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Celiac disease

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CELIAC DISEASE

Charles L. Sturdevent

Senior Thesis

UNIVERSITY OF NEBRASKA

COLLEGE OF MEDICINE

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INTRODUCTION

The subject of celiac disease starts with the publication in 1888 of a paper "On the Coeliac Affection" by Dr. Samuel J. Gee(12). In this brief communication we find an exceptionally vivid description of the celiac child as it is known today. Gee did not attempt any explanation of the cause of this condition. Evidently he considered this condition the same as sprue. Possibly he included some cases of infantile atrophy in his description as he mentions that the usual end of the condition is death. However, there is no doubt but that he described and was the first to describe this condition. He made the statement that he was unable to discover any morbid changes in the dead bodies which would account for the symptoms. He attributed the peculiar stools to some extent to a deficiency of bile. However, he was not quite satisfied that the bile was the real cause as he makes the statement that, "whitish stools are not always so wanting in bile as they seem to be; in particular, opaque white food, such as
milk-curd, undigested, will hide the color of much bile."
In another place he brings this out again with the words, "the paleness of the stools is supposed to signify the lack of bile; but the color of feces is a very rough measure of the quantity of bile poured into the duodenum; nay, more, the color of the feces is a very rough measure of the quantity of the bile which they contain." However, he did fail to recognize that the chief failure of digestion was that of fat.

Gibbons (quoted from Parsons), in the following year published a paper, "The Coeliac Affection in Children." Gibbons was first introduced to the subject by Gee himself. In his paper Gibbons also probably included some cases of infantile atrophy as he too mentions the fact that the common end for these patients is death. He attributed the condition to a widespread disturbance of digestion that was probably of nervous origin. He states definitely that this condition is not the same as sprue as seemed to be Gee's opinion. He also thought that the stools contained bile, but showed no sign of recognition of the fact that the chief disorder was the failure of digestion of fat and that the stools were fatty in nature. Curiously enough the reason he gave for his thought that
the stools did contain bile was that if there had been an absence of bile it would lead to excessive fat wastage in the stools. He further states that there is no morbid anatomy on the rather dangerous ground that if there was any it would have been known before. There were no autopsies recorded.

With the publication of these two papers there was a long interval of time in which there were no publications concerning this condition. Evidently interest in it had died down.

Then after a long interval in which there is no mention made of this subject in the literature, Bramwell (quoted from Miller) in 1902 published the report of a case of infantilism with fatty stools which he regarded as of pancreatic origin. Thereafter appeared a series of articles by Bramwell, Thomson, Rentoul and others on "Pancreatic Infantilism" which culminated in 1915 by the most important paper of this series. In this paper the after-histories of the various cases were disclosed. Bramwell admitted in this latter publication that there were some cases showing symptoms of fatty diarrhea and infantilism which were not of pancreatic origin. In this paper he disowned this latter group of cases saying that they were probably examples of Herter's intestinal infant-
ilism which had by that time come to be well recognized. He drew the line of differentiation between these two groups of cases on the basis of the failure of the intestinal group to respond to the administration of pancreatic preparations.

The third really great contribution to this subject was made by Cheadle(9) in 1903. He presented six cases. This considered the first time that fat was definitely recognized in the stools and was proven by fat estimations of the feces by Willcox. In this paper the analogy between the protracted and the transient cases was demonstrated. Cheadle contributed the fatty diarrhea to the absence of bile or some disturbance of liver function. It is from this supposed disturbance that he took the name of acholia for this condition.

It is to be noted that, as yet, there have appeared in the literature no detailed accounts of any autopsies.

Herter(25) in 1908 made the next great contribution to our knowledge of this disease. He apparently rediscovered the condition. He was aided by Dr. L.Emmett Holt in his work. Evidently he was unaware of any previous writings since he does not acknowledge any of the work done by former observers. Up until this time the cond-
ition had been considered a digestive fault, which was thought to be some insufficiency of fat-digestion. From his bacteriologic studies Herter concluded that this disease was due to a chronic enteritis and that there was a nonabsorption of fat as a result of this. There was no necropsy evidence to either support or demolish his theory. He drew his conclusions from the finding of an abnormal intestinal flora which was characteristic of the nursing period of the child. His work has since been confirmed to a certain extent by some authors but not by very many.

The next most important paper published was that by Poynton, Armstrong and Nabarro(81) in 1913. In this paper nine cases of chronic and recurrent diarrhea were reported. The chief interest of this paper was that it is centered around the first and only fatal case which was fully investigated after death. The lesions found consisted of a chronic gastro-enteritis, pancreatitis and fatty liver.

Miller(57) brings out a rather interesting point about this condition. He states that during the war celiac disease received a considerable uplift due to being put on the schedule of diseases for which extra meat might be obtained. This very select list included only tuberculosis, diabetes, celiac disease and pancreatic insufficiency.
Under these circumstances the disease emerged from its obscurity and attained wide popularity. As a matter of fact so much popularity that its name was removed from the schedule and it was debased from its exalted position. There subsided what was probably the only epidemic of the complaint which will ever have an existence even on paper.

In 1918 Still's(101) Lumleian lectures were published. These are important from the standpoint of his autopsy findings. Even though he found an enteritis and a pancreatitis, he was hesitant about calling these primary lesions and tended to the opinion that the findings were secondary changes.

Since this time articles have appeared in the medical literature with increasing frequency in reference to this disease. There have been a few writers who have attempted a complete survey of the literature. The most complete of these have been articles by Fanconi, Lehndorff and Mautner, Schaep, and by Thaysen. (quoted from Bennett 3) No such survey has been attempted in the English language. The most complete survey of the literature in English I have found are the articles by Parsons(75) and by Bennett, Hunter and Vaughan(3).
It can be seen from the brief historical review of this subject, this entity, if it be such, has been described under various names and titles. The disease was first called "The Coeliac Affection" by Gee. Cheadles describes the condition as "Acholia" taking its title from what he supposed was the cause of the condition. Herter, finding an abnormal flora of the intestinal tract and seeing that there was a cessation of growth called the disease "Intestinal Infantilism." More recently Thaysen(107) has classed as one of the idiopathic steatorrheas which also includes a very similar clinical condition known as sprue. As to the differences between these they will be included in another part of this paper. Celiac disease is referred to by Thaysen as non-tropical sprue. Then, in addition, it has been named after various authors as "Heubner-Herter's disease" and "Gee-Herter's" disease.

However, there are many objections to attaching the name of any person to a disease. Not the least of these is that the person may already have his name attached to a disease and then we have two diseases named after the same person and this leads to general confusion. It is very apt to lead to confusion anyway and still it does not
tell anything about the disease. This practice of naming a disease after a man is really only a form of hero worship and it is usually more gratifying to the worshipper than it is to the hero. If a man's name is to be attached to a disease purely for a historical record, then, it is best to try for historical accuracy and so from this standpoint this should be called Gee's disease.

Parsons(75) points out that the majority of cases described a chronic intestinal indigestion cannot tightly be regarded as celiac disease, and therefore, unless the prefix severe is used, the name is unsatisfactory.

Miller(55) is greatly in favor of the term celiac disease. He says that since our knowledge of the cause of the disease is in such a nebulous state, the title of this condition and its definition should reflect our ignorance. In addition the term celiac disease is pleasingly vague and it is to be preferred to others. He goes further to say that the definition of this disease as a result must be in clinical terms and carefully non-committal.

Morse(68) criticizes the term celiac. He says that since the term comes from the Greek meaning the abdomen or abdominal cavity it applies equally well to appendicitis and tuberculosis peritonitis. Furthermore, he regards
it as a mistake to give this condition a name and mentions that there will be plenty of time for that when specific etiology and pathology are established. He favors the term severe chronic indigestion.

However, I believe that it might be pointed out that since the whole clinical picture is so characteristic and unlike that seen in any other digestive disturbance of childhood, it should be accepted as an entity and be given a name. Furthermore, I am inclined to agree with Miller that the term celiac disease is the best term. It draws attention to the prominence of abdominal symptoms without committing the user to any theory of causation.

The definition of such a condition as this is quite difficult. In view of the fact that the definite etiological factors and specific pathology are unknown, any definition will of necessity be unsatisfactory to a great extent. As I have mentioned previously, Miller points out that the definition should reflect our ignorance and as a result be placed in clinical terms and carefully non-committal. Miller(63) criticizes the definitions now in use by saying that they err both in what they put in and in what they leave out. The present definitions are apt
to lay too great a stress on the importance of some of the symptoms and not to mention others enough. He uses as an illustration the symptom of fatty diarrhea. This is stressed in most definitions as the diagnostic sign of the disease. This can be overdone. While it is true that this occurs in the typical, classical picture of celiac disease, it has been pointed out by many authors that this condition may occur in mild forms in which there is no diarrhea alba. The stools in these cases contain more fat than normal but they may be a little larger than one normally finds. In addition, it might be mentioned that even in the classical cases there are periods of improvement in which there is no diarrhea alba.

However, in spite of their faults we must still rely on the present definitions of the disease now in use. They can be modified so that they do not say too little or say too much, and so they don't lay too much stress on variable factors.

I think that the best definition I have found for this condition is that given by Potter(80) and this is the one I shall quote. "Celiac disease is a vice of nutrition without serious pathological changes, occurring in artificially fed children of early age, characterized metabolically by
the inability to utilize the fats and the carbohydrates of the food in anormal manner and clinically by an arrest of growth, distended abdomen, and attacks of recurrent diarrhea with large, ill-smelling, pale, loose, porridgy stools." This is the condition as it is found in the typical classical celiac disease.
ETIOLOGY

Various views as to the causation of celiac disease have been put forward from time to time. However, very little more is known about the etiology of this disease than when Samuel Gee first described it. I shall attempt to discuss only the more important explanations of the causation of this condition.

That celiac disease is a digestive disorder has been the opinion of most of the English writers and the majority of the American writers for some time. As a matter of fact this has been the conception of the English writers from the time of Gee down to recent years.

Gee(18) himself does not commit himself to any cause but speaks of the disorder as a kind of chronic indigestion. It is also apparent that he did not quite accept the supposition that the color of the stools was due to the lack of bile.

Numerous investigators have advanced the theory that the essential cause of the disease was a deficiency, either quantitatively or qualitatively, of the biliary secretion.
Cheadle(9) in his article "On Acholia" was the first to attribute this condition to some pathology of the biliary tract. He regarded it essentially as some manner of cessation of the bile secretion.

Other authors have advanced the theory that this might be due to a deficiency of bile salts or some constituent of the bile. Miller(56) advanced the theory that perhaps this might be due to a lack or decrease of the bile salts in the bile. He drew this conclusion from the results of treatment of a case, supposedly successfully, with bile salt preparations.

However, this has not been generally upheld. Parsons(75) in a series of experiments obtained bile by duodenal intubation. From these specimens he has shown that there are bile salts and bile pigments present in normal amounts. However, it has to be borne in mind that the means available for the estimation of bile acids are indirect and afford no information as to the relative distribution of the different acids. Clinically Parsons was unable to affirm either Miller's or any other investigators results with the use of different bile salts and bile acids in treatment.
Macree and Morris (50) regard the elaboration of the stimulus to bile production as the result of action of acid of the gastric juice on the intestinal epithelium and they actually called it secretin. Furthermore, they postulate that in celiac disease there is an alkaline condition of the intestine which results in a deficiency in bile secretion and therefore of bile salts, and this apparently is their conception of the underlying cause of the disorder. The only evidence they have to offer in support of this hypothesis is the effects of adding sodium acid phosphate to the diet. This they found resulted in an increased absorption of calcium. Although it is true that achlorhydria may occur in celiac disease yet the contents of the duodenum are certainly not alkaline in nature although they are more so than the stomach. Neale (69) found that such contents removed by duodenal intubation have a normal pH.

Some authors have advanced the theory that the principle agent was a deficiency of the pancreatic secretion.

The greatest argument against this is that in the stools the fats appear to be in the form of fatty acids and soaps, or in other words, they appear as split fats and not as neutral fats. It is hard to conceive that
could be some deficiency in pancreatic secretion or some pathology of the pancreas great enough to cause all of the disturbances present in celiac disease and still have the fats appear in the stools as well split as they are. Necropsies have failed to show any consistent pathology of the pancreas which might account for this condition and this is only another point against this theory of causation. In addition several observers have, duodenal intubations, collected and examined the intestinal contents for a lack of pancreatic secretions. They have found that the pancreatic enzymes are present in their normal concentration and that they are active.

Even the gastric juice has been suspected by some. That part of the gastric secretion which has been thought to be faulty is the secretion of hydrochloric acid. It has frequently been shown that there is a gastric achlorhydria in some of these children. In opposition to this is the work of Faber (quoted from Parsons). He found that achlorhydria often occurs in children who are suffering from the acute infectious diseases of childhood and noticed that this condition might exist for months after recovery. He regarded the condition as a hematogenous gastritis. In view of this it may be mentioned that the
occurrence of this in children suffering from celiac disease is no greater than it is in children suffering from other conditions. Also, it has been shown that the type of test meal used will influence to some extent the type of reaction obtained.

The gastric enzymes have been found by Neale to be normal in cases of celiac disease. Thus it does not seem, from the evidence presented by various authors, that this condition is essentially due to a gastric achlorhydria. There is sufficient evidence to the contrary to be conclusive that celiac disease is not due to such a hypothesis. Miller, however, has always concluded that celiac disease is a digestive fault and not an organic disease. This may be true, yet it is difficult to either prove or disprove with the evidence that we have at our disposal.

There is another theory of digestive fault advanced by Freise and Jahr(17). They found in their study of this disease roentgenologically that there was a hypermotility of the intestinal tract. From this they advanced the theory that this hypermotility was the cause of mal-absorption from the intestinal tract as it did not allow the food to stay in contact with the absorbing epithelium for a sufficient length of time. In support of this they
their experience with a case in which they caused the rapid movement of the intestine to slow down by the use of opium or atropine. They reported that this caused a marked increase in the utilization of food and that it became almost normal accompanied by a marked clinical improvement. They advanced the theory that this hypermotility was due to a vegetative neurosis forming a part of a weakness of the whole nervous system of these children. Such a theory is hard to believe and in addition there have never been any confirmation of their findings. I will admit that there are definite symptoms of nervous character, however, I am inclined to think that these are secondary in character.

The conception that celiac disease is due to an enteritis owes its origin to Herter(25). He thought that the failure in fat absorption was due to an inflammatory disease of the intestine, which in its turn was due to the persistence of and overgrowth of an intestinal flora characteristic of the nurslng period of life. He drew attention to the fact that as long as an infant remains on an exclusively milk diet the organisms present in the stool are all gram positive, but that once a mixed diet was taken the bacterial character of the feces changes
completely and the predominant organisms are then gram negative. In celiac disease Herter found that there was a persistance of this flora of the nursling period. The conclusions of Herter have not met with general acceptance and particularly among the English writers. However, there have been some observers that have confirmed Herter's findings to a certain extent. The chief of these in this country have been Brown and his coworkers(6). They have found that there is a persistent Gram positive flora as long as the active symptoms exist. However, farther than this they were unable to confirm Herter's findings. The chief argument against this theory is the fact that it has never been supported at autopsy. In addition there are some observers who have isolated a dysentery bacillus (type Flexner modified) and in addition have isolated it at autopsy. They have also found that some of these children in which they were unable to isolate the organism gave an agglutination for it. However, it has been shown that this does not occur in any greater frequency than this same phenomenon is found in normal children.

As I have mentioned, the greatest objection to the enteritis theory is that it cannot be demonstrated at autopsy and in addition it can be differentiated clinically
from celiac disease. So I do not believe that at the present time there is any foundation for the belief that this is an enteritis.

There is another feature of this disease which has been attracting attention recently. That is the question of the possibility of celiac disease being the same as sprue.

Thaysen(108) drew attention to the fact that there was a marked similarity between the two diseases clinically at least. As a matter of fact, he classified the two diseases under the heading of idiopathic steatorrhea and called the two conditions tropical and non-tropical sprue. There is no doubt but that these two diseases are very similar clinically. However, Parsons(75) points out that there are essential differences. While it is true that achlorhydria is frequent in both conditions Parsons has never been able to demonstrate the condition of achylia in celiac disease and it has not infrequently been found in sprue. In addition he points out that the anemia of celiac disease is chiefly of secondary character and characteristic of the nutritional anemias of infants. However, in sprue he found that practically all patients who die present a megaloblastic type of anemia which is not at all char-
acteristic of celiac disease. In the majority of cases of sprue there is evidence that there is a magalocytic response on the part of the bone marrow. Another very interesting point is that sprue practically never occurs during childhood.

Another theory which must be considered but has never been borne out by any other investigator in that of Ryle(90). In Ryle's estimation Miller's theory of a digestive disorder is untenable. He advances his theory on the strength of finding at the operating table obstruction of the lacteal tree during a laparotomy. The patient had presented the symptoms of fatty diarrhea with wasting. The obstruction found was due to enlarged mesenteric glands. After operation, at which time the glands were resected, the symptoms cleared up. He submits the following statement in regard to celiac disease, "I would submit that the causal pathology of celiac disease cannot be regarded as fully investigated until it has been demonstrated at operation or autopsy that there is or is not some obstruction of the lacteal tree or thoracic duct." There is no other work of this kind which would tend to support this. Ryle claims that the reason this is not found at autopsy is that the lacteals are enlarged only during life.
The only account I find of anyone attempting to prove or disprove the theory of Ryle's in found in the work of Parsons(75). He managed to inject the lacteal tree at autopsy and failed to find any suggestion of enlargement of the lacteal tree which might be due to obstruction. Thus I believe that the weight of evidence against this theory outweighs the evidence in favor of it.

The theory that celiac disease is a metabolic disorder is based on the researches of Hill and Bloor(29) and Sperry and Bloor(99). In these works they concluded that the fecal fat was not dependent upon the food fat but on a reexcretion of fat from the blood. This has been disproved and will be more fully discussed in the section on metabolic studies.

That celiac disease is a deficiency disease due toavitaminosis has been postulated by many authors and particularly Rice(86). This is not strange in that every disease of obscure origin sooner or latter is attributed to this cause. That there is a vitamin deficiency is true. However, when the pathology of absorption is considered in this disease and the complications are taken into consideration it is hard to imagine that there would not be a vitamin deficiency. But, this deficiency is,
in all probabilities, a secondary factor and not a primary one.

Forsyth(14) advanced the theory that the cause of celiac disease was of probable toxic origin. He found symptoms of celiac disease in a child which cleared up following a change of milk supply which was found to contain a good deal of boric acid as a preservative. However, this is the only case on record and this condition has developed in many children who have never received milk that might have been preserved with boric acid. I hardly think that this theory is worth considering except from the standpoint of a curious case.

As all other disease of obscure origin celiac disease has been laid at the door of endocrine disorders. This theory, although Herter suggested in his monograph that there might possibly be a pituitary factor, is based on an autopsy done by Schick and Wagner (quoted from Parsons). This was based on the results of one autopsy which disclosed some pathology of numerous endocrine glands. I believe the best criticism of this theory is found in Morse article (68) which I shall quote:

"This symptom complex has been attributed, of course, as everything is sooner or later, to a dys-
function of the endocrine glands. Since no one knows what these glands, with a few exceptions, do or do not do to the system as a whole or to each other, it is very easy to lay any symptom at their door. It is equally hard to prove or disprove any claims which are made regarding them. As far as I am able to find there is no convincing evidence either on one side or the other — merely assumptions, guesses, and conjectures."

After such a criticism it would appear that there is nothing more to be said or done except, perhaps, for its followers to shed a few tears of regret on the dead body of the endocrine theory.

There are some very interesting facts which have been found regarding this condition. This condition has been found mostly in United States and England. The next most common place of occurrence is in Germany and Austria. It seems to be almost entirely absent from the Latin countries (Italy and France) and from Russia and Hungary. It is found in the countries of northern Europe, Denmark, Netherlands and the Scandinavian countries.

In addition this condition seems to be more common in girls than in boys. Although some authors claim that in their cases there is no difference the survey of the literature which I have made convinces me of this point.

There also seems to be a definite age incidence. This disease is most commonly found between the ages of
nine months and two years although it may occur at almost any other time during childhood. Recently there has been some tendency to find this condition in adults and adolescents and in this group of patients it has been referred to as nontropical sprue. In the majority of these cases they presented symptoms of celiac disease when they were children.

The majority or all of these children have been difficult feeders on the bottle. This condition is never seen in children while at the breast and in such children if it occurs at all it is after weaning. Taylor(105), in his comments on seven cases says, "in the light of this it would seem that the best way to produce this condition is to feed a susceptible child throughout his second year on a diet rich in milk, fat, and potato and then subject him to some parental infection." It seems that this condition is commonly seen then in children who have not only been difficult feeders on the bottle but also who have had a diet that is superabundant in carbohydrate. The part that these things play in the etiology of this disease is as yet undetermined.
Thus I think that it is easily seen from this review of the various theories as to the possible causes of celiac disease that comparatively little is known for sure about the condition from the standpoint of causation.
PATHOLOGY

So far as can be determined there is no known morbid anatomy of celiac disease. Postmortem examinations are somewhat rare, and the abnormal appearances that have been found in the course of such examinations are either due to secondary infections or to malnutrition.

The presence of pale stools and steatorrhea has led to the supposition that perhaps the liver or the pancreas would show some change. This has not been borne out by their examination at autopsy. Although the liver is most often reported as being small and in some cases there have been lymphocytic infiltration and interlobar and interlobular fibrosis of the pancreas reported, it is thought that these are not severe enough to explain the symptoms and are probably secondary.

However, the majority of the reports seem to indicate that there is no definite pathologic lesion which can be demonstrated at autopsy in these cases. Most of the present writers agree with this belief and their own investigations lead them to this conclusion.
Gee makes the statement in his paper on the absence of any signs of this condition at autopsy. He says, "naked eye examination of dead bodies throws no light upon the nature. Nothing unnatural can be seen in the stomach, intestines or other digestive organs. Whether atrophy of the glandular crypts of the intestine be ever or always present I cannot tell."(18).

Poynton, Armstrong and Nabarro (181) reported the first case which was fully investigated after death. In this they found that the walls of the colon were thickened. On opening the colon solitary follicles stood out. The mucus membrane was thickened, corrugated and dotted with areas of very acute congestion. There was no breach of the surface but there was much mucus coating of the membrane. This was the general finding throughout the intestinal tract.

The liver was enlarged, pale and soft and showed an extreme fatty change. The gall bladder and ducts were natural. The spleen was soft, large and pale. The heart was small and wasted. No tuberculous glands were found and the pancreas appeared normal.

On histologic examination there was found an acute congestion of the mucus membrane and submucosa; marked,
small, round-celled infiltration. There was an increase in the perivascular fibrous tissue in the muscular coat and advanced fatty changes in the cells of the secretory glands. This was the general finding throughout the intestinal tract.

In the liver there was an extreme fatty degeneration. The fatty changes were complete at the periphery. The amount of fatty change around the portal vein was less extreme.

It was found that there was an interstitial fibrosis which showed both interlobar and interlobular types. The secretory portion of the pancreas was essentially normal although there was some desquamation of the lining epithelium of some of the ducts. However, this was not sufficient to explain any of the symptoms.

The spleen showed engorgement, slight thickening of the capsule, an increase in the perivascular fibrous tissue and an increase in the extent of lymphoid follicles.

There was a condition of congestion and cloudy swelling found in the kidney.

In addition to these investigations there was also an investigation made of the bacteriological content of the intestinal tract. The cultures were made from scrap-
ings of the bowel wall. From these plates were made and it was possible to isolate a modified form of Bacillus dysenteriae of the Flexner type.

These are the results of the first reported autopsy of a case of celiac disease. I believe that the majority of these findings are not significant of a disease quite as long and drawn out as the history of this patient showed, and any findings are much more apt to be secondary changes than they are primary changes. The fatty infiltration of the liver and the cloudy swelling of the kidney are, in my estimation, secondary changes as the result of some toxic condition. The author failed to report in the autopsy his conclusion as to the cause of the death of the patient.

Stil(102) in his Lumleian lectures on celiac disease reports an autopsy of a case of his which was very similar to the one just described. In this he was of the opinion that the changes found were secondary and could not account for the symptoms of this disease.

In 1921 Miller(58) reported an autopsy of a case in which he was unable to find any changes, either grossly or microscopically which might account for the symptoms of this condition. This is the usual finding at autopsy in celiac disease. The children in whom this disease proves fatal die not of the celiac disease but of intercurrent
infections to which they are exceedingly susceptible.

Up until 1923 there had only been 15 autopsies reported on children supposedly suffering of this disease. This is mentioned by Taylor(105) in his article "Celiac Disease." In commenting on this he says that at least ten of these are to be thrown out as there is no evidence that they were cases of celiac disease. Of the remaining five cases, three showed a small celled infiltration and fibrosis, particularly about the pancreatic ducts, and one also showed fatty degeneration of the liver. He doubts whether more than one of these represents the usual type of celiac disease. At any rate it is fully as probably that the lesions found followed long, continued indigestion with its irritative bowel contents and abnormal bacterial flora as that they were causative of the disease. In the other two cases, which are clearly typical of celiac disease, the necropsy showed no changes which could in any way account for the symptoms present. In particular it is to be noted that in neither of the two were changes found in the liver, duodenum or pancreas. Agglutination tests with the Flexner and Shiga types of Dysentery bacillus are negative as to their value as it has been found that they occur in normal children with
no signs of the disease and the incidence of this occurrence in celiac disease is no higher than it is in normal children.

The results noted by the various authors I have mentioned have been the usual results of all investigators even up to the present time.

There are some men that have reported various findings but they are easily ruled out. Ryle(90) in 1924 reports a case of fatty diarrhea in which a laparotomy was performed on a patient and enlarged mesenteric glands were found and with the removal of these the patient's symptoms cleared up. From this finding he advanced the theory of obstruction of the lacteal tree as a cause of the symptoms in celiac disease. He remarks that although the lacteals may be seen to be distended at operation on a patient taking a normal diet does not necessarily imply that they should remain visibly enlarged after death in patients who have been on a low fat diet and have died of some terminal infection.

In order to disprove this or at least to investigate the condition of the lacteal tree in such cases at autopsy, Parsons and Neale(75) managed to inject from the submucous coat of the intestines the lacteals, lymphatic
vessels and lymph glands of the mesentery. The results of these showed clearly that at any rate in their particular case there was no lymphatic obstruction. No other investigator has been able to support Ryle's hypothesis so far as I was able to find record.

Schick and Wagner found in one case some changes in the pancreas, thyroid, suprarenals and thymus and drew the conclusion that this was probably the cause of the condition. Thus the endocrine theory of etiology started. However, numerous other well attested postmortem examinations have failed to show any indication that pathology of the endocrine glands might have anything to do with the disease.

The latest report in the literature which I have been able to find of an autopsy of a case of celiac disease was that recorded by Hess and Saphir(23). In this they report three cases. In every case the findings were similar. It revealed a broncho-pneumonia of recent development which was supposedly the cause of death. Other findings were a chronic enteritis, and severe changes in the pancreas in every case. He does not uphold the findings of Schick and Wagner that there were changes in the endocrine system. In commenting on the
lesions in the small intestine he says that none of the changes were severe or of apparent long duration. He was of the opinion that they were more likely the result of the celiac disease.

Therefore, after reviewing the literature on the pathology found at the autopsy table I believe that it is safe to say there is, so far as we know at present, no definite morbid anatomy demonstrable which can account for the symptoms or the etiology of celiac disease. Whatever changes it is possible to find at autopsy are probably of secondary nature.

Although the studies of cases at autopsy have been rather disappointing from the standpoint of finding definite morbid anatomy or pointing out the nature of the essential factor of the disease, studies of metabolism have been somewhat more illuminating but are still far from being conclusive.

We are all aware that the essential feature of this condition is the presence of a steatorrhea and the resultant absence of stored fat in the fat depots. It seems to be the opinion of the majority of the investigators that the fat in the stools is well split. It has been
pointed out by many writers that the amount of fat in the stools even in quiescent periods is greater than the normal. Miller (59) pointed out that mild or non-diarheal forms of the disease can occur. In these cases there were large stools which were more bulky than normal and fatty determinations of these showed that there was an increase in the amount of fat in them. Thus, it has been established that there is some abnormality somewhere in the fat metabolism. Whether it is because the fat is not properly digested, not absorbed from the intestine, improperly utilized, or whether it is due to reexcretion into the intestine from the blood stream is not known for sure and a great deal of research has been done on the problem from a chemical standpoint.

From the standpoint of fat wastage in the stools there are two principle schools of thought. One is that the fat in the feces is due to excretion of fat from the blood into the intestine. Other contention is, that the fat in the feces is due to malabsorption of fat and therefore largely dependent on the food fat for its source.

In 1922 Hill and Bloor(29) showed by a series of experiments on cats and dogs that the source of the fecal
fat was not dependent on food fat. They did not postulate any definite source of fecal fat but remarked that the constancy of composition of fecal fat suggested the idea of fat excretion into the intestine.

This was borne out by the experiments of Sperry and Bloor (99) in 1928. In this series of experiments they studied the fecal fat of cats and dogs. They separated it into fractions and studied these fractions in order to determine their source. They came to the following conclusions: That the fecal fat does not come from unabsorbed food fat. They admit that there is some influence of dietary fat, however, as they found an increased excretion of solid fatty acids on a diet high in solid fatty acids and a similar increase in liquid acid excretion on a diet high in liquid fatty acid. In addition they noted a marked similarity between blood and fecal fat with regard to the ratios of solid to liquid fatty acids and the melting point of the non-volatile fatty acid fraction. Thus it is probable that the fatty material of the feces has its origin largely in the blood.

The work of these authors was supported by the work of Holmes and Derr (quoted from Parsons) in 1923.
Further support of the hypothesis that the fecal fat in celiac disease is due to increased excretion from the blood was received by the work of Rowntree (quoted from Parsons). In his experiments on vitamin A retention in celiac children he found that these children were excreting more vitamin A in the feces than they were taking in in their diet.

However, all workers admit that the part played by the throwing off of fat containing epithelium from the intestinal walls and the possible source of fat from the bacterial flora of the intestine is not definitely determined. Fanconi (quoted from Haas) explains the throwing off of large quantities of fat through the feces as being of this origin. However, not enough work has been done along this line as yet to definitely draw any conclusions. However, it undoubtedly plays a part not only in celiac disease but in the contribution to the fecal fat in normal children.

It seems that if the source of fat in celiac disease is due to increased secretion of fat from the bloodstream into the intestine, either directly or indirectly, then there should be an increased or high lipid content of the blood. Moncrieff and Payne(65) found in their exper-
iments with blood fat of children suffering with celiac disease, that there was a hyperlipemia. However, this has never been duplicated except by Bauer(2).

The majority of the investigators are of the opinion that the increase of fecal lipid is not due to malutilization with increased excretion from the blood but that it is due to malabsorption of fat.

Parnes(75) has conducted a series of determinations of the fecal fat which are in support of the theory of malabsorption and I shall quote from them. He carried out balance experiments on several cases of celiac disease and infantile atrophy. In none of these was he able to support the contention that almost as much fat appears in the feces after a fat free diet as after one containing the normal amount of fat. In fact he found just the opposite. In all cases he was able to markedly lower the amount of fecal lipid by giving a low fat diet or a fat free diet. Thus it seems that there must be some influence of food fat on the fecal fat. He tried a series of experiments where the iodine and saponification numbers of the fat both in the food and feces and then compared the two. He found that in celiac disease, the iodine and saponification numbers, although not exactly the same as
those of the food fats, rose and fell in parallel with the changes in the numbers in the food fats. These experiments I believe would warrant the conclusion that the fecal fat is dependent to some extent at least on the food fat.

As I have mentioned, if the excessive fecal fat was due to increased excretion from the blood then there should be a hyperlipemia, that is drawing an analogy between the hyperglycemia and glycosuria. This was supported by the work of Moncrieff and Payne and also by that of Bauer in one case. However, there is no other work that supports this and the work done since that time tends to show just the opposite.

Patterson (quoted from Parsons) demonstrates that except under closely controlled conditions blood fat figures are quite unreliable. He showed that exercise in the fasting person mobilizes fat and tends to raise the blood fat. However, if estimation is carried out while resting after a nights fast, the results are constant for the same person. He found that a considerable variation in the range of the different individuals was present but noted that the range is lower in celiac than in normal children. Thus it would seem from these experiments that
there is actually a hypolipemia instead of a hyperlipemia. These results were confirmed by later work by Parsons (75).

McClure and Huntsinger (quoted from Parsons) pointed out that the increase in fatty acid concentration of blood after ingestion of oleic acid is not due solely to an increase of oleic acid but in part to the mobilization from the various fat depots.

Parsons showed that in celiac children there was a delayed rise in the blood fat curve after ingestion of fat. There is an almost immediate rise in normal children as I have already pointed out. This rise in blood fat in normal children is due to the mobilization of the fat from the fat depots. These depots have been depleted in the celiac child and so the late rise which occurs is probably due to absorption. Even so there is still a hypolipemia.

I believe that the evidence quoted is enough to support the theory of malabsorption rather than the theory of malutilization with the source of the fecal fat the blood stream.

In addition to the errors in metabolism of fat it has been suspected clinically and, more lately, proven that there is also some error in the carbohydrate metabolism.
Miller in his many articles on celiac disease, has often mentioned that he regards the errors in carbohydrate metabolism as second only to the errors in fat metabolism. Some investigators even go so far as to say that they regard the carbohydrate metabolism as the chief abnormality in this condition, and to regard the metabolism of fats as relatively unimportant. The most important of the latter is probably Morse (68).

It has long been observed clinically and generally agreed upon by most investigators that the frothy, yeast appearance of the stools in this disease is, in all probability, due to the fermentation of carbohydrates. It has been further noted clinically that one of the main causes of so-called relapse during a period of improvement is the adding of carbohydrates to the diet too soon. It seems that some of the carbohydrates are more apt to cause trouble than the others. For instance, some of the fruit sugars or invert sugar as in found in the banana seem to be tolerated very well while sugar such as cane sugar, dextrose, and particularly starches are not tolerated at all apparently for a long time and when they are added to the diet it must be done with extreme care. Thus the observations from a clinical standpoint would seem
to point to some abnormality of sugar metabolism. Whether it is due to malabsorption or not is hard to tell.

Since carbohydrate balance experiments are practically impossible, attempts have been made to estimate the degree of absorption by estimating the blood sugar values. Along this line there have been many determinations. The most important of these is the work brought out by MacLean and Sullivan (41), Thaysen and Mørgaard (107) and Thaysen's attempts to determine the source of the low blood sugar curve (108). Most of the authors agree that there is a low blood sugar curve in this condition and practically all the results are the same so the ones which were originally done in this country are all that I shall discuss. Both MacLean and Sullivan and Thaysen and Mørgaard's articles came out at the same time apparently independent of each other.

MacLean and Sullivan reported observations carried out in fourteen cases. In all fourteen cases they found that there was a low blood sugar curve after the ingestion of dextrose. Furthermore, they reported that there was no rise in the blood sugar when galactose was administered but that there was a four plus urine sugar following the administration of the galactose. They say that after the administration of dextrose there was a rise in the blood sugar during the first hour but that this rise was subnormal
proving that some sugar was absorbed. The four plus urine sugar after the administration of galactose would seem to indicate that even in the face of the lack of blood sugar rise there was some absorption from the intestine of sugar.

Thaysen and Morgenard made an investigation of the effects of administering both fructose and dextrose in equal parts. Following the administration of this, blood sugar curves were obtained which were similar to those of a control and also to those of supposed normal children. This suggests that there is probably a more normal metabolism and utilization of the invert sugars and probably explains the reason for the increase tolerance for bananas over some of the more usual sources of sugar in the diet.

In summing up their conclusions from their experiments MacLean and Sullivan claim that the low blood sugar curve found after ingestion of carbohydrate in patients with celiac disease must be explained in one of three ways: a low renal threshold for carbohydrate; lack of absorption of carbohydrate; or an endocrine dyscrasia.

A low renal threshold has been ruled out pretty well. The large frothy stools characteristic of this
disease would suggest lack of absorption of dextrose as an etiologic factor in the flat blood sugar curve. There are several facts which do not fit in with this according to MacLean and Sullivan. They claim that the fact that the blood sugar rose for an hour showed that there was some absorption of sugar. Then the blood sugar curve was also flat following the administration of dextrose intravenously. In addition there was a four plus urine sugar following the ingestion of galactose. This too indicated that there was some absorption from the intestine. Thus they conclude that with the evidence of a lowered renal threshold ruled and and fair evidence of lack of absorption ruled out, that the possibility of an endocrine disturbance is not untenable.

Thaysen(108) claims that the low blood sugar curve cannot be due to defective absorption or destruction of dextrose in the intestinal tract. He gives reasons for this belief as follows:
1. the blood sugar curve is low just as often after parenteral administration as it is after oral administration.
2. The respiratory quotient rises to about one after the ingestion of dextrose showing metabolism and absorption has taken place.
3. The respiratory quotient is higher following a carbohydrate diet than on an ordinary diet.

In the end Thaysen advances the theory that the origin of the low blood sugar curve is uncertain but is probably due to some toxic effect on the endocrine glands which regulate the blood sugar content.

It has been found by the injection of epinephrine that there is a fair reserve of glycogen.

Parsons has pointed out that it is doubtful whether such definite conclusions as those of Thaysen can be drawn from the respiratory quotient, because Cathcart and Markowitz have shown that the values obtained are really the resultant of all the metabolic processes and do not necessarily indicate the metabolism of any particular food material.

The case of Poynton and Cole82 showing a high blood sugar and glucosuria is rather interesting to mention. Although it might be argued that this is evidence of an endocrine disturbance in celiac disease it is more likely that it is a case of diabetes occurring in the celiac child. There are only three other such cases on record.

There is a very interesting parallel between the hypoglycemic and hypolipemic curves. The very similarity of
these two curves suggest that both are probably of the same origin and that common origin is faulty or delayed absorption.

That there exists other defects in metabolism besides that referable to carbohydrate and fats is well recognized. It is a well established fact that there must be some error in either the absorption or utilization of the minerals as well. It was shown by McCrudden and Feles (44) that there was a disproportionate loss of calcium, phosphorus, and magnesium through the feces and that the amounts of these substances appearing in the urine is very low. As a matter of fact, complete balance studies showed that there was a negative calcium, phosphorus, and magnesium balance. Since this time this has been recognized by many investigators principally Telfer(106), Holt, Courtney, and Feles(31) and by Macrae and Morris(50).

There have been numerous attempts to explain this loss of minerals through the feces. It has been noted that during the better periods, which are characteristic of this defect, this still exists even though there has been great improvement in the fat and carbohydrate absorption. McCrudden(48) was the first to notice this. This was suggested by the failure to grow following clinical im-
provement of these cases. Further balance studies have shown that although the fats and carbohydrates were much better, there still existed the defect in utilization or absorption of the minerals.

Numerous attempts have been made to explain this. It was thought this might be due to the fact that with the greatly increased fatty acids and soaps in the feces that the various mineral elements were going to waste by forming these and thus they were eliminated instead of being absorbed. In their experiments McCrudden and Pales (46) were unable to demonstrate this hypothesis. They found that although there was a large loss of calcium in this way it was not great enough to account for the total loss of calcium. Furthermore they were unable to determine how all of the calcium in the feces was combined and they found that only fifty percent of the calcium in the feces was in the form of soaps. He found that the calcium in the feces was combined in the abnormal in about the same fashion as it was in the normal. Furthermore, he goes on to say that one would be tempted to say that the disturbance of calcium does not lie in the intestine. However, it is quite clear that the loss of calcium and other minerals is through the intestine and
and not through the urine as the concentration of these substances in the urine is smaller than normal.

It has often been noted that with the lack of absorption and phosphorus in these cases it seems strange that rickets does not develop more often than it does. I believe that it is generally understood that in order for the typical infantile rickets to occur it is necessary that there be rapid growth. In these cases growth has practically ceased so there would not be any tendency to the development of rickets. It is known that with the apparent disturbances there must be a deficiency of vitamins and particularly of the fat soluble vitamins. It seems possible that perhaps in this lies the answer to the question of abnormality of mineral metabolism in this disease. This has been suggested by Ford(13) who, after a series of experiments, came to the following conclusions:  
1. There is an increased retention of calcium oxide and phosphate in celiac disease which is, with antirachitic treatment similar to that found in infantile rickets.  
2. The increase in urinary excretion of phosphates, decrease in ammonia and increase in acidity of the urine during healing is similar in the two disease.  
3. Marked reduction of fecal output of calcium oxide and
and phosphorus pentoxide occurs in both with anti-
rechitic treatment.

4. In view of these findings and in conjunction with the
recognized clinical, x-ray, and blood chemistry changes,
there is little room for doubt that the rickets of celiac
disease is of the same nature as ordinary infantile rickets.

That there must be some basis for the avitaminosis
theory of non-retention of the minerals and particularly
magnesium and phosphorus are supported by the experiments
of Macrae(49) in the healing of celiac rickets. Other
articles in support of this are the findings of Holt,
Courtney and Fales(31) in their experience in the treat-
ment of cases with cod liver oil for the condition of
arrest of growth which occurs in these cases. They say
that the results were far beyond their expectations.

Thus from the review of the findings of various authors
which have noted and made observations of the effect of
various vitamin preparation on various phases of mineral
metabolism in celiac disease, but particularly in relation
to the calcium metabolism, that the possiblility of the
of the absorption of calcium and so supplying the skeleton
with articles necessary for growth, although due to some
extent undoubtedly to malabsorption through the intestine,
is, in all probabilities a vitamin deficiency and particularly of the antirachitic vitamin.

The work done on proteins in this disease have not been as extensive as they have in the cases of the other food materials, where there is obviously more difficulty in either absorption or utilization. However, what work has been done, particularly the latter work shows that there is some indication that there is some deficiency in the protein metabolism, but not to the great extent that there is of the other food materials. This accounts for the fact that the high protein diets are so efficient.

Herter(25) was one of the first to introduce protein diets in this condition. He supposed that the reason they were so successful was that they reduced the media favorable for the growth of an aberrant intestinal flora to a media that was more unfavorable for their growth.

McCrudden and Fales(47) carried out some experiments with a high protein diet and did chemical studies of the nitrogen in the feces. They found that the nitrogen in the feces was decreased on a high protein diet and cited this as an example that the high nitrogen of the feces on the usual diet could not be due to an inadequacy in digestion or absorption of the protein. In addition,
they determined that the plane of metabolism of the elements of the soft tissues can be raised without affecting either growth or the calcium metabolism. Previous to this on carrying out series of balance studies these same authors (43 and 44) had determined that the metabolism as a whole was on a low plane. However, they found the distribution of the nitrogen and sulphur among the various urinary constituents to be normal and and a normal ammonia content of the urine with increased ethereal suophates. They were unable to find any abnormal compounds of nitrogen or abnormal amino acids in the feces. The nitrogen content of the feces was no greater than normal.

However, more recent observations do not agree entirely with this. Freise and Jahr (quoting from Parsons) found 17.3 and 12.3 per cent of protein in the stools compared with 9.3 and 9 percent in two normal controls. Fanconi states that the child with celiac disease eliminates up to 50 percent of the nitrogen in the stools, whereas in the normal child the figures are from 13 to 20 percent.

Parsons(75) states that the results of balance experiments with protein depend on the condition of the stool; in nondiarrheal periods it is quite satisfactory.
Thus it is seen that although there is some abnormality in the absorption of proteins from the intestinal tract it is not as severe as that of the carbohydrates or the fats and during quiescent periods it is almost negligible.
SIGNS AND SYMPTOMS

The original description of this condition was by Dr. Samuel Gee in 1888. He was a very keen clinical observer and his description has never been surpassed. For that reason I shall quote it directly from his original article.

"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 this disease are yielded by the feces; being loose, not formed, but not watery; more bulky than the food taken would seem to account for; pale in color; as if devoid of bile; yeasty, frothy, an appearance probably due to fermentation; stinking, stench often very great, the food having undergone putrefaction rather than concoction.

"His stomach is the kitchen, where the meat is often but half sod, for want of heat."

"The pale, loose stool looks very much like oatmeal porridge or gruel. The hue is somewhat more yellow, other wise more drab. The paleness is commonly supposed to signify lack of bile; but the color of feces is a very rough measure of the quantity of bile poured into the duodenum; nay, more, the color of the feces is a very rough measure of the quantity of bile which they contain. Whitish stools are not always so wanting in bile as they seem to be; in particular, opaque, white food, such as milk-curd undigested, will hide the color of much bile.

"Diarrhea alba is a name employed in India to denote the coeliac affection; not that it is always
a coeliac flux, more liquid and larger than natural, but they are not always more frequent than natural; it may be that the patient voids daily but one large, loose, whitish, stinking stool. Diarrhea chylosa is another name used formerly and which seems to mean the feces consist of chyle unabsorbed.

"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 the hand than to the eye, the flesh feeling soft and flabby. Muscular weakness is great; muscular tenderness is often present.

"Cachexia, a fault of sanguification, betokened by pallor and tendency to droopy, is a constant symptom: The patients become white and puffy; the loss of color sometimes such as to resemble the cachectic hue of ague or splenic disease: the spleen is sometimes enlarged. Examination of the blood by the microscope shows nothing noteworthy, unless such molecular matter in the form of clear distinct particles or aggregated masses; but this is no peculiarity.

"The belly is mostly soft, doughy and inelegant; sometimes distended and rather tight. Wind may be troublesome and very foetid. Appetite for food differs in different cases, being good, or ravenous or bad. Heat of the body is mostly natural; sometimes children are said to be hot at night, and especially so over the belly.

"To diarrhea alba add emaciation and cachexia, and we have a complete picture of the disease. At times the bowel complaint is overlooked: the wasting, weakness, and paleness are what is noticed, and are thought to be due to another than the true cause."

Thus it is seen from this excellent description of the disease, that the characteristics of the fully developed case of celiac disease is as follows:

1. The passage of large, pale and offensive stools containing considerable amounts of split fats.
2. Wasting, which may reach an extreme degree.
3. Abdominal distension.
4. Severe stunting growth amounting to infantilism.
5. Anorexia and certain other nervous symptoms.
6. The not infrequent presence of deficiency symptoms.

After Gee's description I do not believe that there is a great deal which can be added to the description of the disease from a clinical standpoint. So I shall now consider some of the more important individual symptoms and their possible origin.

The most characteristic feature of this condition is the stools. They are large, loose, not formed but not watery in character. It has been proven that the stools contain large amounts of fat. These are well split and only a small proportion of them appear as neutral fats. The major portion of them are in the form of fatty acids and soaps. The source of the fat is probably the food and the balance of the evidence points in that direction. The presence of these is probably due to a malabsorption of fat as I have pointed out previously. The fats in the feces form a very interesting point in differential diagnosis. Parsons(75) points out that if the stools do not contain over 2 Gm. of fat daily then the condition
cannot be regarded as celiac disease. This figure errs on the small side because usually the amount of fat in the stools is much greater and may even surpass 20 Gm. daily.

Another very important symptom of this disease is wasting. This has been pointed out by all the observers in their articles on this condition and is usually attributed to the fact that there is a loss of subcutaneous fat. This soon becomes obvious and reaches an extreme degree. This condition is first and most noticeable in the limbs. Miller (64) has pointed out that the gluteal wasting is all out of proportion to the rest of the wasting and classes this as a valuable diagnostic sign. In contrast to the wasting there is the distension of the abdomen and an apparent fullness of the cheeks.

As I have mentioned, the abdominal distension is in direct contrast to the wasting of the limbs. The origin of this finding has been generally agreed to be due to a hypotonic condition of the muscles of the abdominal wall and of the intestines with distension due to large fluid contents of the small bowel and to flatulent distention of the colon. These points have been rather conclusively proven by roentgenological examination and a condition of megalocolon is usually found. The best description of the
feel of the abdomen in these cases is that given by Parsons (75). He says that the abdomen has a doughy feel; the shin is soft and never presents that harsh, dry, granular appearance and feel which to him is characteristic of abdominal tuberculosis. Some authors have described or compared the feel of the abdomen to that of a rather plump young adult. It has been pointed out by many observers that this condition may persist for years after there are no other clinical signs of celiac disease.

There is a marked retardation of growth. This is often the thing that brings the child to the doctor, and quite often this is the first suspicion one has of the condition with which he is dealing. Gee (18) did not overlook this symptom but it is to Herter (25) that we owe the recognition of the importance of it. As a result of this the child appears to be stunted in his growth and if it persists it will even affect his future growth. It has been noted by many, roentgenologically, that there is a delay in the appearance of the ossification centers of these children and a definite osteoporosis with a great fragility of the bones. This was first noted by McCrudden and Fales (48). Some authors report that not only is there a delay in appearance of ossification centers but in un-
treated children or in those with very severe cases and who do not respond to treatment very well, there is even a delay of puberty.

Freeman(40) would explain this lack of growth on the basis of improper absorption of food. He quotes the work of Fleischner in which he showed that failure to gain in weight is accompanied by failure in proper growth. Also showed that failure to gain in weight and in length can both be due to improper food absorption. McCrudden and Fales (48) after a series of experiments were of the opinion that the general retardation in development is secondary to a failure to develop of the skeletal system. The disturbance of calcium metabolism associated with the frail, thin bones, strongly suggest that the bones have not sufficient calcium in proper form at their disposal. Levinsohn(40) I believe sums up the knowledge of explanation of this symptom the best by listing the various theories of possible explanation and then questioning the whole works. I do not believe that at the present time there is any accurate or definite explanation which can be given for this symptom.

These children suffering from celiac disease seem to show definite nervous manifestations. These are shown
by the anorexia, inability to please them with anything; it has been noted by many observers that these patients are extremely difficult at times. During periods of improvement they are exceptionally fine children; they like to play, behave well and are very little trouble. However, during the diarrheal relapses they are very difficult to get along with, will take little or no food, do not play and apparently are quite miserable. They are fretful and irritable and cry at the slightest excuse. They seem to be quite morose and moody.

In addition to the above there are other symptoms worthy of mention. One in particular is the rapid establishment of physical and mental fatigue. This is a very characteristic feature of this condition. Its explanation is quite difficult. Attention was first called to this symptom by Herter(25). It is considered by some to be of great diagnostic importance.

There is a definite, demonstrable degree of anemia. This too was first given great importance by Herter. Gee did not altogether neglect this symptom in his report of the disease but did not attach the significance to it that latter writers have. It was found by Herter to be a secondary anemia of the type usually seen in infants with
nutritional deficiencies. This is undoubtedly the explanation of this sign of the disease. Complete balance experiments carried out by Telfer(106) have shown that the retention of iron in this disease is very slight and that administration of iron compounds will help this considerable.

The retention of mentality in spite of the physical maldevelopment is a very outstanding characteristic of this disease and one which is not explainable so far as I can see and in no case have I found in the literature any reasonable explanation of this.

Another symptom which should be mentioned is pyrexia. In the majority of the literature there is very little mention made of this as a symptom. It may or it may not occur. Most authors seem to regard this when it does occur as a sign of some intercurrent infection.

The diagnosis of celiac disease is still based on Welter's postulates(25). These are as follows:

1. Halted body development.
2. Retention of mentality and good cerebral development.
3. Definite thinning and protrusion of the abdomen.
4. Measurable degree of anemia.
5. Rapid establishment of bodily and mental fatigue.


Miller(63) mentions six very similar points of diagnosis of celiac disease. He mentions that the weight for the height is much nearer normal than the weight for the age which is usually very greatly subnormal. Another point which he mentioned is that the fat wastage persists even when the rest of the digestion is normal.

There are some diseases which it is desirable to differentiate this condition from. These are mainly: diarrhea of rickets; abdominal tuberculosis; chronic enteritis; sprue; and pancreatic steatorrhea.

Miller(63) mentions that the difference between celiac disease and the catarrhal diarrhea of rickets is comparatively easy. In rickets the loss of fat is not as extensive nor as persistent. Small children with celiac disease show few signs of rickets while in older children, rickets of a low calcium type may develop as a complicating factor.

Abdominal tuberculosis may produce a fatty diarrhea in two ways: (1) by inflammation and ulceration of the intestine, and (2) by the obstruction of the lacteals due to large mesenteric glands. Harper(23) points out that
although this may produce a fatty diarrhea it can be excluded by the absence of tuberculin reaction and absence of enlarged glands in the abdominal cavity and of the absence of other signs of tuberculosis.

Sprue, according to most of the authors, occurs so rarely in children that it is hardly worth mentioning. Parsons(75) has pointed out that often in sprue there is an anemia of a megalocytic type and that there is often a true achylia neither of which condition is ever present in celiac disease. It might be remarked, however, that clinically the two diseases are almost the same.

Numerous authors have pointed out that one of the reasons for not accepting the chronic enteritis theory of causation of celiac disease is that chronic enteritis can be differentiated clinically from celiac disease. It is mentioned that there is a failure of digestion of all of the food in chronic enteritis. There may or there may not be an excess of fat in the stools. Wasting is more severe than the lack of growth. Stools tend to show mucus and undigested food which is almost always definitely absent in celiac disease. On a low fat diet the percentage of fat in the stools drops to a lower figure than in true celiac disease.
Another condition which has been suspected of being an etiological agent in celiac disease but which can be distinguished from celiac disease is pancreatic steatorrhea. Harper (23) points out that this condition is very rare and when it does occur it is usually congenital. The stools are large, pale, offensive, and oily. The diagnostic feature is the distribution of fat in the feces. The amount of neutral fat is much over 33 percent of the total fecal fat and this is a failure of fat splitting which does not occur in celiac disease. In this condition the neutral fat shows itself in the stool as separated oil or grease which congeals on cooling. This type of stool does not occur in celiac disease.

There are some complications of celiac disease which are worth mentioning.

Probably the most important of these are intercurrent infections, either enteral or parenteral, to which these children seem to be strangely susceptible. This is the most common cause of death in this condition. This possibility has been recognized since the time of Gee.

Other complications are those occurring as a result of vitamin deficiency -- namely, rickets, scurvy, edema, purpura and beriberi.

The most common of the deficiencies which are apt to occur are those of the fat soluble vitamins, vitamins A and D. Particularly the latter. That rickets is a
complication of celiac disease is a well recognized fact. Several authors have reported cases of rickets complicating celiac disease and it has become a type known as celiac rickets. The type of rickets which occurs in this condition is of the low-calcium type which is usually seen in older children. This has been clearly demonstrated roentgenologically by many investigators but principally by Macrae(49) and Parsons(72). This condition can be prevented or cured by the use of some form of anti-rachitic therapy preferably ultra-violet radiation or some form of vitamin D in some solid form as viosterol. Ford(13) in 1933 showed quite conclusively from his studies that the rickets of celiac disease and infantile rickets are probably the same disease.

Haas(21) has reported a case of beriberi in late infancy which he concluded to be a result of celiac disease. He rejects the possibility that celiac disease and beriberi are the same disease. Since beriberi is due to an absence of vitamin B from the diet and celiac disease is characterized by an inability to utilize or absorb carbohydrates, the chief carriers of vitamin B, it seems that celiac disease can cause beriberi. In all probabilities this is so and thus beriberi is a complication of celiac
disease due to the inefficient absorption and utilization of the contents of the digestive tract.

It is thought by Parsons(75) that the edema of celiac disease might possibly be due to a vitamin B deficiency.

Scurvy has often been found as a complicating factor in this condition and it is known to be a vitamin C deficiency.

Thus it seems that there can easily be a secondary avitaminosis in this condition which should be guarded against as much as possible if these conditions mentioned are to be avoided. Haas(21) points out that the banana is a source of all the vitamins except D and A and that this is well tolerated by the celiac child.

In the light of this it seems that one should be very careful in the management of these children to see that they are not unnecessarily exposed to infections of any type as these are the most common causes of fatalities and these children are very susceptible to them. In addition, a good source of the vitamins should be added to the diet as soon as the child can tolerated them in order to avoid the danger of one of the deficiency diseases.
CLINICAL COURSE AND PROGNOSIS

The onset of this disease is usually slow and insidious. However, it may be apparently sudden following an acute parenteral infection, particularly if the infection has enteral symptoms.

All clinicians agree that the course of this disease is very long and drawn out, lasting for several years as a rule. Holt, Courtney and Fales mention that little can be expected in definite improvement in less than a year and usually the treatment must be intensive for about three years with restrictions on the diet for many more. The course of this disease is usually one of periods of improvement with occasional relapses. During these relapses all the ground gained may be lost and have to start over from the beginning. It is generally noted that the more the improvement shown the farther apart and the less severe are the relapses.

Numerous clinicians, principally Haas(22) have reported cases of cure without nutritional relapse. Reuben(34) reports experience with on such case and makes the statement that the usual relapses do not occur if there are no
indiscretions of diet. Also, that if the quantity and quality of the food are increased very slowly and gradually such relapses are unlikely. Although they have reported such cases these are in the minority.

The majority of the observers are of the opinion that with good and sufficient early treatment there may be little deformity following the disease. Kerley and Craig(35) comment that they have been unable to find record of cases in the literature that have reached maturity. Kerley has observed 3 cases of evident celiac disease in childhood which have ranged from 16 to 24 years of age. In all three cases there seemed to be a runting in growth and the mental capacity was of inferior quality. I don't believe that he made mention of the fact that these patients had or had not received adequate care and possibly these findings could be laid to this. The greater majority, however, believe that ultimately there will be complete recovery except that there is apt to be some stunting of growth. Marriott(52) believes that the child will be below normal in height, weight, and general development for many years. In most of the articles I have seen this seems to be the general trend of opinion. As a matter of fact it is generally agreed that the child is not apt
to be entirely free from symptoms or danger of relapse until the time of puberty which is recognized as being the time of complete cure. Levinsohn(40) makes special mention of the fact that the cause of the cure is as mysterious as the cause of the disease.

However, in spite of the more or less optimistic prognosis of the majority of clinicians, there are some facts which must be borne in mind. These are the possibility of complications which may and are apt to occur if one is not on the lookout for them and doesn't take precautions against them. The complications which may occur can and do greatly influence the course of the disease.

Mortality statistics of this condition are very hard to quote as there has been little attention paid to this phase. Gee makes comment on the fact that the common end of these children with this disease is death. However, this is not the trend of opinion today. The number that actually die from the disease itself is, in all probabilities very small. The majority of the deaths occurring are due to the complications. The most common of the complications that are the cause of death are the parenteral, or intercurrent, infections.
That intercurrent infections are the common cause of death in these cases was also recognized by Gee. Thus it must be borne in mind that while treating these cases that until great clinical improvement has occurred these children must be guarded as much as possible from getting any superimposed infection.

There are other complications which may and do occur and which are likely to seriously influence the course of this disease. This is the group of deficiency diseases. These are more or less common in this condition and may play a large part in the amount of deformity which is left as a result of this condition. These can and should be guarded against as much as possible by the addition to the diet good sources of vitamins at the earliest possible moment.

Thus, I believe that the prognosis in the majority of cases is good even though the course is slow. However, it must be constantly borne in mind in dealing with these children that the complications are apt to be of serous consequence and should be guarded against as much as it is possible.
TREATMENT

In view of the fact that there is no known etiology and no definitely known or proven pathology, there is no specific treatment for this condition. However, metabolic studies have offered a possible solution for therapy until the organism can adjust itself to the normal condition once more.

Metabolic studies have shown that the condition is a digestive insufficiency due either to malabsorption or malutilization of the food. The balance of evidence at the present time rests with the malabsorption theory. Furthermore, it has shown that there are serious errors in fat and carbohydrate tolerance as well as retention of minerals and that the error in absorption of proteins is much less and, therefore, they are better tolerated than the other foods. Metabolism studies in regard to the use of drugs has shown that in general they have very little, if any effect, except for the vitamin preparations.

Thus it is clearly evide t that the principle form of treatment is dietary. In addition, this dietary should
follow certain lines: The principle of dietary management is a diet which is high in protein and low in fat and in carbohydrate. As can be seen by analogy to metabolic studies this is the only sensible type of diet to prescribe. Furthermore, the value of this type of diet has been borne out so well by clinical observation and experience of the various investigators that they unanimously agree as to this principle of diet. However, when it comes to the management of the diet, the materials and food stuffs to be used in the diet, there are almost as many variations as there are authors. So in this paper I shall only attempt to give a review of some of the more common diets found to be in use.

It has been noted since the time of Gee(12) that this condition never developed in the breast fed infant. I have not been able to find a single report of a case which has occurred at this time of life. Furthermore, it has been noted by many observers that in very severe cases, where human milk could be obtained it was a lifesaving measure. Thus it seems that breast milk is the best food these children could have. However, this is impossible except at times in cases of emergency. So it becomes necessary to make a substitute which is easily
assimilated and utilized by these children. That cow's milk, as is, is one of the worst things that can be given was also first noted by Gee. He recommended that a substitution of Asses milk be made. This observation was also made by Still(103). Parsons(75) has explained this as probably due to the fact that in asses milk there is a low fat content and its protein is nearly half lactalbumin which is easily digested. In addition Gee gave rare beef or underdone mutton.

The first high protein diet as such was recommended by Herter(25). He found this very beneficial and attributed its effects to the formation of a media in the intestine unfavorable for growth of an abnormal intestinal flora.

The next and greatest contribution to the treatment of celiac disease was that of the three-phased diet and the use of protein milk which was first introduced by Howland in 1921 (22). His three stages were as follows: (1) in the first stage the dietary consists only of protein as protein milk; (2) in the second stage protein milk is still the basis of the diet plus the addition of other almost pure protein substances as curd without whey, scraped meat, certain forms of cheese, egg white and eventually the whole egg; and (3) the stage in which carbo-
hydrates are added. Howland considered the carbohydrate intolerance of the intestine, as he termed it, to be the most important factor. He says that the third stage of the diet is really the most difficult phase of the whole diet and the carbohydrates must be added very carefully.

This idea was almost universally adopted and used by the majority of the clinicians and this is particularly recommended by Sauer. The idea of a three-phased diet is still carried out by the majority of the physicians, however, the substances used in the diet are changing somewhat. For instance, more and more reports are appearing in the literature indicating that protein milk has been found so unsatisfactory that its use was of necessity discontinued and other products have been substituted. Kerley(36) for instance found in has cases that the use of protein milk was so entirely unsatisfactory that he found it necessary to discontinue it and substitute some other form of protein. He used a casein preparation which he had made for him and reports that his results with the use of this have been excellent.

The most complete investigation of the apparent undesirability of protein milk which I have been able to find was that conducted by Martha VanKirk Nelson(70).
In her investigation of the dietary she decided from numerous metabolic observations that the fat in the quantity found in protein milk was undesirable and was probably the disturbing factor. It is interesting to note that numerous observers have recommended the use of lactic acid milk. Potter(30) in commenting on the use of this in the dietary mentions that when it is used in place of protein milk, it reduces the odor of the stools.

Another change of Howland's diet which has been almost universally adopted has been the administration of carbohydrates. It was found clinically that apparently these children could easily assimilate and utilize the carbohydrate which is found in bananas and that as a result carbohydrate in the form of bananas could be added to the diet at a much earlier date. The first article which I was able to find on the use of the banana was published by Haas(20) in 1924. Since this time the use of the banana has been incorporated into almost every diet. In commenting on a case of beriberi resulting from celiac disease Haas(21) pointed out that not only was the banana a valuable source of carbohydrate but that it was also a valuable source of the vitamin with the exception of fat soluble A and D. Particularly was it a good source of E.
This is the general trend of opinion concerning the diet in this condition at the present time. The three-phased diet management of Howland is still followed out but there seems to be an increasing tendency toward the substitution of other protein products for protein milk. The factor in protein milk which is probably at fault is probably the fat content. Since every author seems to have his own plan of management I have merely tried to give the more outstanding principles of dietary treatment which have been more or less universally adopted by the various investigators reporting on this subject.

There are other phases of treatment which I feel should be mentioned even though they are not of much value except for relief at times of some of the more distressing symptoms. This is in principle drug therapy. In the face of a severe diarrhoea some investigators have mentioned that bismuth and soda and a little opium should be given to control it. Iron should be given for the anemia. Miller, Webster, and Perkins(56) and some others have reported increased absorption with the use of some bile-salts compound. However, this has not been generally accepted and metabolic and clinical observations tend to point away from this form of treatment as being of no value generally.
One must consider the various vitamin preparations in view of the fact that there is often a demonstrable deficiency of these substances. The majority of these can be added to the treatment through the use of food which is a good source of these. As for instance, the banana as a source of most of the vitamins and particularly vitamin B. These should be added to the diet as soon as they can be tolerated. However, in the consideration of the fat soluble vitamins A and D this is not so easy as the essential feature of the disease is fat wastage in the stools. Vitamin D can be administered in the form of viosterol which seems to be better tolerated than the majority of the other preparations. However, if it is possible, I believe that ultra-violet radiation is the best form of vitamin therapy from the standpoint of this condition and adding the vitamin early. Macrae(49) has shown that the antirachitic powers of this form of therapy are very great and that the only other form which approaches it in the administration of cod liver oil which these children seem to tolerate badly.

The other means of therapy which has been mentioned in the literature is the use of various endocrine prep-
treatments. This line of therapy has been generally unsuccessful and most writers mention it only to condemn it. In addition one might add that at the present time there is no evidence which would seem to indicate that it would be of any value, that is from pathological and metabolic studies.

I think that I have satisfactorily demonstrated that the treatment of this disease is almost entirely dietary and, that although there are as many different diets as there are investigators reporting on the subject, all diets follow the same general line of principle. That is, they all agree that the diet should be one which is high in protein and low in carbohydrate. The majority of the writers have accepted Howland's principle of a three-phased form of management. This is at present the most ideal form of treatment which can be offered and both clinical and metabolic observations show that it is a sound procedure to follow. Its almost universal acceptance would seem to indicate its value.


43. McCrudden, F.H. and Fales, H.L., Chemical studies on intestinal infantilism; the relation of endogenous to exogenous metabolism; nitrogen and sulphur distribution and chlorimeter experiments, J.Exper.Med. 15:113-118, 1912.


57. Miller, R., Celiac and allied types of infantilism, a retrospect and bibliography, Brit. J. Dis. Child. 18:11-17, Jan-March 1921.

58. Miller, R., Fatal case of celiac infantilism with comments on morbid anatomy of coeliac disease, Lancet 1:743-746, Apr. 9, 1921.


99. Sperry, W.M. and Bloor, W.R., Fat excretion; the qualitative relations of the fecal lipoids, J.Biol.Chem. 60:261-287, 1924.


