cells filled with large fat globules. Along with this the lacteals are found to be milky, and when stained fat is fed along with cetyl sulphate the fat depots are heavily stained, whereas the liver is not. This again points to lipolysis not being essential for fat absorption and different paths of absorption being followed by fats and fatty acids. In Frazer's experiments with cetyl sulphate it seems likely that inhibition of lipolysis was almost complete. That fat was absorbed in amounts which were quite normal was attributed by him to the emulsifying action of cetyl sulphate, which would be expected to produce fine particles of fat in the intestinal lumen. These could be taken up directly by the intestinal cells if his view is correct.

To my mind these experiments with cetyl sulphate provide the best evidence that has yet been put forward that, in the rat at all events, fat may be absorbed without hydrolysis if it is finely enough emulsified. Cetyl sulphate is a particularly valuable tool because, besides its surface active properties, it inhibits lipase. The fine emulsion it produces would normally lead to a more rapid action of lipase, and hence production of fatty acid. But this being prevented enables the effect of emulsification alone to be studied.

Emulsification

Emulsification, its degree of fineness, and the conditions which bring it about are very important in fat digestion and absorption. I should therefore like to say more about them at this stage.

Because fat is insoluble in water its digestion takes place at the interface between the fat globule and the surrounding medium which contains the fat-splitting enzyme. The more finely divided the fat—i.e., the more it is emulsified—the greater will be its surface area and, other things being equal, the more rapidly will it be split up into fatty acids and glycerol. According to Frazer, fine emulsification is also a prerequisite for absorption of fat in its unchanged state. It is clear, therefore, that in the small intestine there will be two competing processes for disposing of the fat which enters it from the stomach. The more finely the fat is emulsified the greater will be its chance of being split up into fatty acid and glycerol, both of which can be absorbed in solution. But, also, the greater will be its chance of being absorbed in particulate form.

We have as yet no answer to the question how much of the fat travels by what we may call the fatty acid route and how much is taken up as neutral fat. It is, however, obvious that whatever proportion, if any, is absorbed in particulate form depends almost entirely on the existence of conditions in the intestine which will facilitate the production of a very fine emulsion.

This leads us to consider what those conditions are. We are again indebted to Professor Frazer and his colleagues for some experiments that have thrown a great deal of light on them.

There is general agreement that the reaction of the contents of the small intestine varies between a pH of about 6.5 and 8.5. A prerequisite for particulate absorption of unchanged fat is therefore the existence of a stable, finely divided emulsion between that pH range. It has been shown by Frazer that, if olive oil is placed in a rat's stomach and the animal is killed three to four hours later, its small intestine contains a white emulsion of fat consisting of negatively charged particles less than 0.5μ in diameter. The emulsion is stable for several hours.

This shows that administration of oil does provide the kind of emulsion that would be required for particulate absorption. By studying systematically the emulsifying effect on olive oil of single, paired, and triple combinations of bile salts, oleic acid, soap, glycerol monostearate, and soap formed at the oil-water interface by the reaction between oleic acid and sodium carbonate, Frazer and his collaborators found one triple combination that provided the requisite kind of stable emulsion. It consisted of bile salt, oleic acid, and glycerol monostearate. The oleic acid and monostearate were dissolved in the oil and a 1% solution of bile salt formed the aqueous phase. On mixing, emulsification was spontaneous over the pH range 6-8.5, the particle diameter averaged less than 0.5μ , and the stability was all that could be desired.

It is not difficult to produce emulsions of fat in an alkaline medium, but it is when the reaction is even slightly acid, as in the duodenum; hence the special importance of this new discovery by Frazer. If this sort of combination is that used normally in the intestine, it implies that a stepwise hydrolysis of fat takes place with monoglyceride as at least one of the phases. I am not aware of any demonstration that when lipase acts on fats the three component fatty acid molecules are split off one at a time, although this might well be so. In fact, the only difficulty in accepting this three-component system as one which may be responsible for emulsification in the small intestine is the lack of experimental evidence that a monoglyceride stage exists as a phase in the action of lipase on fats. There seems to be no theoretical objection to this, so possibly, in the future we may expect to see some proof of it by experimental means.

Importance of Bile

It will be observed that this work on emulsification provides a new function for bile salts and therefore emphasizes the importance of bile in the digestion and absorption of fat. All the following functions may be attributed to bile salts. In digestion they have two roles: besides increasing the surface area by aiding emulsification of fat they have an adjuvant effect on lipase itself, speeding up its action several times. In the process of absorption they are believed to play several parts. One of these is to dissolve fatty acids, probably by forming soluble complexes with them.

Wieland and Sorge have shown that one of the bile acids—deoxycholic acid—forms definite compounds with fatty acids, the so-called choleic acids. They have suggested that these acids, coupled with glycine or taurine, may therefore play a part in enabling fatty acids to enter the intestinal cells. Verzar and McDougall suggest that bile salts form a layer at the surface of the intestinal cells, where they produce water-soluble and diffusible complexes with fatty acids and so assist the entry of the latter into the cells. Finally, according to Frazer and his collaborators, they are necessary for producing the stable emulsions of fat with particles less than 0.5μ in diameter and capable of existence in a pH range of 6–8.5 which are postulated as necessary for particulate absorption of fat.

In spite of this variety of ways in which bile salts assist fat absorption, they do not seem to be absolutely essential. It is one of the interesting problems of absorption why they are not.

The most trustworthy evidence for this comes from experiments on dogs in which a biliary fistula had been established. Munk has described how in animals treated in this way and fed on diets containing varying amounts of suet or lard, or, alternatively, with the fatty acids derived from them, a considerable amount of the fat or fatty acid was absorbed. The figures for the quantity of fatty acids taken up during the passage of the food through the intestine were always a little higher than those for the corresponding amount of neutral fat. Also, the lower-melting fat was absorbed better than the higher-melting one. Thus lard was absorbed to the extent of 67% and suet to 35% when the daily intake was 70 g., the corresponding figures for the fatty acids being 73% and 42%.

Other experiments on human subjects with biliary obstruction bear out these results. Schmidt, for instance, describes the findings on three cases in which the average fat utilization was 74%. In two of these the obstruction was complete.

These results leave no room for doubt that although the presence of bile in the intestine assists fat absorption it is by no means essential.

In the experiments of Frazer and his colleagues on emulsification the only stable emulsion obtained at the pH found in the upper part of the small intestine was obtained in the presence of bile acids and monoglyceride. These, however, could not have been present in the experiments of Munk on the absorption of fatty acids, which I have just described. It seems a reasonable conclusion, therefore, that large amounts of fat and fatty acid can be absorbed under conditions which do not fit in with those so far shown to be necessary to produce fine emulsions at the slightly acid reaction of the intestine.

I have pointed out earlier that the solvent action of bile for fatty acids was the one property which led to the abandonment of the particulate absorption theory about fifty years ago. Since so large an absorption of fat or fatty acid can take place in the absence of bile, we are led to the conclusion that some other solvent for fatty acids must be present or that some undescribed emulsifying system exists which can explain the remarkable degree of absorption obtained when bile is absent. It is important to bear in mind that the diet used by Munk in his experiments was a mixed one and contained a large proportion of meat. Possibly digestion products of protein and especially amino-acids in high concentration may assist in emulsification, or in stabilizing emulsions, or in actually combining loosely with fatty acids so as to assist their absorption. This must remain a speculation, however, until experimental evidence about it can be obtained.

Absorption of Paraffin

One other set of recent experiments on the absorption of oil emulsions is of importance. It is the work of Frazer, Schulman, and Stewart on the absorption in the rat intestine of emulsions of paraffin. These observers found that 50% emulsions of liquid paraffin stabilized with cholesterol and sodium oleate or sodium cetyl sulphate could be prepared with an average particle diameter of 0.5μ or less. These when introduced direct into the rat's intestine were absorbed to the extent of 36 to 43% in a period of six hours. It will be observed that no bile salt was used in making these emulsions, so these experiments show again that bile is not essential for absorption of fine emulsions. With coarser emulsions, in which many particles had a diameter of 1 to 2μ or more, the absorption was very much reduced.

These experiments show that, provided an oil emulsion is finely enough dispersed, it can be absorbed in the rat's small intestine. Some alarm has been expressed on this account at the use of medicinal paraffin as a medicament and in cooking. It has been suggested that if paraffin is absorbed it would tend to accumulate in the body in undesirable situations, since it is not oxidizable, or, if it is, then only with great difficulty. So far as I am aware, no evidence has been produced that the fine dispersion of paraffin which Frazer and his colleagues have shown to be necessary before absorption can take place is obtained when the oil is taken by mouth in the normal way. On the experimental side it may also be recorded that Channon and Collinson many years ago gave 100 ml. of emulsified paraffin daily to a pig for 54 days. On extraction of the fatty substances from its liver 2.2 g. of unsaponifiable material was obtained, which was possibly derived from the 5.4 litres of oil that had been administered. This does not suggest that absorption of paraffin takes place in an amount that would be of material importance.

Steatorrhoea

A final topic that must be considered briefly is whether diseases involving defects in fat absorption have taught us anything about the physiology of the process. In certain fields of physiology it is true that a study of disease has helped to throw light on physiological processes, but that can hardly be said of disorders in which fat absorption is at fault. It is true that biliary obstruction causes steatorrhoea, but that fact has not explained the reason why. Similarly, pancreatic disease, or in extreme cases complete pancreatic obstruction, interferes with fat absorption.

Those who uphold what I have termed the classical view of the mechanism of fat absorption would state that this was due to defective hydrolysis of fat caused by the partial or complete deficiency of pancreatic lipase. That would seem to be a satisfactory explanation. At first sight it also counters the modern view that fine emulsification is all that is necessary in order that fat absorption may take place. But we have to remember that the failure of both bile and pancreatic juice to enter the small intestine may result in the non-production of the necessary conditions for that fine dispersion of fat which is regarded as essential for its absorption. Hence the faulty absorption which is associated with diseases of the pancreas and bile ducts has not helped in explaining the mechanism which we wish to have made clear.

Another disease in which steatorrhoea occurs is tropical sprue. I am indebted to my colleague Dr. D. A. K. Black for his views on the defective fat absorption which is a well-known sign in this condition. First, there is no evidence of a selective failure of fat absorption. The steatorrhoea seems to be part of a general impairment of absorption. This in itself does not help us in our search for the true mechanism of the absorption process. Secondly, the percentage absorption of fat does not vary with the amount of fat in the diet. In five patients, for instance, whose daily fat intake was increased from 65 g. to 95 g. the percentage absorbed did not show any significant change. This does give a clue to the kind of mechanism which is involved. The defect cannot be a purely physical one, otherwise the absolute amount of fat absorbed would not depend on the quantity in the diet. Thus some biochemical defect, such as one in the enzyme systems concerned in fat absorption, is indicated. It is interesting that Munk, in his studies of fat absorption in dogs, in the absence of bile found a similar relationship to hold, provided that the normal capacity for dealing with fat was not exceeded.

A third discovery which Black and his colleagues made is in harmony with the view that the defect in tropical sprue is a biochemical one—that is, that administration of yeast extract in this condition has a favourable influence on fat absorption. This suggests that some accessory food factor is possibly lacking. Apparently it is not nicotinic acid, riboflavin, or folic acid. Its identity, therefore, if there is any truth in this suggestion, still remains to be discovered.

Conclusion

Perhaps I have said enough to show that I regard the processes of fat absorption as still not completely understood. The intelligent use of some of the new isotopes which the physicists are now putting into our hands could undoubtedly help in solving some of the outstanding problems, and I hope that in due course these new methods may be made use of. I can certainly commend to any young physiologist the study of fat absorption as well worthy of his attention.

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MODERN TRENDS IN RADIOLOGY*

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In this paper it is my intention to stimulate thought by taking stock and critically examining the prevailing tendencies and so obtain a perspective which will enable us to see where we are going.

The radiological age may be divided into three periods—(1) that which heralded the advent of radiology; (2) the period of distrust; (3) the period of idolization—the modern trends.

When Roentgen's remarkable discovery was made known to the world, the Press (Brailsford, 1946a)—both medical and lay—heralded it as a means of sparing patients not only the pain associated with disease but also that which was, and still is, inflicted when other methods of examination are conducted. First impressions are often the most important and deserve the fullest consideration, and these first impressions were so strong that they stimulated radiological research throughout the world to such a degree that during the year 1896 most of the possibilities of radiology were envisaged, techniques developed, and explorations begun. Continuous progress since then has been essentially refinement of technique, concomitant with ever-improving equipment. Unfortunately many enthusiastic workers in the earlier years did not preserve the scientific accuracy in their observations that is so essential for progress. Because interpretations were read into radiographs which were far in excess of what was reasonably possible—a tendency which has not been entirely overcome—clinicians were taught to distrust radiology; but the more careful workers in radiology, by painstaking study of the normal and by correlation with pathology, convinced clinicians that they could render much help in the elucidation of clinical problems. Some radiological evidence is self-explanatory even to the layman, and this has resulted in the misconception amongst the inexperienced, both qualified and unqualified, that all radiographs are self-explanatory. In the light of the previous high standard of clinical medicine it is amazing that this serious misconception,

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