A MOUNT SINAI HOSPITAL
MONOGRAPH

A MOUNT SINAI HOSPITAL MONOGRAPH ON

The Malabsorption Syndrome

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SYMPOSIUM

The Malabsorption Syndrome

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FOREWORD

The publication of this symposium on the malabsorption syndrome is timely. The syndrome occurring in the adult has been variously termed "nontropical sprue" (Homes and Starr) and "idiopathic steatorrhea" (Bennett, Hunter and Vaughn). Recently and more appropriately the label "idiopathic malabsorption syndrome" has been attached to it. Most observers feel that there is a close association between the adult affection and the celiac syndrome of childhood. There are some who would not agree with the editor that tropical sprue is but a variant of the so-called idiopathic malabsorption syndrome. Certainly the tropical variety tends more often to be reversible, so that the absorption defect may be only temporary. It seems to be associated more often with a more severe anemia with a greater tendency toward glossitis and stomatitis and with more severe diarrhea. Tropical sprue responds more consistently to the administration of folic acid. However, as Dr. Adlersberg has stated, everyone with tropical sprue or the idiopathic malabsorption syndrome may have the same basic metabolic defect. Perhaps many of those with tropical sprue may have the defect to a lesser extent, i.e., the abnormality remaining occult until the occurrence of a precipitating factor, such as long-standing undernutrition or chronic infection or infestation. It may very well be that the so-called metabolic defect is greater among persons in the colder climates and the trigger mechanism may not need to be so striking.

This syndrome has attracted a good deal of attention recently because of an attempt to define more clearly the underlying defect, and it is for this reason that many observers have become more interested in differences that exist in the syndrome as it appears in various parts of the world. More important, newer technics have appeared for the differentiation of the anemias that occur in association with the syndrome. Furthermore, some of the newer absorption tests employing labeled fat and radioactive B_{12} have great promise. These more recent diagnostic methods will certainly facilitate the differential diagnosis between primary pernicious anemia and the primary malabsorption syndrome. The labeled fat tests will unquestionably prove helpful in the differential diagnosis of idiopathic steatorrhea from the steatorrhea of pancreatic insufficiency. The popularity of the gluten-free diet and the increased utilization of ACTH and adrenal steroids has added a good deal to our therapeutic armamentarium and increased our fundamental knowledge of the affection.

The contributions from our British colleagues record experiences which they are particularly well qualified to relate, i. e., electrolyte disorders (Cooke) and histologic studies based upon material obtained by jejunal biopsies (Shiner).

All of these facets and many others are covered in this monograph. It is fitting that the group from Mt. Sinai should record their experience in this manner. They have had a large contact with the spruelike state and are recording at this time an extensive follow-up on ninety-four patients. The long association together

of this group of workers who have participated in the study of this syndrome adds considerably to its value. Group efforts of this type are often rewarding because of the opportunity for frequent conferences and for exchange of ideas on the same group of patients.

This monograph should serve a valuable purpose to those interested in the research and in the clinical aspects of the malabsorption syndrome. Factual and theoretical data have been well summarized. I congratulate Doctor Adlersberg for his diligent and understanding devotion to the study of malabsorption through the years.

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Philadelphia, May 1957

INTRODUCTION

A classical description of the clinical entity presented in this symposium, the malabsorption syndrome, reads as follows:

"Wherefore they have flatulence of the stomach, continued eructations, or a bad smell; but if these pass downwards, the bowels rumble, evacuations are flatulent, thick, fluid or clayey, along with the phantasy, as if a fluid were passing through them; heavy pain of the stomach now and then, as if from a puncture; the patient emaciated and atrophied, pale, feeble, incapable of performing any of his accustomed works. But if he attempts to walk, the limbs fail; the veins in the temples are prominent, for owing to wasting, the temples are hollow; but also over all the body the veins are enlarged, for not only does the disease not digest properly, but it does not even distribute that portion in which the digestion had commenced for the support of the body; it appears to me, therefore, to be an affection, not only of the digestion, but also of the distribution."

Aretaeus the Cappadocian (second century A.D.) is credited with the above earliest description of this disorder (1). Hanes believes that "although it is admittedly difficult to identify ancient description with modern disease entities, yet one familiar with the sprue syndrome will hardly fail to recognize the lineaments of sprue in Aretaeus's graphic portrayal" (2). Paraphrasing Aretaeus' last sentence we like to consider him a precursor of those who believe that the malabsorption syndrome is an affection "not only of the digestion but also of the metabolism."

After an interval of many centuries Samuel Gee presented towards the end of the 19th century his studies "On the Coeliac Affection" (3).

"There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially apt to affect children between one and five years old. Signs of the disease are yielded by the faeces, being loose, not formed, but not watery; more bulky than the food eaten would seem to account for; pale in colour as if devoid of bile; yeasty, frothy, an appearance due to fermentation; stinking, stench, often very great, the food having undergone putrefaction rather than concoction. . . ."

"The causes of the disease are obscure. Children who suffer from it are not all weak in constitution. Errors in diet may perhaps be a cause, but what errors. . . ."

"Naked-eye examination of dead bodies throws no light upon the nature of the coeliac affection; nothing unnatural can be seen in the stomach, intestines, or other digestive organs. . . ."

"The patient wastes more in the limbs than in the face, which often remains plump until death is nigh. In the limbs emaciation is at first more apparent to hand than to eye, the flesh feeling soft and flabby . . . the belly is mostly soft, doughy, and inelastic; sometimes distended and rather tight. Wind may be troublesome and very foetid. Appetite for for food differs in different cases, being good, or ravenous, or bad. . . ."

"When recovery is incomplete, the illness drags on for years; the patient getting better on the whole, but being very subject to relapses of his complaint. While the disease is active the children cease to grow; even when it tends slowly to recovery, they are left frail and stunted. . . ."

This contribution of Samuel Gee is considered "a classic, and very little has been added to Gee's clinical and pathologic observations by subsequent writers" (2). It is of interest that in Gee's opinion children and adults were similarly

affected. Gee was probably the first author to express, as early as 1888, the view that celiac disease in children is analogous to sprue in adults.

During this century and especially in the last two decades there has been increasing interest in the clinical manifestations as well as in laboratory and autopsy findings in the malabsorption syndrome. Important information has been contributed in various parts of the world, especially in Britain, Scandinavia, the United States and other American countries, as may be seen from the extensive references appended to the subsequent articles of the symposium. Increasing evidence supports the concept that tropical sprue, non-tropical sprue, often referred to as the idiopathic steatorrhea syndrome, and celiac disease of childhood, are clinical varieties of the same metabolic disorder, primary or idiopathic malabsorption syndrome. Nevertheless some authorities in the field (4) are of the opinion that these conditions are "outwardly similar but inwardly dissimilar". A critical analysis reveals however that these dissimilarities, interesting as they may be (5), are too superficial to warrant definition of tropical and non-tropical sprue and of celiac disease as independent clinical entities. Celiac disease as seen today appears to be a milder variety of the malabsorption syndrome occurring in children. None of the clinical features are limited to this form of the malabsorption syndrome. The complications of celiac disease such as retardation of growth and rickets are fully explained by the onset of the symptoms of the disorder in childhood. On the other hand similar complications may be seen in adults with sprue, such as osteomalacia with various degrees of bone changes (6). The response of celiac disease to gluten-free diets again is not specific since adults with malabsorption syndrome, especially the milder forms, also may respond satisfactorily.

Although "cure" was more frequently observed in celiac disease and in the tropical variety of sprue than in non-tropical sprue, recent extensive studies revealed persistence of the metabolic abnormality and radiologic small bowel signs in seemingly asymptomatic celiacs (7) and in patients with "cured" tropical sprue (8).

The high familial incidence of celiac disease is well documented (9). Students of tropical sprue frequently report the occurrence of the disease in several members of the same family ("sprue houses") (10). In non-tropical sprue familial occurrence is no rarity according to our own observations and those of many others (10–12).

In the broader view of today primary malabsorption syndrome may be defined as a genetically transmitted metabolic disorder. Intestinal malabsorption and hematologic changes are the main facets of clinical interest. There are in addition many other metabolic abnormalities not necessarily related to the absorptive and hematic difficulties as will be demonstrated in some of the following papers. Profound disturbances in genetically controlled, enzymatic chain reactions apparently affect intestinal absorption as well as the metabolism of proteins, lipids, electrolytes and water. Despite the genetic anlage, the malabsorption syndrome may become manifest at various periods of life. In analogy

to other inherited errors of metabolism, e.g., diabetes, malabsorption syndrome may become clinically manifest in infancy or childhood as celiac disease, or later in life as tropical or non-tropical sprue. Actually a number of our patients with non-tropical sprue presented celiac disease in childhood. The stress of tropical climates, preceding tropical or non-tropical infections, malnutrition and probably wheat or rye gluten are important precipitating factors or triggering mechanisms. These factors will convert a predisposed person with "latent malabsorption syndrome" into a patient with "manifest malabsorption syndrome".

Primary malabsorption syndrome must be strictly separated from secondary malabsorption syndromes. In primary malabsorption syndrome there are no clinical roentgenologic or post-mortem evidences of gross organic disease entities involving the gastrointestinal tract, pancreas or liver. In secondary malabsorption syndromes gross pathologic alterations may be encountered in the gastrointestinal tract, such as extensive lymphosarcoma or amyloidosis of the small bowel and/or the mesenteric lymph glands, intestinal lipodystrophy or certain forms of jejunoileitis; or after-effects of surgical procedures, such as extensive resection or exclusion of parts of the small bowel; or pathologic conditions in the pancreas, such as pancreatitis or carcinoma; or changes in the liver or biliary tree, such as mechanical biliary obstruction. Secondary malabsorption syndromes mimic the primary form but can be differentiated on clinical grounds, by the use of laboratory procedures and eventually by biopsy or autopsy.

The symposium presented in this volume is primarily concerned with primary or idiopathic malabsorption syndrome. The physiologic aspects of intestinal absorption are presented first. Abnormalities in the metabolism of proteins and lipids, of water and electrolytes are then discussed as well as disturbances in the intestinal uptake of vitamin B12 and in pancreatic enzymes. The subsequent papers deal with pathologic findings based on autopsy and biopsy studies. The presentation of the clinical aspects is based on analysis of a selected group of 94 patients observed over an average period of 5.2 years at The Mount Sinai Hospital. Special articles are devoted to the changes in blood and bone marrow, to hemorrhagic manifestations, to neurologic and bone complications. The roentgenologic appearance of the small bowel is discussed extensively. The management of malabsorption syndrome is presented with special reference to dietary management, including gluten-free diet, and steroid therapy. The last paper is devoted to an important secondary malabsorption syndrome: the diagnostic and therapeutic problems encountered in patients with extensive resection or exclusion of the small bowel. It was impossible to include all aspects of malabsorption syndrome in the symposium, e.g., there is no comprehensive discussion of celiac disease.

The symposium presents many recent advances in our knowledge of malabsorption syndrome. It is apparent, however, that there are considerable gaps in our knowledge particularly with regard to the basic mechanisms responsible for the disorder. This presents a challenge to all those who are actively interested in this baffling clinical entity.

The Editor is very deeply obliged to his colleagues at The Mount Sinai Hospital, contributors to this symposium, for their unlimited and enthusiastic interest in preparation of the papers. He wishes to express his appreciation to Dr. Cooke in Birmingham and Dr. Shiner in London, the two "extramural" contributors to this symposium, for their willingness to participate in this venture.

The Mount Sinai Hospital
New York, March 1957

DAVID ADLERSBERG, M.D.
Editor

REFERENCES

1. *Aretaues the Cappadocian: Extant Works*. Edited and translated by FRANCIS ADAMS, London. Sydenham Soc. 1856, p. 350.
2. HANES, F. M.: *Sprue, in Tice's Practice of Medicine, Hagerstown, Md.* W. F. Prior, Inc. 1943, Vol. 4, p. 171.
3. GEE, S.: On the Coeliac Affection. S. Barthol. Hosp. Report., 24: 17, 1888.
4. MANSON-BAHR, P.: *The Dysenteric Disorders*. Baltimore, 1943. The Williams & Wilkins Co.
5. BOSSAK, E. T., WANG, C. I., AND ADLERSBERG, D.: Clinical Aspects of the Malabsorption Syndrome (Idiopathic Sprue). Observations in 94 Patients. This volume, page 112.
6. HARTLEY, J.: Osseous Changes and Fractures in Malabsorption Syndrome. This volume, page 172.
7. DI SANT' AGNESE, P. A.: Idiopathic Celiac Disease II. Course and Prognosis. Pediatrics, 11: 224, 1953.
8. GARDNER, F.: A Malabsorption Syndrome in Military Personnel in Puerto Rico. A.M.A., Arch. Int. Med., 98: 44, 1956.
9. THOMPSON, M. W.: Heredity, Maternal Age, and Birth Order in the Etiology of Celiac Disease. Am. J. Human Genetics, 3: 159, 1951.
10. THAYSEN, T. E. HESS: Non-tropical Sprue, Copenhagen, 1932, Levin & Munksgaard.
11. DAVIDSON, L. S. P., AND FOUNTAIN, J. R.: Incidence of the Sprue Syndrome with some Observations on the Natural History, Brit. Med. J., 1: 1157, 1950.
12. COOKE, W. T., PEENEY, A. L. P., AND HAWKINS, C. F.: Symptoms, Signs and Diagnostic Features of Idiopathic Steatorrhea. Quart. J. Med., N.S. 22: 59, 1953.

THE PHYSIOLOGY OF INTESTINAL ABSORPTION

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It is both appropriate and logical to discuss the physiology of normal intestinal absorption in a symposium devoted to the clinical syndromes of malabsorption. It is doubtful however whether the incomplete state of our knowledge of these processes can at present shed much light on the fundamental defects of the clinical states. Indeed there is reason to believe that unraveling of the pathophysiology of absorption will rather facilitate our understanding of the normal processes. Be that as it may, it is the function of this review to summarize some of the current concepts and hypotheses of absorption from the small intestine.

For this purpose, *absorption* is the process by which materials are transferred from the lumen of the gut across the intestinal mucous membrane to blood and lymph vessels: the transport of nutriments from the exterior milieu to the interior milieu; a process which Fisher and Parsons have neatly labelled *translocation* (1).

In any generally comprehensive schema intestinal absorption represents a special example of the permeability of natural membranes. While some progress has been made towards such comprehensive generalization, the details of which may be found in the monograph of Davson and Danielli (2), the intestinal membrane is such a complex tissue that few overall generalizations can be made with safety at present.

In the regulation of absorption it should be remembered that when materials are presented to the normal intestinal membrane in appropriate form, these are absorbed independent of bodily requirements. There is only one important exception to this statement. Iron appears to be the only nutritive material whose absorption is regulated in keeping with bodily needs (see below). For all other substances it is *intake* and thus hunger and appetite which regulate the quantities absorbed.

Digestion as related to absorption. The main components of the diet are complex, large molecules which do not easily penetrate the intestinal membrane, with few exceptions, and if they do penetrate are poorly utilized. To facilitate absorption, these dietary substances of high molecular weight are broken down to smaller ones which are water-soluble, diffusible, or have active groups by a series of enzymic catalyzed hydrolyses. This preliminary process is properly designated as *digestion* and falls outside the scope of the present review. In the case of fat, however, the role of the digestive secretions, especially bile salts and the lipolytic enzymes, are so intimately concerned with the problem of absorption that some consideration of fat digestion must be included in the discussion of fat absorp-

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tion. Indeed, one of the fundamental not yet completely resolved problems in the field is the extent to which fat, especially triglyceride fat, must be split prior to absorption.

The structure of the membrane. Substances moving across membranes, and the intestinal membrane specifically, fall in the main into two groups: (1) those which move by diffusion according to their concentration gradients, moving from regions of higher to lower concentration, so called passive movement and (2) those able to move against a concentration gradient, a process which requires the expenditure of energy, so called active transport or selective absorption. Further, a substance (such as glucose) may exhibit both kinds of behavior. The cellular mechanisms responsible for the active absorption or transfer of the second group are almost completely unknown, although they are obviously connected with the fundamental structure of the absorbing membrane.

In man, as in most animal species, the main cell of the intestinal epithelium is a cylindrical cell (22 to 26μ by 6 to 9μ). Interspaced among these is a mucous secreting cell, the goblet cell. It is not clear whether the mucous secretion forms a continuous surface layer, as is believed to be the case in the stomach.

The free border of the intestinal epithelium, since it is the focal point of transfer, has been the object of histological study for more than a century and only recently is its nature beginning to be clarified. All workers have recognized a striated border at the free surface of the intestinal cell, but opinion has been divided between ascribing a pore-canal system to it or a rod-like tubular structure.

The most careful studies of this border by the light microscope appeared to favor the canal theory (3). However, more recent analyses with the use of the electron microscope have demonstrated that the striated border on the free surface of the absorptive cell is composed of a palisade of columnar rodlets, with blunt rounded tips, closely packed together. The striking electron micrographs of Granger and Baker (4) deserve careful attention from all interested in the fundamental aspects of the process of absorption. These authors have estimated that a single columnar cell must bear nearly 3,000 such rodlike processes, and a square millimeter of intestinal surface some 200 million. Their presence appears to increase the absorptive surface of the gut about 30 fold.

The more recent studies of Sjöstrand and Zetterquist (5) with ultra thin sectioning and electronmicroscopy have confirmed and clarified the nature of the the rod-like processes of the epithelial border. This functional increase in surface area is consistent with the other anatomical characteristics of the small bowel: its great length, the mucous folds (Kerkring folds or *valvulae conniventes*) and most strikingly the finger-like reduplication of the mucosa, the intestinal villi. In man it has been estimated that there are 18 to 40 villi per square millimeter of intestinal surface, and an increase of surface area due to the villi of about 7 fold.

Movement of the villi following feeding seems to be clearly established, and there is fragmentary evidence that a humoral mechanism may be involved as well as a local neuro-mechanical one. The significance of this villous movement in the process of absorption however is far from established. An important "pumping" role has been ascribed by Verzar to villous contraction in emptying

the central lacteal of absorbed fat and will be touched upon again in the section on fat absorption.

Methods of research. Progress in revealing the cellular mechanisms involved in absorption has been hindered by the lack of truly physiological methods of investigation. Experiments which involve concomitant studies of intestinal contents and the blood and lymph represent an end result of digestion, translocation, transport and intestinal utilization rather than absorption alone.

Prior to 1925 most of the available information was derived from the study of animals with permanent intestinal fistulas, ligated loops of intestine, by weighing of different parts of the body or by study of histological preparations of mucosa. Then Cori (6) introduced the method of feeding a known amount of substance by stomach tube to rats and killing them after a given period. The amount of the substance remaining in the intestine was then determined quantitatively. This method represented a great advancement and was a source of reliable information.

In 1934 Miller and Abbott (7) first described their double-lumened, single-ballooned tube which was utilized in the study of human absorption. Two years later these same investigators (8) overcame many technical difficulties by the development of a triple-lumened tube with two balloons. These tubes offered a satisfactory method of controlling the site of absorption and length of segment, and, by the introduction of known concentrations and recovery, aided the study of osmotic relationships, motility and their affect on absorption. Others (9, 10, 11, 12, 13, 14, 15) later found modifications of this method of investigation to be fruitful.

Technical methods for research in absorption were then virtually at a standstill until 1949, when Fisher and Parsons (1) described the first *in vitro* apparatus. This consisted of the establishment of two complete circulations, an inner and an outer. The two circulations were separated by a length of animal small intestine such that the inner circulation (mucosal) was completed by the lumen of the intestine, and the outer circulation (serosal) flowed around the intestine. Transfer of a substance from the inner to the outer circulation could take place only by way of the intestinal wall. The success of this apparatus is partially dependent on the feature that the mucosal cells are minimally deprived of oxygen. The structure of the apparatus is such that the physical factors (temperature, pH, solute concentration and concentration gradient) could be controlled.

Other forms of *in vitro* apparatus (16, 17), methods (18), and modifications of these (19, 20, 21, 22, 23) soon followed. The introduction of radio-active isotopes in conjunction with both *in vivo* and *in vitro* studies has been revealing (21, 24). It is from these sources that knowledge of the actual mechanisms, particularly of glucose and amino acid absorption, is slowly evolving.

Progress in the study of fat absorption has been considerably advanced by several technical methods: (1) the introduction of a technique for collecting lymph from the intestinal or thoracic duct in unanesthetized animals by Bollman, Cain and Grindley (25); (2) the development of analytic methods for the estimation of glyceride mixtures and isolation and separation of fatty acids and

phospholipids and (3) the use of isotopically labelled fatty acids, glycerol and glycerides.

FAT ABSORPTION

The mechanism of intestinal fat absorption, an understanding of which is probably central for a complete analysis of the malabsorption syndromes, is a complex as yet incompletely resolved problem, about which much controversy has been collected during the last fifty years. We intend merely to indicate some of the strands of this tangled knot.

Site of fat absorption. From histological studies it has been demonstrated that fat can be absorbed at all levels of the small intestine. What is not known is the site of preferential or maximal absorption. Recently some experimental evidence has suggested that the distal small bowel is more important for fat absorption than the proximal. Kremens and co-authors (26) have demonstrated in the dog that sacrifice of the proximal 50 per cent of the small intestine could be tolerated, but that removal of the distal 50 per cent led to a profound interference with fat absorption. Studies in the rat have indicated that such may be the case in this species as well, the third quarter of the small intestine being most important for fat absorption (27).

The intraluminal phase. It seems clear that neutral fat can be absorbed only if there is hepatic secretion of bile salts and pancreatic secretion of lipase. The bile salts, glyco- and tauro-cholate, appear to have no lipolytic activity themselves but act by emulsifying fat prior to lipase action, thus increasing enzyme substrate contact. Recent studies have shown that these salts function as do other effective detergents by a fat-attracting portion (CH_2 and ethyl groups) and a water-attracting portion (OH, SO_3 or COOH groups). This arrangement results in the formation of micelles in which the hydrocarbon fat-attracting portion lies in the center, and the polar (OH, SO_3, or COOH) portions on the outside in contact with the surrounding aqueous solution (27A).

In the classical or lipolytic view of fat absorption, promulgated by Pflüger, triglyceride fat in the presence of bile salts and lipase is split completely to fatty acids and glycerol. These products, absorbed in water-soluble form, are then resynthesized in the intestinal cell to neutral fat which enters the lymphatic vessels of the gut and ultimately reaches the venous circulation by way of the thoracic duct. The bile salts return to the liver by way of the portal vein. A great deal of the evidence for this view was derived from the classical observations of Munk and Rosenstein in 1891 on a patient with a lymph fistula of the thigh. A high proportion of fat fed to this patient could be recovered from the fistula, mostly in the form of neutral fat, after ingestion as triglyceride, free fatty acid or amyl esters of long-chain fatty acids.

The lipolytic theory was refined by the studies of Verzar and his collaborators, summarized in their monograph "Absorption from the Intestine" (28). The absorption of fatty acids would be accomplished by the formation of water-soluble complexes with the conjugated bile acids (glycocholic and taurocholic acid) at the slightly acidic pH of the upper small gut. This group of investigators also put

forward the concept that the synthesis of neutral fat from the absorbed glycerol and fatty acids proceeds through an intermediate phosphatide step, under the control of the adrenal cortex. This step involving phosphorylation was believed to be inhibited by high concentrations of phlorhizin and by iodoacetic acid. But the general outlines of the lipolytic hypothesis were essentially unaltered.

A vigorous experimental critique of this theory has been advanced by A. C. Frazer since 1934, to which the term "partition theory" has attached, although this theory too has undergone modification at its author's hand (29). Frazer interpreted his evidence to mean that there are two pathways for fat absorption: (1) highly emulsified particulate neutral fat can be absorbed directly through the intestinal cell to enter the lymph, and (2) fatty acids (derived from lipolysis) enter the portal circulation to be deposited in the liver. A series of studies on the emulsifying action of monoglycerides in the presence of bile salts and on the absorption of highly emulsified paraffin in glyceride mixtures were interpreted as supporting the direct absorption of unsplit fat at particle sizes 0.5μ or smaller.

Recent studies involving newer methods for collecting mesenteric lymph and using isotopically labelled fats and fatty acids have diminished the force of Frazer's partition theory, at least as originally formulated. Bloom and coauthors (30) showed that C^{14} labelled palmitic acid could be recovered to the extent of 92 per cent in lymph, and similar results have been obtained for stearic, palmitic and pentadecanoic acids. These results, which were interpreted as being inconsistent with the partition hypothesis, have been critized since glyceride vehicles were used for the fatty acid feedings. However, experiments in which free fatty acids were fed have yielded substantially the same results, the only difference being the slower rate of absorption of the free fatty acids as compared with the glycerides. This type of evidence is extremely strong support for the lipolytic theory, and the resynthesis of neutral fat by the intestinal mucosa.

That several mechanisms may be operative however is indicated by two important lines of evidence: (1) Frazer has consistently stressed the point that complete hydrolysis of glycerides to fatty acids and glycerol before absorption is not an obligatory step. Reiser and co-workers (31), and others, recently have shown that some portion (50 per cent or more) of absorbed fat has been hydrolyzed down to monoglycerides but not to smaller molecules. This certainly would seem to indicate that lipolysis need not be complete. This fat, whatever its degree of lipolysis before absorption, is recovered as resynthesized triglyceride fat in the lymph. In this context it is of interest that recent evidence indicates that glycerol liberated during lipolysis is absorbed via the portal system, and utilized for the synthesis of triglycerides or phospholipids in the intestinal cells or contents to only an extremely small extent. (2) Studies in several laboratories have shown that there is a differential partition between the chyle and portal blood as between long- and short-chain fatty acids (2)—fatty acids of 10 carbon atoms or less are absorbed by the portal vein while the longer-chained fatty acids of dietary fat are absorbed by the lymphatics. Thus Bloom and others feeding C^{14}-labelled fatty acids to rats found that 84 to 85 per cent of stearic acid, 59 to 82 per cent of myristic acid, 15 to 55 per cent of lauric acid, and only 7 to 19 per

cent of decanoic acid was recovered in the lymph (32). It is of interest in this context that, of the common dietary lipids, only cows' milk is relatively abundant in shorter-chain fatty acids.

In conclusion, although neutral fat need not be hydrolyzed completely before absorption, the major portion of dietary fat is split to monoglycerides, fatty acids and glycerol in the intestinal lumen in the presence of bile salts and pancreatic lipase. The long-chain fatty acids are absorbed and enter the mesenteric lymph as triglycerides and the short-chain fatty acids enter the portal system as such, along with glycerol.

Cellular mechanisms of fat translocation. Within 1½ to 2 hours after a fatty meal in animals, sudanophilic material can be recognized histologically within the intestinal cell. Whether neutral fat or fatty acids is fed, lipoid material can be seen in the striated lumenal border of the cell. The mechanism of this passage is not clearly understood at present. At the pH of the intestine (6.7 to 6.8) the fatty acids are probably presented to the membrane in several forms: ionized molecules (RCO_2), neutral molecules (RCO_2H), as complexes with bile salts and perhaps as soaps (alkaline salts). Pflüger's original concept that absorption as soaps was the most important mechanism fell into disrepute with the demonstration of the actual pH of the intestine on the acid side of pH 7; yet recent studies by Schmidt-Nelson have indicated that as much as 10 to 25 per cent of the fatty acids could exist as soaps at this pH. The importance of soaps in the problem of calcium absorption will be touched upon below.

Most theories of cell membranes postulate a lipoid layer at the surface and these fatty substances could thus easily diffuse into the membrane. What is difficult to explain is their diffusion out of the membrane into the aqueous interior of the cell. Verzar (28) believed that an active process of transport is involved since phlorhizin, which is supposed to inhibit phosphorylation, and monoiodoacetic acid, which inhibits glycolysis, both inhibit the transport of fat across the mucosal cell. In this formulation the fats are transformed into phospholipids in the course of this transfer. It is of considerable interest in connection with the therapeutic aspects of this symposium that Verzar and his colleagues ascribe a regulating function to the adrenal cortex over this stage. In adrenalectomized rats there was a marked impairment of fat absorption. From histologic evidence they concluded that the entrance of fatty acids into the cell continued, but that the resynthesis of fatty acids was inhibited in the adrenalectomized animals. Surprisingly, with the cortical extract of Swingle and Pfiffner (1935) they were able to correct this defect.

Mucosal phospholipid formation during absorption. When labelled stearic acid was fed to rats either as glyceride, free acid, or as cholesterol ester, about 10 per cent of the total lymph fatty acid was recovered in the form of phospholipid (33). There is also available evidence that during absorption of fat, the amount of neutral fat and fatty acid of the gut increases, but the amount of phospholipids remains relatively constant. There are changes, however, in the quantitative fatty acid composition of the intestinal phospholipid depending on the fat being absorbed. This led Sinclair in 1929 to postulate that phospholipids were involved as intermediates in the resynthesis of triglycerides and in the intracellular trans-

port of fatty acids (34). Studies of labelled phosphate have also indicated an increased turnover of the phosphorus portion of phospholipids of the intestinal wall during fat absorption. However, there has been much difficulty in accounting quantitatively for the conversion of all fat to phospholipid during transport, but Bergstrom and Borgstrom point out that it is the phospholipid of the epithelial cell and not of the whole gut which must be involved in this process (35).

The inhibition by phlorhizin of fat absorption is ascribed by some workers not to a specific action on phosphorylation but to inhibition of a variety of enzymatic processes which couple oxidation to phosphorylation in the generation of high-energy phosphate bonds.

In conclusion, the hypothesis that every molecule of fat passes through a phospholipid stage in getting from the lumenal to the lacteal border of the intestinal cell remains an interesting but unproved one.

The fine fat particles, having accomplished their passage across the intestinal cell, pass into the lymphatics of the villus. Frazer (29) has stated that this is in accordance with the behaviour of other negatively charged particles which when introduced into the tissues tend to pass into lymphatics rather than blood capillaries. From histological evidence Verzar believes that the muscular contraction of the villi produces a pumping action which tends to empty the central lymph channel and thus move the chyle on. This remains controversial at present. Wells and Johnson (57) deny that shortening of the villi empties the lacteals.

The absorption of other related lipid substances. In the absorption of sterols from the gut specific mechanisms appear to be operative. Cholesterol in the presence of bile salts is readily absorbed. However allocholesterol (an isomer of cholesterol), the four isomers of dihydrocholesterol, coprosterol (a reduction product of cholesterol produced by intestinal bacteria), cholestanol (a tissue reduction product of cholesterol secreted in limited amounts into the gut), as well as phytosterols of plant origin are poorly if at all absorbed. Since all these substances are emulsified by bile, and many diffuse through artificial membranes, it appears that there is marked specificity of the intestinal transport system. Verzar believes that esterification of cholesterol is an essential step in absorption, and that other sterols may not be absorbed because of the absence of appropriate enzyme systems. Under ordinary circumstances the cholesterol presented to the gut is almost entirely free cholesterol, yet a considerable portion of that recovered in the thoracic lymph is in the form of esters. Absorption of cholesterol appears to involve some esterification, and is enhanced by fat as well as bile in the digestive mixture.

In view of the lymphatic transportation of cholesterol, it is puzzling that recent studies appear to indicate that cortisone, hydrocortone and testosterone (not too dissimilar in basic structure from cholesterol) appear to be absorbed from the intestine by the portal venous route. Lecithin appears to be broken down to its constituents which are absorbed as such.

The enterohepatic circulation of bile salts has been discussed already. It is of interest that glycocholates and taurocholates are better absorbed from the jejunum and ileum than from the duodenum.

The absorption of substances dependent on fat absorption, or related to fat absorp-