5-1-1936

Non tropical sprue (chronic idiopathic steatorrhea)

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NOM - TROPICAL SPRUE
(CHRONIC IDIOPATHIC STEATORRHEA)

by

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April, 1938
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INTRODUCTION

Non-tropical sprue is a chronic disease of unknown etiology, occurring in adults, characterized primarily by mal-absorption of fat, and secondarily by emaciation, anemia, tetany, osteoporosis, a flat glucose tolerance curve, megacolon, and various other deficiency symptoms. The mal-absorption of fat evidences itself by the presence in the feces of abnormally high amounts of fat, inevitably well split. No pathology can be demonstrated to account for this fat loss.

Its name is derived from its similarity to a disease ordinarily considered tropical and known as sprue. Most observers now believe that sprue is not confined to the tropics and that the syndrome under discussion is identical with sprue. Elsewhere in this paper the relationship of these two conditions will be discussed more exhaustively; it is mentioned here simply to announce that although the purpose of this discussion is to present the syndrome of non-tropical sprue, observations from tropical sprue will be quoted if valuable and applicable.

Then, too, the relationship of celiac disease, which by common consent is considered a pediatric disease, to non-tropical sprue is in dispute. In this case, however, the opinion is overwhelmingly in favor of considering the two identical. Therefore, in the definition non-tropical
sprue is described as a "disease...occurring in adults", to differentiate it from celiac disease, which is probably the same syndrome occurring in children. Observations drawn from celiac disease will also be quoted if valuable and applicable.
The primary feature of non-tropical sprue is steatorrhea, that is, excessive loss of fat in the stool. Diarrhea may or may not be present; but it is found at some time or another in almost every case. When diarrhea is present, attention is focused on the stool condition comparatively early and the steatorrhea consequently recognized early. Quite often, however, especially when the condition is non-diarrheal, some of the secondary deficiency symptoms may become so prominent as to mask the true nature of the disease. The commoner symptoms are:

1. Emaciation, impairment of growth, and infantilism.
2. Tetany and osteoporosis.
3. Anemia.
5. Megacolon.
6. Flat glucose tolerance curve.

Findings which have been described less frequently are:

7. Prominence of the abdomen (Herter 1903).
8. Pigmentation of the skin (Bennett, Hunter, and Vaughan 1932).
9. Peripheral edema (Snell 1935), and ascites (Cee 1888).
10. Tendency to gastric achlorhydria (Blumgart 1923).
(13) Acral paresthesia (Holmes and Starr 1939).
(13) Sub-acute combined sclerosis (Weir and Adams 1935).
(14) Leucopenia (Bowen-Davies 1934).
(15) Xerophthalmia (Riddell 1933), and various other evidences of hypovitaminosis (Thaysen 1934, 1935).

The original description of this syndrome by Gee (1888) can hardly be surpassed for accuracy and conciseness:

"There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially apt to affect children...Signs of the disease are yielded by the faeces; 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...The patient wastes more in the limbs than in the face...muscular weakness great...Cachexia, a fault of sanguification, be-tokened by pallor and tendency to dropsy, is a constant symptom; the patients become white and puffy...The belly is mostly soft doughy and inelastic, sometimes distended and rather tight...While the disease is active, children cease to grow; even when it tends slowly to recovery, they are left frail and stunted."
MORBID ANATOMY

No characteristic morbid anatomy has ever been demonstrated to satisfactorily account for the syndrome of non-tropical sprue, although a few investigators have claimed such on inadequate bases.

Gee (1888) stated: "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." Gibbons (1889) expressed the same opinion, finding no marked changes in the intestines. Whipple (1907) published a report entitled: "A Hitherto Unrecognized Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues". In an autopsy on a man, thirty-six years of age, he found deposits of neutral fats, fatty acids, and giant mononuclear and polymuclear cells in the intestinal mucosa and submucosa and in the mesenteric glands. The latter were affected to the greatest degree, and furthermore showed a chronic inflammatory reaction with replacement of much of the gland tissue by fibrous scar tissue. This patient's complaints had been loss of weight and strength, a peculiar multiple arthritis, chronic productive bronchitis, dilated abdomen, and diarrhea. Stool examination had revealed that up to 80 per cent of the dried feces was composed of fat, almost entirely as
fatty acids and soaps. No evidence of tuberculosis could
be demonstrated either pre- or post-mortem. The patient
had a fairly severe degree of hypochromic anemia, with a
red blood cell count of 4,000,000 and 54 per cent of
hemoglobin. Whipple's comment is interesting:

"As one looks back upon the history of
this case in connection with the remark-
able observations at autopsy, it is
difficult to resist the conclusion that
we are here dealing with a definite and
hitherto unrecognized clinical picture with
which we shall meet again."

He suggests the term "Intestinal Lipodystrophy" to desig-
nate this condition.

The evaluation of Whipple's case is not easy.

That there was a definite morbid anatomy present is un-
doubted. But two other considerations enter here. First,
were the pathological findings primary or secondary in
relation to the steatorrhea, or even merely incidental?
Secondly was this a case of non-tropical sprue? Certainly,
aside from finding a morbid anatomy not considered as
typical, it might, from the descriptions of the symptoms,
be an example of the syndrome under discussion. As a
matter of fact, this case is not accepted as one of non-
tropical sprue (Vaughan 1935), but is rather classed with
Ryle's (1924) cases of steatorrhea from obstruction of the
lacteals. Ryle (1924) presented three cases of fatty
diarrhea due to tuberculosis of the mesenteric glands, in
which the syndrome closely simulated non-tropical sprue;
there are points of differentiation, however, which will be mentioned later in the paper. Suffice it to say here that in the face of many autopsy reports finding no pathological anatomical changes is the alimentary tract and its lymph glands, and in view of the insufficiency of the data on this patient, Whipple's (1907) case is best not considered as non-tropical sprue.

Miller (1921) examined a case of celiac disease dying from influenza, and was unable to find any chronic changes in the pancreas, liver, intestines, or elsewhere to account for the prolonged failure in fat digestion.

In 1923, Blumgart reported "Three Fatal Adult Cases of Malabsorption of Fat", undoubtedly non-tropical sprue, and thereby probably focused the attention of the medical world on this syndrome. Pathologically the significant changes were confined to the intestines and the mesenteric lymph nodes. In all three necropsies only incidental changes were found elsewhere. The small intestine showed small granular elevations of the mucosa, usually gray in appearance. Microscopically, these elevations were found to consist of phagocytes containing ingested fat. The phagocytes were large and mononuclear, and contained a foamy reticulated cytoplasm. The mesenteric lymph nodes were noticeably enlarged and hyperplastic, and contained similar phagocytes.

Blumgart's (1923) observations have not been
confirmed by other writers. Lehndorff and Mautner (1927) could find no structural changes in the intestines to account for the defective absorption, nor could Macrae and Morris (1931) in two fatal cases of celiac. In one autopsy Parsons (1931) and his associate, Neale, showed the patency of the lacteals and lymphatic vessels by injecting methylene blue. Bloch (1932) preserved the abdominal viscera by injecting formaldehyde immediately after death in two celiacs, and at autopsy no pathological changes were found to account for the disease in either case.

Pathological findings have been described in cases reported as belonging to the syndrome under discussion, which on more careful analysis prove to be other entities. Radl and Fallon (1932) described a patient with a sprue-like picture, but this patient had an extensive duodenal ulceration with marked stenosis of the second and third parts of the duodenum. Such a case, just as Fairley and Kilner's (1931) case of gastro-jejuno-colic fistula simulating sprue, is interesting, especially in consideration of the pathogenesis of the steatorrhea; but under the present concept of the disease, they cannot be accepted as cases of non-tropical sprue. In January, 1935, three autopsies on "celiac disease" were reported by Hess and Saphir (1935), describing severe fibrosis of the pancreas in two of these. Then in December, Parmelee (1935) presented two cases of congenital steatorrhea, both showing similar fibrosis in
the pancreas; he considers this an entity distinct from celiac disease, and that the two of Hess and Saphir's cases belong to this group.

Summary of autopsy findings shows that there is no characteristic morbid anatomy which may be considered primary in non-tropical sprue.

Recently, Snell (1935) has claimed characteristic roentgenologic findings on the small intestine in cases of non-tropical sprue studied by him at the Mayo Clinic. His description follows:

"In the usual case the duodenum was dilated and the mucosal markings were thickened. In the jejunum and ileum there was definite smoothing out of the irregular shadows of the valvulae conniventes and clumping of the barium in smooth sausage-like masses. After the bulk of the opaque meal had passed, remnants of barium adhered to the walls of the jejunum, giving it a peculiar, 'fleck-like' appearance. In the more severe cases, the markings of the valvulae conniventes were entirely lacking. Dilatation of the jejunum was common although the contractions incident to peristalsis were readily observed fluoroscopically. Hypomotility was the rule in active cases. The regression of the changes and restoration of the mucosal pattern toward the normal, coincident with improvement in the clinical symptoms were quite striking."

These findings have not been confirmed by other observers, nor have they been correlated with post-mortem findings; therefore their significance must await further observation.
SYMPTOMS AND FINDINGS: THEIR PATHOGENESIS

I STEATORRHEA

An excessive amount of fat in the feces is a constant — as a matter of fact is the essential — feature of non-tropical sprue. The upper limit of normal for the lipoid content of the stool is considered as one-fourth (Parsons 1932) to one-third (Macrae and Morris 1931) of the dried weight of the stool. In Bennett, Hunter, and Vaughan's (1932) series of fifteen cases, the fat content of the feces ranged from 45.6 percent to 71.2 percent of the dried weight, the average being 56.5 percent. In patients who were personally observed by Thaysen (1932) the output of fat for twenty-four hours varied from 15.9 grams to 66.7 grams. The average was 36.6 grams, which is about triple the average daily output for normal persons. The average loss, furthermore, was about a third of the fat which was ingested, in comparison to the normal of 3 to 5 percent. In both of these series', as well as in those of all other observers, as Macrae and Morris (1931) and Parsons (1932), neutral fat forms only a small percentage of the total lipoid present, the large bulk being found as free fatty acids and soaps.

It is obvious, from the foregoing, that in non-tropical sprue, fat-splitting is excellently performed, but fat absorption is seriously impaired. The problem,
then, apparently resolves itself into determining the cause of the malabsorption.

When Gee (1888) first described idiopathic steatorrhea, he noted the common paleness of the stool, stating: "The paleness is commonly supposed to signify lack of bile; but the colour of the faeces is a very rough measure of the quantity of bile which they contain." Later, Cheadle (1903) described six patients who were suffering, in his opinion, from Gee's disease. He also observed the paleness of the stools, and unlike Gee, concluded that they were free from bile. On the basis of this belief he renamed the condition "acholia", and published his findings under that title. It was found later that the bile is normally secreted but that hydrobiliurbin, which imparts the normal brown color to the stool, is reduced to the colorless form leuko-urobilin (Mackie 1933). The acholia concept of the malabsorption was thus entirely discarded. However, in 1930, Miller suggested the possibility of a bile-salt deficiency as the cause of the malabsorption. He based his opinion on therapeutic results from the use of bile-salts in three cases of celiac disease. From similar data, Macrae and Morris (1931) arrived at the same conclusion. This possibility must be seriously considered, especially in view of the fact that Wieland's theory of the choleic acid principle of fat absorption is the one most favorably considered today. This theory postulates that deoxycholic
acid has the important function in transporting inacuble substances such as fatty acids through the intestinal wall by its hydrotropic action. If this concept be true, then a deficiency of bile salts could obviously produce just such a steatorrhea as is found in non-tropical sprue. However, such a deficiency has never been proven. Duodenal intubation and examination of the contents has shown normal findings of both pancreatic and biliary constituents. Parsons (1932) carried out some experiments to discover, if possible, whether there was any lack of deoxycholic acid in celiac disease. It was found that the fat balance was not improved by the addition of deoxycholic or dehydroxycholic acids, and that diffusion rates of the mixtures of bile and fatty acids were the same in celiac as in normal children (Parsons 1932). In another communication (1931) the same investigator states that he has never been able to demonstrate the absence of bile-salts or bile pigments in the stools of celiac cases. Unless further evidence be advanced in its favor, then, the bile-salt deficiency theory cannot be accepted.

Ryle (1924) presented three cases of steatorrhea from obstruction of the lacteals by tuberculous mesenteric lymph glands. Since the great bulk of absorbed fat takes the lacteal route to the systemic circulation, the pathogenesis of the steatorrhea in his cases is obvious. However, in opposition to his suggestion that lacteal ob-
striction is the cause of the malabsorption of fat in celiac
disease and non-tropical sprue, there are numerous autopsy
reports in which no such condition was found, and Parsons
(1931) conclusively demonstrated the potency of the lacteal
system in one fatal case of celiac disease by injection
with methylene blue.

An entirely different concept of the pathogenesis
of the steatorrhea was proposed by Moncrieff and Payne (1938).
They suggested that celiac disease is a primary disorder
of fat metabolism associated with an increase of the fat in
the blood and in the feces, where possibly it is being
excreted. They thought that not mal-absorption but mal-
utilization is the primary fault, a defect of fat metabolism
analogous to the defective utilization of sugar in diabetes;
and that the steatorrhea is a leakage of fat due to a fat
plethora in the blood, analogous to alimentary glycosuria
on a high sugar intake. These investigators drew their
conclusions from determinations of the percentage of fatty
acid in the blood of six celiac children and five controls,
under similar resting conditions; and where the fatty acid
content of the controls ranged from 0.142-0.208 grams per
one hundred c.c., the celiacs ranged from 0.275-1.17 grams
per one hundred c.c. Further evidence was based on two
cases of theirs, both apparently celiac disease. In one
the blood fat was 0.145 per cent two hours after feeding
skimmed milk and casein. She died shortly and post-mortem
examination showed large masses of tuberculous mesenteric glands obstructing the lacteals. The second showed 0.422 per cent after the fat-free meal. She died of bronchopneumonia, and autopsy revealed no pathology at all in the abdomen, corresponding, therefore, with the usual concept of celiac disease. The conclusion was that in tuberculous peritonitis with obstruction to absorption of fat, the blood fat content was low, while in celiac disease the high blood fat content caused a massive excretion of fat into the feces.

This concept of Moncrieff and Payne (1928) is lent some support by the experimental work of Sperry and Bloor (1924) on cats and dogs. Feces fat from cats and dogs, fasting and on standard diets were separated into fractions and the composition of these fractions studied with special reference to the source of the fatty material. They postulated that it does not arise directly from the food on the strength of the following observations:

(1) In many cases almost as much fatty material appeared in the feces on a fat-free as on a fat diet.

(2) There was a considerable output in fasting which was similar in properties and in the relation of its components to that excreted when food was given.

(3) The composition of the food fat was different from that of the feces fat.
Sperry and Bloor (1924) stated their conclusions as follows:

"There is a marked similarity between the blood and fecal lipoids with regard to the ratios of solid to liquid fatty acids and the melting points of the non-volatile fatty acid fraction which makes it probable that the fatty material of the feces has its origin largely in the blood."

Other investigators have criticized this conclusion of Sperry and Bloor (1924) and denied that the blood is the source of fecal fat. Parsons (1932) in balance experiments on more than one hundred atrophic children, as well as in those carried out on children suffering from celiac disease, was unable to find any evidence that almost as much fat appears in the feces after a fat-free diet as after one containing a normal amount of fat. In fact, in infantile atrophy he was able to reduce the output of fat in the feces to 0.3 gram daily when the fat intake was reduced to 1.5 grams. Then in regard to Sperry and Bloor's (1924) statement that the composition of food fat is different from that of the feces fat, Parsons (1932) repeatedly noticed that when children were having cod-liver oil or linseed oil, the extracted fat was much softer than when they were having butter or lard, indicating even by casual observation that the melting point, and therefore presumably the composition, of the fecal lipoid was affected by the
food lipoid. Furthermore iodine values of the fecal fats, taken as a whole, although not identical with the food fats, showed similar variation, rising and falling together. The results obtained in normal children and in celiacs were similar.

Although certainly not by intention, the two above-mentioned reports, that of Moncrieff and Payne (1928) and that of Sperry and Bloor (1934) become intimately intertwined. Because if the formers' assertion that the blood fat in idiopathic steatorrhea is high should be true, then it lends support to the latters' conclusions, from animal experiments, that fecal fat has its origin largely from the blood. This would in turn lend weighty support to the formers' theory that idiopathic steatorrhea is a metabolic disease characterized by excessive excretion of fat into the intestine.

However, other investigators have almost unanimously contradicted Moncrieff and Payne's (1928) assertion that the lipemic level in idiopathic steatorrhea is higher than normal. Macrae and Morris (1931) found values for blood fat in their celiac cases always within normal limits. Fanconi (1928) reports low normal or even subnormal values for the blood fat. He further states that in celiac disease the blood-fat curve after oral administration of olive oil or butter is flatter than normal. In Parson's (1932) series, the blood fat on thirty-four normal children and twenty-three celiacs, under controlled conditions, averaged
C.474 grams per one hundred c.c. for celiacae and C.617 for normals, indicating that the blood fat has a lower value in celiac disease than normal. Not only were the values set at a lower level, but the lipemic curves after administration of sixty grams of olive oil showed delayed rise and lowered magnitude of the rise. Chesney and McCoord (1934) reported on the vitamin A curve of the serum following administration of bailever oil to celiac children and controls. It was found that the rise of vitamin A in the serum of the celiacae was much less than in the normal children, and that the maximum rise occurred later after the ingestion of the oil; also that during the phase of clinical improvement, the rise was more marked. Thaysen (1935) determined the fasting blood fat in forty-six normals and seven patients with idiopathic steatorrhea. The normal patients averaged 540 mgm. per cent, while the latter averaged about 400 mgm. per cent. He further observed that following the administration by mouth of 100 grams of olive oil to thirteen persons with normal fat absorption there was an average rise of 50 per cent of the fasting value. Opposed to this the rise of the blood fat after a similar meal in active steatorrhea patients averaged only 28 per cent. One patient with non-tropical sprue, however, in a period of clinical improvement, showed a rise of 52 per cent over a fasting level of 450 mgm. per cent.

The experience of all these observers proves
rather conclusively that the blood fat content in idiopathic steatorrhea tends to be lower than normal, and that it certainly is not high as Moncrieff and Payne (1928) claimed. Parsons's (1932) work at least casts a justifiable doubt on Sperry and Bloor's (1924) conclusion that feces fat is normally derived largely from the blood. He suggests that the small amount of fat which may not be derived from the food can be attributed to other sources, such as desquamated epithelial cells, bacteria, and the digestive secretions. All of the evidence presented above definitely negates the possibility that the steatorrhea in non-tropical sprue is due to a massive excretion of fat from the blood; and, for the present, at least, it must be considered as being due to a mal-absorption of ingested and digested fat.

Summarizing the knowledge on the pathogenesis of the steatorrhea, we may say that fat digestion is normal but fat absorption is markedly impaired, and the reason for the malabsorption is no better understood today than when Gee (1888) first described the syndrome. Undoubtedly, when we will have learned the reason for this malabsorption, we will know the etiology of non-tropical sprue.

Diarrhea, as a complaining symptom, is much less common in idiopathic steatorrhea of adults than children. In only five of Bennett, Hunter, and Vaughan's (1932) fifteen cases of non-tropical sprue was diarrhea
a recognizable clinical manifestation during the periods when they were under the observation of the writers. Twelve of the fifteen cases, however, gave a history of long standing diarrhea, and all had experienced it at some time or other. It is apparent, then, that actual diarrhea is not an essential part of the picture in non-tropical sprue, and its absence should not mislead the clinician into assuming the stool is normal.
SYMPTOMS AND FINDINGS: THEIR PATHOGENESIS

II DISTURBANCES IN CALCIUM AND PHOSPHORUS METABOLISM

Probably the commonest secondary symptoms in idiopathic steatorrhea are those produced by disturbances in the calcium and phosphorus metabolism. These symptoms are: tetany, rickets, osteoporosis, and deformities due to softening of the bones.

Herter (1908) was the first to call attention to the frequent occurrence of rickets in children suffering from celiac disease, or, as he termed it, "intestinal infantilism". The next reference to calcium disturbances was made by Langmead (1911). In a paper entitled "Colonic Tetany", he presented fourteen cases, all in children, characterized by: "(1) Relapsing tetany; (2) dilatation of the colon; and (3) abnormal and offensive motions". From his more detailed description it is obvious that these patients were celiacs. All of these cases showed dilatation of the colon, and it is interesting to note that Langmead (1911) recognized that the tetany "was related more closely to the state of the motions than to the amount of dilatation of the bowel."

The first authentic adult case of idiopathic steatorrhea published was described by Findlay and Sharpe in 1920 under the title "Adult Tetany". This patient was
a woman, fifty-two years of age, who had had celiac disease in infancy and childhood, had never weighed over eighty-four pounds, showed evidence of rickets, and had recurrent diarrhea and tetany in adult life. Furthermore these investigators demonstrated steatorrhea, mostly as split fat products.

In his classical paper, already mentioned, Blumgart (1923) described tetany and low serum calcium in two of the three cases of non-tropical sprue. Scott (1923) called attention to the disordered calcium metabolism in tropical sprue.

Others who have since described disturbances of calcium and phosphorus metabolism in sprue, non-tropical sprue, and celiac disease are too many to allow their enumeration.

From a perusal of these symptoms - tetany, rickets, osteoporosis, and deformities due to softening of the bones - it is obvious that the basis of all is a calcium deficiency. It was early recognized in idiopathic steatorrhea that the feces commonly carried away an excess of calcium in addition to the excess of fat. Herter (1908) carried out very accurate analyses of calcium intake and output on his cases of "intestinal infantilism", and his figures definitely show a subnormal retention. He attributed the hypo-absorption of calcium to the formation of insoluble soaps with the excessive amounts of fatty
acid, although he realized full well that only a relatively small percentage of the calcium lost in the feces was present as soaps. In explanation he stated that normally there is some amount of calcium lost in the stool, and the added small percentage lost as soaps, if continued over a long period of time, is enough to produce a deficiency. Later investigations have shown that the calcium lost as soaps does not play the essential part in producing the deficiency.

McCrudden and Fales (1918) reported balance studies of calcium and phosphorus in two cases of "intestinal infantilism". Both cases showed a greatly increased excretion of calcium by bowel and diminished urinary excretion. Similarly, the amount of phosphorus lost in the stool was greatly increased, and the ratio of fecal to urinary phosphorus was reversed, being 3:1, in contrast to the 1:3 ratio in a normal control. One of their two cases showed a slightly negative balance for calcium, and in the second they report an almost unbelievably high negative balance, 183.3 per cent of the intake being excreted, 98 to 99 per cent of the total of which was by the feces. On the strength of this they postulated that in addition to the lack of absorption there is also an increased excretion of calcium through the intestine. The slightly negative balance has been a common finding in idiopathic steatorrhea, but the high figures quoted in their one case has not been
repeated by any other observer. Their idea of excessive excretion of calcium into the bowel has no support, then, in studying the pathogenesis of the calcium deficiency.

Langmead (1911) correctly surmised the cause of tetany in his cases of celiac disease, which he called "colonic tetany", calling attention to the loss of calcium by bowel. However, his idea as to the pathogenesis of the latter, which he admitted to be purely conjectural, was that there might be a leakage of calcium from the body due to inefficiency of the parathyroid glands, basing his theory on experimental tetany produced in dogs by parathyroidectomy. The tetany of idiopathic steatorrhea, however, was later shown to be definitely separate and distinct from parathyroid tetany. Aub and his associates (1932) note the following points of similarity between the two: (1) Low serum calcium level, and (2) low urinary calcium excretion; but the following points of dissimilarity: (1) Low serum phosphorus level, and (2) high fecal calcium excretion, in idiopathic steatorrhea, but not in parathyroid tetany. Hunter (1930) also stresses the fact that in hypoparathyroidism the serum calcium is low and the plasma phosphorus is high, while in steatorrhea both are low. Apparently, then, the pathogenesis of the calcium deficiency in non-tropical sprue cannot be looked for in parathyroid deficiency.

Findlay and Sharpe (1920) ran calcium balance
experiments on their case of adult celiac disease previously mentioned and found a subnormal retention. However, they also found an increased excretion of methyl guanidine in the urine, and attributed the tetany to the increased production of the latter as the result of some alteration in metabolism. Since this patient had one condition known to be able to produce tetany, namely calcium deficiency, and since the guanidine findings have not been confirmed, there is no reason to consider this theory in the pathogenesis of the tetany in non-tropical sprue.

Barach and Murray (1920) presented a case of sprue with tetany and low blood calcium. In discussing the pathogenesis of the calcium deficiency, they give the possibilities of (1) the calcium carried on with the fat and its absorption through the diseased intestinal mucosa insufficient to maintain proper balance, and (2) owing to the prolonged intestinal irritation, the excretory rate of this substance by the fecal route may have been increased. Both possibilities have been proven untenable. The calcium loss directly with the fat has since been shown to be insufficient in itself to produce the deficiency (Macrae and Morris 1931); the malabsorption is not due to a diseased intestinal mucosa, but to other factors, which can be effectively corrected (Linder and Harris 1930); and Snell (Curry 1932) has pointed out that calcium deficiency can occur without an increased intestinal rate.
Probably the best study on the calcium metabolism in idiopathic steatorrhea was done by Linder and Harris (1930). Working carefully on three patients, they drew conclusions which have since been rather generally accepted as regards the pathogenesis of the calcium deficiency. They found that the calcium loss seemed to depend more on the fat excretion than on the fat intake, that is, if a high intake could be absorbed, there would be no excessive calcium loss, and if a low intake could not be absorbed, then the calcium loss would become excessive. However, they also found that if all the soaps found in the stool were present as calcium soaps, it would still not be nearly enough to account for the calcium present. Irradiated ergosterol had an immediate effect in providing a positive calcium and phosphorus balance in one patient with a low fat intake, and in another just as soon as the fat was restricted. Their conclusion was — and this is to date the best theory explaining the calcium deficiency in non-tropical sprue — that the vitamin D-containing sterols were being lost along with the other fats in the steatorrhea. In this concept the calcium becomes chiefly a hypovitaminosis D symptom; the qualification "chiefly" is advisedly inserted because two other factors cannot be entirely excluded: (1) The small percentage of calcium lost as soaps, and (2) the greater calcium loss with higher fat excretion, which Linder and Harris (1930) interpret as being due to some
physical interference of the fat bulk with calcium absorption.

Bauer and Marble (1932), Snell (1932), and Wampler and Forbes (1933) have all confirmed Linder and Harris' (1930) findings that irradiated ergosterol greatly increases the absorption of calcium in non-tropical sprue. The independent observations of Parsons (1928) is even stronger confirmation of the hypovitaminosis D concept of the calcium deficiency. He showed that celiac rickets can be completely cured, irrespective of the fat intake, by ultra-violet light irradiation and/or the administration of irradiated cholesterol or ergosterol.

Aub et al. (1932) from a study of one case of non-tropical sprue thought that a decreased acidity of the gastric contents was a factor in the decreased calcium absorption. Macrae and Morris (1931) reached a similar conclusion; they gave acid sodium phosphate by mouth, in celiac disease, and reported increased calcium retention. Telfer's studies on calcium and phosphorus metabolism (1923, 1924) lends some support to this possibility. He pointed out that:

(1) The absorption of calcium is initially dependent upon the free acid of the gastric juice, which plays an important part in affecting the solubility of calcium salts in the diet;
(2) Absorption is normally restricted by the alkaline reaction of the intestinal secretions, which tend to neutralize and so cause precipitation of the lime in solution as insoluble phosphate; and

(3) The free absorption of calcium is probably limited chiefly to a comparatively small portion of the upper part of the intestinal tract while still in acid solution.

The possibility of gastric hypoacidity or anacidity influencing calcium absorption in idiopathic steatorrhea cannot be ruled out; but the strong support of the hypovitaminosis D concept, together with the occurrence of calcium deficiency in non-tropical sprue with normal gastric chlorhydria is evidence enough to minimize the role of hypoacidity in the production of calcium malabsorption. This point was effectively demonstrated by Bauer and Marble (1932). They experimented on a patient with non-tropical sprue, who had a serum calcium of 4.5 mgm. per cent, phosphorus of 1.5±2.0 mgm. per cent, osteomalacia, and achlorhydria, and who showed a high calcium and phosphorus excretion. The fat intake was restricted with no effect on the absorption of calcium and phosphorus. Then dilute hydrochloric acid was also started, and increased slightly the calcium and phosphorus absorption, but had no effect on the steatorrhea. Then irradiated ergosterol in
small doses was added, and the calcium and phosphorus absorption increased greatly. Finally the hydrochloric acid was stopped, with no effect noticeable.

Summarizing the pathogenesis of the calcium disturbances in non-tropical sprue, we may say that it is essentially a mal-absorption due to hypovitaminosis D, which is produced by the excessive loss of vitamin D-containing sterols along with the other fats in the steatorrhea; and that minor factors which may enter into the pathogenesis are:

(1) Calcium lost as soaps, by union with the excessive amounts of fatty acid;
(2) Some interference with calcium absorption by the physical bulk of the unabsorbed fats; and
(3) Decreased acidity of the gastric contents.

In idiopathic steatorrhea the low serum calcium, when present, is accompanied by a low serum phosphorus content. In two cases of non-tropical sprue with tetany, reported by Bauer and Marble, they found a calcium of 6.7 mgm. per cent with a phosphorus of 1.86 mgm. percent in one (1931), and a calcium of 4.5 mgm. per cent with a phosphorus of 1.8 mgm. per cent in the other (1932). Findings of all other investigators have been similar. As previously stated, Hunter (1930) and Aub et al. (1932) stress the concomitant lowering of the calcium and phosphorus values in differentiating this disturbance from parathyroid disturbance.
However, the mode of loss of the phosphorus appears to differ in individual cases. Thus McCrudden and Fales (1912) found the phosphate in the stool to be three times the amount of the phosphate in the urine in a case of celiac disease, reversing the ratio they found in a normal control. And, on the other hand, Aub et al. (1932) reported in their case a high urinary phosphorus excretion, and hence a high partition of phosphorus in the urine as compared with the feces. Macrae and Morris (1931) and Linder and Harris (1930) both state that the fecal phosphorus value is high, the urinary value low. Bauer and Marble found conflicting conditions in their two cases mentioned above (1931, 1932). In one the phosphorus in the stool was low, in the urine was high; while in the other, the fecal output of phosphorus approximated the intake, and the urinary value was extremely low.

In searching for an explanation for these apparent contradictions, the work of Telfer (1922) probably offers the strongest possibility. He reports that the excretion of calcium, phosphorus, and the fatty derivatives are inter-dependent, calcium being eliminated chiefly as the phosphate and to a lesser extent as insoluble soaps. Normally forty per cent of the total phosphorus excreted appears in the urine, sixty per cent in the feces. With acid formation in the intestine, less phosphorus is excreted by the feces, more by the urine. It was found that the degree of deviation of phosphorus to the urine was roughly proportional
to the amount of fatty acids in the feces, and consequently
to the extent to which fatty acids had displaced phosphate
from its normal combination with calcium in the intestine.
An excess of calcium salts restricts an increased quantity
of phosphorus to the intestine, and if the fat and phos-
phorus intake is low, excess calcium in the diet will decrease
the urinary phosphorus. Telfer's (1922) studies show that
phosphorus excretion is dependent on various factors,
deviation of which can account for the apparently contra-
dictory findings reported in idiopathic steatorrhea. He
also offers a reason (1924) for the low serum phosphorus
accompanying a low calcium, stating that the fixation of
phosphorus in the skeleton is dependent on that of calcium,
and he found that in a diet unbalanced with regard to the
mineral elements, the absorption of an excess of phosphorus
is followed by excretion in the urine. This factor, to-
gether with the excess fecal excretion as calcium phosphate
due to reasons already summarized, adequately explains the
low phosphorus values.

Given the calcium and phosphorus deficiency in
non-tropical sprue, and having explained its pathogenesis,
a discussion of the mode of production of its symptoms -
tetany, rickets, osteoporosis, and bony deformities - appears
not to be essential to a paper of this scope, and is,
therefore, omitted.
SYMPTOMS AND FINDINGS: THEIR PATHOGENESIS

III ANEMIA

Probably the next commonest secondary symptom in non-tropical sprue is anemia. Gee (1888) noted that "Cachexia, a fault of sanguification, betokened by pallor and a tendency to dropsy, is a constant symptom." All three of Blumgart's (1933) patients had moderately severe anemias. Bennett, Hunter, and Vaughan (1932) described in detail fifteen cases of non tropical sprue, and Vaughan (1935) added seven cases seen since the earlier publication to the series. Of these twenty-two cases, anemia was found in fifteen. Thayaen (1935) reported finding anemias in thirty-five cases in forty-five patients with non-tropical sprue.

There are three types of anemia seen in idio-pathic steatorrhea. The two common types are:
(1) Macrocytic hyperchromic anemia, and
(2) Hypochromic anemia.

The third type is:
(3) Erythroblastic anemia, of which type only two cases have been reported, both by Bennett Hunter and Vaughan (1932).

Different figures are given by different observers for the relative frequency of the two commoner types of anemia. Vaughan (1935) states that of the fifteen cases of
anemia in her group of twenty-two patients with non-tropical sprue, nine showed a hypochromic type, four were of a macrocytic hyperchromic type, and two had an erythroblastic anemia. In her opinion, then, the hypochromic anemia is the commonest. Vaughan (1935) also quotes several references, who have similarly found the hypochromic type of anemia in idiopathic steatorrhea, but on examination, the bulk of these references are on observations from celiac disease.

Thaysen (1935), on the other hand, recognizes and admits that the anemias of celiac disease are almost always hypochromic, but insists that the hyperchromic type is by far the commoner in non-tropical sprue. His accumulated statistics show that among forty-five cases of non-tropical sprue, thirty patients, or almost 70 per cent, had hyperchromic anemias. Blumgart's three cases (1923) all showed moderately severe anemias of the hyperchromic type, with a color index well over one in each case. Holmes and Starr (1939) reported five cases of non-tropical sprue, four of which had anemias, all macrocytic in type. Summarizing fifteen cases of non-tropical sprue seen at the Mayo Clinic, Snell, Camp, and Watkins (1935) state that the anemia in most of the cases was macrocytic.

Apparently, then, the anemia of non-tropical sprue may be either macrocytic or hypochromic in type, with the former probably predominating. Mackie's (1933) findings may explain the variability of the reported statistics. He
stated: "In its earliest phases the anemia is of the simple hypochromic type, subsequently becoming hyperchromic and megalocytic. In the majority of instances the color index is unity or above at the time the patient first comes under observation, and may vary from time to time in the same individual." One case of his, especially, illustrated the variability of the anemia. This patient had a hyperchromic anemia of moderate degree. Liver extract by mouth had no effect; then, when given intravenously, the anemia cleared up nicely. Soon afterwards, however, it ceased improving and became worse instead, even though liver was still being given; but now it was hypochromic in type. Iron was substituted for the liver and the anemia responded beautifully. Thaysen (1935) also recorded a similar alternation of the anemia from the hypo- to a hyper-chromic type, or vice versa, in ten among thirty-two cases.

Description of the blood picture follows:

(1) Hypochromic anemia. Patients in this group may have either a normal red cell count and reduced hemoglobin or both elements may be reduced. The outstanding feature in this group is the marked anisocytosis and variability in the density of red cell staining. Some cells appear well filled with hemoglobin and some look like mere rings. A Price-Jones curve on seven of Vaughan's (1935) patients showed the variability, which is a measure of the degree of anisocytosis, to vary from 7.318 per cent to 15.9 per
cent, with an average of 11.57 per cent, which is well above the upper limit of normal 7.38 per cent. In the majority of her cases definite megalocytosis was also present. In a case of idiopathic steatorrhea reported by Bowen-Davies (1934), with blood studies by Price-Jones, a severe anemia was recorded, characterized by megalocytosis and hypochromia, with the net result being a low color index.

(3) Macrocytic Hyperchromic Anemia. The hyperchromic anemias of tropical and non-tropical sprue are apparently indistinguishable from each other, but differ from true Addisonian pernicious anemia. Bennett, Hunter, and Vaughan (1932) differentiate them on the following points: In pernicious anemia poikilocytosis is invariable, the indirect van den Bergh is usually positive, and free hydrochloric acid is never found in the gastric juice. In the sprues, on the other hand, poikilocytosis is rare, the indirect van den Bergh is usually negative, and free hydrochloric acid can almost always be demonstrated in the gastric juice. Ashford (1930) further differentiated the macrocytic anemias of sprue as being "hypoplastic" - meaning that there is no well defined reticulocyte rise on liver therapy - as opposed to pernicious anemia, which he calls "dysplastic". However, Porter and Rucker (1930) describe marked reticulocyte responses in non-tropical sprue, and Castle and Rhoads (1932) report similar reticulocyte
crises in sprue.

(3) **Erythroblastic Anemia.** This type has been reported in only two cases of non-tropical sprue, both in Bennett, Hunter, and Vaughan's (1933) series. Both patients had a severe hypochromic anemia showing great anisocytosis, both macrocytes and microcytes being present in the stained film. The nucleated red blood cell count varied between 182 and 384 per one hundred white cells counted, the majority having small pyknotic nuclei.

(4) **White Cell Count.** Bennett, Hunter, and Vaughan (1933) report that a slight leucopenia or normal white count is usually found, showing no significant variation in the differential cell count or appreciable shift in the Arneth count. A leucocytosis occurs only in intercurrent infections. Thaysen (1935) believes that a relative lymphocytosis is common in idiopathic steatorrhea. In only one case has a severe leucopenia been recorded - in Bowen-Davies' (1934) case previously referred to, with the macrocytic hypochromic anemia. This patient had only 800 white cells per cubic millimeter when he presented for treatment. Nucleotide K96, found to be of value in agranulocytic angina, had no effect here, but parenteral liver therapy brought about an almost miraculous rise in the leucocytes as well as the other blood elements.

The pathogenesis of the anemia in idiopathic steatorrhea, although not fully understood as yet, is
fairly well on the way to solution. Obviously, the variability of the blood picture points to a double deficiency, which may co-exist or be present singly. The hypochromia is undoubtedly due to an insufficiency of iron, as witness the therapeutic effect of large doses of iron in this type of anemia. However, no work on the iron metabolism in idiopathic steatorrhea has ever been reported; so the mode of loss is not known. Neale, Smallwood, and Shippam (1935) think that the absorption of iron goes hand in hand with that of fat and calcium, and the anemia tends to disappear with improved fat absorption. Yet, on the other hand, deficiency of iron may be evident many years after the cessation of the steatorrhea and the stabilization of the calcium metabolism, and conversely normal absorption of iron may occur in the presence of steatorrhea and calcium starvation.

In the hyperchromic anemias of sprue Castle and Rhodes (1932) found that liver extract always produced improvement, and Porter and Rucker (1930) reported similar results in non-tropical sprue. The former (1932) postulated three possible mechanisms or combinations of them which may be involved in the production of the "conditioned deficiency". These are:

(1) Lack of the extrinsic factor in the diet.
(2) Lack of the intrinsic factor in the gastric juice.
(3) Difficulty in absorption by the gastro-intestinal tract.
of the hematopoietic substances which are the products of
the interaction between the extrinsic and intrinsic factor.

Their first possibility - lack of the extrinsic
factor in the diet - must be minimized because it is so
seldom found in non-tropical sprue. Their second possibil-
ity - lack of the intrinsic factor in the gastric juice -
is also minimized by the reported (Vaughan 1933) excellent
therapeutic results of marmite in the macrocytic anemias of
idiopathic steatorrhea. Marmite, which is a rich source of
Castle's extrinsic factor, must be predigested with normal
gastric juice to be effective in pernicious anemia, whereas
there is a definite lack of the intrinsic factor, but in
idiopathic steatorrhea it has a definite hematopoietic
effect without predigestion. Their third possibility -
difficulty in absorption - is the most probable. This is
supported by the finding that it requires massive doses of
marmite or liver extract by mouth to affect the anemia.

Snell (1935) especially approves of this concept, reporting
that substances which produce a remission in pernicious
anemia act slowly or not at all when given by mouth in non-
tropical sprue, whereas parenteral injection of an active
fraction will result in rapid and complete remission.

As was the conclusion in discussing the patho-
genesis of the steatorrhea, the reason for the malabsorp-
tion is not known. Probably when the one is discovered,
the other will also be understood. There are still questions
in relation to the anemia, as yet unanswered, whose solution must depend upon further data. For example, why do some cases with the most marked steatorrhea show no anemia - Ashford (1930) says that in not more than half of his cases was there any considerable anemia, and that several fatal cases had practically no anemia - while in other cases the steatorrhea is apparently so minor a symptom that it is overlooked as the attention is focused on the anemia - Thaysen (1935) reports such cases. Then, too, noting the great variability of the anemia in adults, why is it that in children, that is, in celiac disease, it is almost invariably hypochromic and microcytic in type (Neale, Smallwood, and Shippam 1935). And why, in the same patient should the anemia shift from an iron deficiency type to a liver deficiency type spontaneously (Mackie 1933); granting that the loss of one factor produces one type and the loss of another factor the other type, what controls the relative amounts of loss of the two factors, and makes it shift with the stage of the disease?
Thaysen (1939) was the first to point out the low blood sugar curve in non-tropical sprue. He stated that only 5 per cent of normal people show a rise of less than 40 mgm. per cent in the glyceric curve when determined by the method of Hagedorn and Norman-Jensen, while a very large percentage of patients with idiopathic steatorrhea show a maximal rise of less than 40 mgm. per cent. His observations have since been amply confirmed, especially by MacLean and Sullivan (1939) and Macrae and Morris (1931) on celiac disease, and by Bennett, Hunter, and Vaughan (1932) on non-tropical sprue. In a later publication Thaysen (1935) asserts that the low blood sugar curve is found with equal frequency in non-tropical sprue, celiac disease, and sprue. According to the same observer (1934) neither pancreatic steatorrhea nor steatorrhea in intestinal amyloidosis or tuberculosis is accompanied by a low blood sugar curve. Macrae and Morris (1931) similarly believe that the flat glyceric curve is pathognomonic of the active celiac disease, finding that the curves in six cases of non-celiac steatorrhea were normal in height. Bennett (1934) also has found the flat sugar curve in non-tropical sprue, celiac disease, and sprue, but
not in steatorrhea from other causes or in severe diarrhoea.

The pathogenesis of this low blood sugar curve in idiopathic steatorrhea has been, and is even now being, hotly disputed. There are three definite possibilities which must be considered in this regard:

1. Low renal threshold for sugar.
2. Poor absorption of sugar from the intestine.
3. Abnormally fast removal of sugar from the blood stream.

The first possibility - low renal threshold - is immediately ruled out by the work of MacLean and Sullivan (1929). They found flat dextrose tolerance curves in all fourteen cases of celiac disease studied by them, and in every case, simultaneous urinalysis showed no glycosuria. Loss of sugar through the kidney, therefore, cannot account for the low curve.

We are left then, with the possibilities of poor absorption and fast removal - and both have their hearty advocates. Thaysen is an especially strong proponent of the latter, in support of which he has performed some very clever experiments (1929). To evade the influence of lowered absorption or of a destruction of dextrose in the intestine, he gave intravenous injections of twenty grams of dextrose to six patients with idiopathic steatorrhea. Compared to forty-five normal people under similar conditions, three of the six curves were definitely abnormally low and fell rapidly to the fasting level. It is obvious
that poor absorption was not a factor in producing these low curves, and Thaysen (1929) postulated that the same forces which produced the low curves on intravenous administration of dextrose should be responsible for the flat curve on oral administration. Then he also ran fifteen respiratory quotients determinations on eight patients, who were given seventy grams of dextrose in 700 c.c. of water after twelve hours of fasting, and found that the respiratory quotient rose, as in normal persons, to or nearly to the straight quotient of carbohydrate oxidation forty-five minutes after ingestion - the average of the fifteen being 0.953. His conclusion from this finding is that the rise of the respiratory quotient towards that of straight carbohydrate metabolism proves that the ingested dextrose must have been absorbed.

Macrae and Morris (1931) do not consider Thaysen's arguments very convincing. They criticize his reports on the low curve following intravenous administration of dextrose, claiming that he did not consider the effect of change of blood volume in that experiment. They, themselves, however, overlook the fact that his results were controlled by similar experiments on forty-five normal people. Those curves which he labelled low, were low only in comparison to the curves of the normals under similar conditions. The effects of intravenous administration of glucose on the blood volume is thus automatically nullified. Then also,
although not denying Thaysen’s findings on the respiratory quotient, Macrae and Morris (1931) differ on their interpretation of its significance. They admit that glucose absorption does take place, but postulate that there is a delay in absorption. Against this view is the fact that over half of the flat blood sugar curves fall to the fasting level or even lower in normal time, about two hours after the ingestion of glucose, as shown clearly by the curves in their own series. One argument of Macrae and Morris (1931) however, in support of the malabsorption concept of the low glycemic curve has not been adequately answered. They note that in the steatorrhea due to tuberculous peritonitis with obstruction of the lacteals the glucose tolerance curve is normal; and reason that only the absorption pathway for lipoids is affected, allowing normal absorption of the blood-borne foodsstuffs. On the other hand, they argue that in idiopathic steatorrhea, where the intestinal epithelium or its immediate environment is at fault, there is concomitant malabsorption of fats and carbohydrates. Since the pathogenesis of the fat malabsorption is not yet understood, any argument linking the flat sugar curve with it does not carry too great a conviction. Furthermore, admitting that fat is the most difficultly absorbed of the foodsstuffs, then it is hardly understandable why glucose, which is the most easily absorbable, should in this syndrome be poorly absorbed, while protein absorption is little
if at all affected.

Thaysen (1935) seems to have all the best of this argument, with his postulate that the flat glycemic curve of idiopathic steatorrhea is due not to impaired absorption but to an increased rate of removal from the bloodstream. However, his theory as to the cause of the increased removal is rather hazardous, and he admits that there is no proof, but theorizes that "probably it is due to some toxic effect on the endocrine glands which regulate the blood sugar content." (Thaysen 1929).

MacLean and Sullivan (1929) are similarly of the opinion that the flat curve does not necessarily signify poor absorption. In one instance they gave galactose instead of glucose, and although the blood sugar curve showed no rise, the urinal showed a four plus sugar content. Their conclusion was that adequate absorption could occur without evidencing a change in the glycemic level, provided that removal occurred equally as fast. Furthermore, they also found flatter than normal curves on intravenous administration of dextrose. Theorizing the possibility of an endocrine dyscrasia, their guess as to the actual reason for the rapid removal of the glucose from the bloodstream is as vague as Thaysen's.

Recently, Himsworth (1934) suggested an explanation that need not involve the assumption that there is any derangement of carbohydrate metabolism. In a non-diabetic subject the sugar tolerance curve is strongly influenced
by the diet which the patient is taking. If fifty grams of glucose are given to a healthy fasting subject who has been living on a diet composed almost exclusively of fat, the resulting blood sugar curve will be indistinguishable from that of a mild diabetes mellitus. If the same test is repeated on the same subject, but when he has been taking a diet composed solely of carbohydrates, the blood sugar curve then will be of the flat type. Himsworth (1934) postulates that from the point of view of the food absorbed, a patient with steatorrhea is comparable to the subject taking a carbohydrate diet, and such a diet results in a flat glucose tolerance curve. Such an explanation is very attractive; the serious objection, however, comes from the strong assertions that a flat glycoemic curve is not seen in any of the other types of steatorrhea (Macrae and Norris 1931, Bennett 1934, Thaysen 1935). If Himsworth's (1934) argument applies to one, it should apparently apply to the other. For the present this is one more of the problems which must be left unsolved.

Summarizing, a flat glucose tolerance curve is very commonly found in non-tropical sprue; it is probably due not to malabsorption of sugar from the intestine, but rather to rapid removal from the blood stream; the reason for the increased removal rate is unknown.

Although not found in the literature on non-tropical sprue, it might be of interest to mention here
that in the literature on celiac disease there are some clinicians who have concentrated strongly on the carbohydrate aspect of the disease. Notable among these are Howland (1931) who suggested renaming it "carbohydrate intolerance" and originated the protein milk treatment, and Hana (1932) who stated that the chief fault is in absorption and utilization of carbohydrates, and who is the most ardent advocate of the banana diet. Such opinions have no cognizance at all in non-tropical sprue, and have no support in celiac disease, either, among scientific investigators.
SYMPTOMS AND FINDINGS: THEIR PATHOGENESIS

V DISTURBANCES IN GROWTH

Infantilism, emaciation, and dwarfism were early recognized as being very common concomitants of idiopathic steatorrhea, especially in the untreated cases. In the first description of the "coeliac affection", Gee (1888) states: "While the disease is active, children cease to grow; even when it tends slowly to recovery, they are left frail and stunted." The disturbances in growth were such prominent features in Herter's (1908) cases that he named the condition "intestinal infantilism". Miller (1920) also recognized the frequency of these findings, and combining the terminology of Gee and Herter, called the condition "coeliac infantilism". Findlay and Sharpe's (1920) patient, who was fifty-two years of age at the time she was reported, had had celiac disease in early life and was definitely stunted, having never weighed more than eighty-four pounds. Of Bennett, Hunter, and Vaughan's (1932) series of fifteen cases of non-tropical sprue, ten patients were dwarfed, but the infantilism of stature was not necessarily associated with mental or sexual infantilism. The dwarfism was in one case associated with failure of development of primary and secondary sex characters without impairment of intelligence. Most of the cases in this series gave histories of long-
standing diarrheas in childhood; the inference being that in these patients the disease, although unrecognized, was present at that time. Thaysen (1935) points this out in emphasizing the greater frequency of infantilism in Bennett, Hunter, and Vaughan's (1932) adult cases of idiopathic steatorrhea than in his own or other series'. Obviously, cases beginning before maturity have a much greater opportunity for growth changes than cases which have begun in adult life. In a survey of clinically cured cases of celiac disease, Neale, Smallwood, and Shippam (1935) confirm the observations on stunting, showing that a fairly well balanced ratio of height to weight is usual for the patient who reaches the phase of established recovery, but the average height reached is under normal.

Emaciation is almost invariable in the active stages, and its explanation is obvious. This "starvation in the presence of plenty" is due, as simply stated by Herter (1908), to "the imperfect absorption of nutritive material". The caloric loss due to unabsorbed fat from an average diet in a patient with non-tropical sprue is sufficient to produce increased protein catabolism; and when a diarrhea is superimposed, the extreme weight loss is not at all surprising.

There is not this unanimity in explaining the pathogenesis of the failure of skeletal growth. Herter (1908) stated: "The amount of calcium lost by the feces as scapes
of calcium was sufficient to have furnished a fair skeletal growth had these calcium soaps been absorbed instead of lost. It is a practical certainty that the loss of calcium and magnesium through the feces is the explanation of the impaired skeletal growth in intestinal infantilism." Miller (1936) postulated that the stunting of growth was a toxic effect, but his suggestion is entirely empirical. Wampler and Forbes (1933) reported a case of celiac disease of eight years duration which they began to treat with liberal doses of vitamin D and a substantial increase in the calcium intake; and in one month changed a very poorly positive calcium and phosphorus balance to a strongly positive balance. Radiograms taken seven weeks after good retention showed heavier shadows throughout the long bones, healing of some fractures, and some progress toward healing of other spontaneous fractures ununited for several years; but there was no improvement in growth. Wampler and Forbes (1933) postulate, therefore, that some other factor must be sought as the cause of the underdevelopment. Their conclusion can be criticized on two grounds. First, seven weeks is not a long enough time on which to judge growth. And secondly, in as severe a case as described, they must consider the possibility that permanent damage to the growth centers had already occurred; and, whereas mild therapy would have relieved the condition early, even heroic measures might be of no avail late.

Undoubtedly, the retardation of skeletal growth
is due to disturbance of the calcium metabolism in part, but Herter's (1938) concept is not strictly correct. It has been shown in the discussion on calcium metabolism that the calcium lost as scabs is not nearly enough to account for the deficiency.

Parsons (1938) gives the best explanation for the skeletal stunting in celiac disease. He considers that the bone changes are due to a combined vitamin D and calcium deficiency, similar to rickets, and that interference with the epiphyseal centers produces stunting of growth and infantilism. It is to be remembered, of course, that this feature is found in non-tropical sprue only when the steatorrhea had its inception before maturity, that is, before bone growth was complete. If the steatorrhea began in adult life, the calcium and vitamin D disturbances of the skeletal system are manifested as osteoporosis, osteomalacia, and bony deformities, as described in a previous section.
SYMPTOMS AND FINDINGS: THEIR PATHOGENESIS

VI GASTRO-INTESTINAL PHENOMENA

A. GLOSSITIS

Herter (1908) first described glossitis in his cases of "intestinal infantilism". His description follows: "The tongue is apt to be somewhat more red than normal, and the papillae swollen...The tongue is at times slightly swollen and on its edges marked by impressions of the teeth."

Blumgart (1923) reported finding evidence of glossitis in two of his three cases of non-tropical sprue. The finding of glossitis has been observed so frequently (Holmes and Starr 1929, Porter and Rucker 1930, Marble and Bauer 1931, etc.) as to warrant the conclusion that it is more than coincidental in non-tropical sprue. Bennett, Hunter, and Vaughan (1933) described changes in the epithelium of the tongue in five of their fifteen cases, and Vaughan (1935) added three more out of the seven cases she saw between the time of the two publications. Thaysen (1935) tabulated a higher incidence, reporting the presence of glossitis in thirty-two out of forty-seven cases, that is about 70 per cent - a percentage comparable to that described in tropical sprue (Low 1927).

The incidence of mouth lesions in celiac disease, is, however, considerably lower than in both tropical and non-tropical sprue, the reason for this difference being at
present unexplained. As a matter of fact the pathogenesis of the glossitis itself is unknown. No constant relationship has been demonstrated between its presence and the presence of gastric achlorhydria (Bennett, Hunter, and Vaughan 1932). Analyzing the same series, one finds no constant relationship between its presence and the presence, type, or severity of the anemia. There is some evidence that the tongue symptoms in idiopathic steatorrhea are analogous to those in pernicious anemia - Porter and Rucker (1930) report striking improvement of the glossitis of non-tropical sprue on liver extract therapy, and Castle, Rhoads, et al. (1935) report similar results in a large series of sprue cases in Porto Rico. However, for the present, its pathogenesis must remain unexplained.

B. GASTRIC CHLORHYDRIA

Different observers have reported varying findings in regard to the hydrochloric acid content of the stomach in idiopathic steatorrhea. Achlorhydria was present in each of Blungart's (1923) two cases tested, and one of the four examined by Holmes and Starr (1928) showed an achlorhydria. Bennett, Hunter, and Vaughan (1932) report that achlorhydria was revealed in two of twelve of their patients.

These reports are especially difficult to evaluate because the authors do not specifically state whether or not they used histamine in attempting to elicit the hydro-
chloric acid. This point becomes important when one notes such communications as that of Snell, Camp, and Watkins (1935) who state that in all fifteen of their cases, free hydrochloric acid was found, sometimes requiring histamine, and that of Parsons (1931) who wrote: "A series of observations... showed that although sometimes achlorhydria was found, there was no achylia gastrica, since free hydrochloric acid could always be obtained with histamine."

Taylor (1922) found achlorhydria in each of five cases examined, but in two of that series free hydrochloric acid returned at a later stage in treatment. Ogilvie (1935) examined the gastric secretion of seventeen children with celiac disease. Of these, all showed free hydrochloric acid at some time or other; but three had no hydrochloric acid at some time, even under stimulation with histamine.

Summarizing all the reports, some hypochlorhydria is probably common in idiopathic steatorrhea, but a true, constant achylia gastrica such as found in pernicious anemia is not part of the picture here. The reason for the impaired secretion of free hydrochloric acid is not known. Its occurrence is apparently in no way related to the character of the anemia (Vaughan 1935).

C. DIARRHEA

Diarrhea is not an essential symptom in non-tropical sprue. In the fifteen cases forming Bennett, Hunter,
and Vaughan's (1932) series, there was a history of long-standing diarrhea in twelve, dating from early childhood in ten, and arising in recent years in one. However, in only five was diarrhea a recognizable clinical manifestation during the periods when the patients were under their observation. Thaysen (1935) agrees that patients with chronic idiopathic steatorrhea may or may not show diarrhea after they present themselves, but that a history of such can usually be elicited. The pathogenesis of the diarrhea is obvious — simply the irritating effect on the intestine of the unabsorbed fat by its mere bulk. The mechanism which causes cessation of the diarrhea will be discussed immediately below.

D. MEGACOLON

Langmead (1911) first emphasized the dilatation of the colon in idiopathic steatorrhea. He presented the cases of fourteen children with relapsing tetany, dilatation of the bowel, and abnormal stools, naming the syndrome "colonic tetany". It has since been commonly reported (Taylor 1922, Miller 1926, Holmes and Starr 1929, Linder and Harris 1930, etc.). It was present in nine out of twelve of Vaughan's (1935) cases in which examination of the colon was made by roentgenography after a barium enema. Four of five cases examined in the same way by Thaysen (1935) also showed dilatation of the large intestine.
The pathogenesis has never been satisfactorily proven. Bennett (1934) along with most other observers who have hazarded opinions, believes that the dilatation is probably due to the bulk of the fecal material and distention caused by gas formation. Thaysen (1935) noticed that characteristically there is a poorly marked sacular pattern of the colon, even of the sections showing no dilatation. This suggested to him that the primary cause of the dilatation of the colon might be a derangement of its innervation producing an atony of the bowel, and that it might be regarded as a lowered vagotonus induced possibly by some damage to the suprarenal glands. If such is the case, he believes that the excessive fecal bulk and gas formation could still be contributing causes. This, however, is no more than a theory, and actually no adequate explanation has been proven.

However, both Bennett, Hunter, and Vaughan (1933) and Thaysen (1935) have definitely established a relationship between the megacolon and diarrhea, showing that the presence of megacolon tends to check the diarrhea, an effect easily produced by bringing about longer retention of the fecal contents. Whether or not it is correct to interpret the dilatation of the colon as a protective mechanism which delays the evacuation of the feces and so checks the diarrhea, it is true of the majority of cases that diarrhea tends to become inconspicuous although chemical examination reveals
that the stools remain fatty.

E. ABDOMINAL DISTENTION

Although apparently not a gastro-intestinal phenomenon, it is included in this category because it is at least partly due to such phenomena.

It has been a fairly common finding in idiopathic steatorrhea. Gee (1883) said: "The belly is mostly soft doughy and inelastic, sometimes distended and rather tight." Herter (1908) includes marked abdominal distention as one of the six cardinal symptoms in his "intestinal infantilism". He suggested that this was due to distention of the colon and small intestine with gas, and after a time partial paralysis of the gut sets in. Miller (1921) thought that distention of the bowel with flatus and feces and an atonic condition of the abdominal wall contributed to the abdominal enlargement, but did not entirely account for it. He thought that this effect was largely due to copious deposits of fat in the omentum, which he found in one autopsy. But this view has little support, and the prevalent view is, as stated by Parsons (1931) that the abdominal distention is due to flatulent distention of the intestine, particularly the colon, associated with hypotonia of the abdominal wall.
No strong evidence of serious derangement of nitrogen metabolism has ever been produced in the study of idiopathic steatorrhea. Herter (1908) wrote that "Protein absorption is relatively much better than the absorption of fat, despite the fact that it is somewhat impaired." McCrudden and Fales (1912) published complete balance studies on two patients with celiac disease. In one the nitrogen in the stool was slightly above normal, and the other showed a high fecal nitrogen but a correspondingly lower urinary value; so both cases showed a normal nitrogen retention. Macrae and Morris (1931) reported that: "The nitrogen percentage of the dried feces seems to be quite within normal limits, so that any excess in nitrogen loss must be the result of the great fecal weight." A very important point was brought out by Parsons (1932) when he stated: "Balance experiments depend on the condition of the stool; in diarrheal periods the absorption of nitrogen is poor, although not to the same extent as fat, but in non-diarrheal periods it is quite satisfactory." This was well illustrated in Anderson and Lyall's (1933) two patients, one diagnosed as idiopathic steatorrhea, the other as pancreatogenic steatorrhea (confirmed at autopsy). When they were placed on a
high fat diet, both had diarrhea with high amounts of fecal nitrogen. When the diet was changed to a low fat content, the idiopathic steatorrhea decreased his diarrhea and concomitantly decreased his nitrogen loss to normal figures. The high azotemia continued in the other patient, however. Thaysen (1935) heartily agrees with this report, and emphasizes that a normal or only slightly raised nitrogen loss in the feces is a very important diagnostic finding, especially in differentiation from a pancreatogenic steatorrhea. Weir and Adams (1935) studied a case of non-tropical sprue, with special reference to utilization of nitrogen and fat, again confirming the statement that when the fat loss is kept low, nitrogen loss is not excessive. When diarrhea is marked and prolonged, however, protein deficiency can occur, and with it, of course, emaciation, low serum protein, and edema.

In summary, there is no essential derangement of nitrogen metabolism in non-tropical sprue.
VIII HYPOVITAMINOSIS

Obviously, a hypovitaminosis of the fat soluble vitamins is a logical symptom to expect in chronic steatorrhea. The common occurrence of hypovitaminosis D has been established and well discussed in the section on calcium and phosphorus metabolism. However, the rarity of vitamin A deficiency symptoms contrasts noticeably with the extreme frequency of vitamin D deficiency. Fanconi (1928) observed xerophthalmia in celiac disease; Schick (Haas 1929) reported one case of xerophthalmia he had seen; a case of night blindness and xerosis conjunctivae occurring in a boy with celiac disease was described by Riddell (1933), in which recovery occurred in ten days with the administration of vitamin A obtained from vegetable sources; and Thaysen (1934) reported a case of non-tropical sprue showing hemeralopia. Parsons (1932) offers a possible explanation for the paucity of hypovitaminosis A findings: "A possible explanation may be inferred from the results of feeding experiments on rats in which xerophthalmia has been found to develop on a diet defective in vitamin A and containing proteins of poor quality more rapidly than in one containing proteins of good value, because in celiac disease there is usually little fault to be found with the absorption of proteins."
The occurrence of abnormal pigmentation in chronic cases of idiopathic steatorrhea is a well-recognized observation. Constam and Partoh (1929) described the case of a woman of thirty-four, with tetany, osteomalacia, and diarrhea, who was probably suffering from non-tropical sprue. They described a skin condition consisting of symmetrical dry, red areas which had appeared in the regions of the wrists, elbows, knees, neck, shoulders, groins, and external genitalia and was diagnosed as pellagra. Bennett, Hunter, and Vaughan (1933) mention that skin lesions were noted in seven of their fifteen cases. Thaysen (1935) found it to be even more common, reporting that seven of the ten patients reported in that paper exhibited pigmented patches. In all cases the pigmentation showed a symmetrical distribution, was yellowish-brown in color, and was sharply defined from the normal skin. All seven stated that the patches of pigmentation were more pronounced during the bad periods of their disease and were less obvious during the good periods.

From its resemblance to pellagra, a vitamin B deficiency has been postulated as the cause of the pigmentation. In the case reported by Constam and Partoh (1929) the lesions disappeared when the patient was given a high vitamin diet. In one patient of Bennett, Hunter, and Vaughan's series (1933) the skin condition was so severe as to be the presenting symptom on admission to the hospital. The patient was given large doses of marmite, a very rich source of
vitamin B, because of her severe macrocytic anemia, and the pellagra-like eruption cleared up in three weeks. They conclude that the abnormal pigmentation seen in non-tropical sprue is probably an expression of vitamin B deficiency. Later, however, Vaughan (1935) mentions favorably Mackay's (1934) suggestion that a lack of vitamin A is more probably involved. This possibility is more remote for several reasons: The nature of the skin lesions are like pellagra, not like those of avitaminosis A; the rarity of eye lesions is hardly compatible with the frequency of skin lesions if vitamin A deficiency is postulated; and the therapeutic effect of vitamin B is apparently striking. Thaysen (1935) is of the opinion that the abnormal pigmentation is definitely due to hypovitaminosis B, and investigations by his associate, Vogt-Müller (1934) have shown that mice placed on a fat rich diet that produced steatorrhea require a considerable surplus of vitamin B₂ to prevent the development of pellagra-like symptoms.

Isolated reports of other hypovitaminosis symptoms can be found in the literature. Haas (1929) presented five cases of celiac disease complicated by symptoms of beriberi, in whom the response to the addition of vitamin B to the diet was prompt and striking. Two of the five patients of Holmes and Starr (1929) had acral paresthesia but no objective signs of combined sclerosis. Weir and Adams (1935) report definite neurological evidence of
sub-acute combined sclerosis in their case of non-tropical sprue. The neurological symptoms in all three of these cases showed marked improvement under liver extract therapy. Scurvy has been reported by Fanconi (1928).

In summary, definite hypovitaminosis D in idio-pathic steatorrhea is very common, hypovitaminosis B is rather common, hypovitaminosis A is apparently rare, and hypovitaminosis C, when found, is probably merely incidental.
IX. LESS COMMON SYMPTOMS

A. INCREASED BASAL METABOLIC RATE

Thaysen (1935) maintains that characteristically there is a slight elevation of the basal metabolic rate in non-tropical sprue, which he considers to be a remarkable finding in persons manifesting such marked wasting as found in these patients. His observations have been disregarded by other writers, neither confirmation nor denial being found in the literature.

B. HYPOTENSION

Thaysen (1935) also claims that hypotension, both systolic and diastolic, is characteristic of non-tropical sprue. This statement has elicited no more discussion than the one above.

C. CLUBBING OF THE FINGERS

Bennett, Hunter, and Vaughan (1938) described clubbing of the parrot-bill type in six of their fifteen cases. This observation, also, has been neither disputed nor confirmed.
D. LENTICULAR OPACITIES

Bennett, Hunter, and Vaughan (1932) reported finding lenticular opacities, resembling by slit lamp, those seen in postoperative tetany, in six of thirteen cases examined by them. Other references to such a condition have not been found, but its presence is not illogical, since in all six cases the serum calcium was low, as it is in postoperative tetany.
RELATIONSHIP BETWEEN NON-TROPICAL SPRUE, CELIAC DISEASE, AND SPRUE

Whether or not non-tropical sprue, celiac disease, and tropical sprue are all one and the same syndrome has been discussed pro and con by various observers; and at the present time there appears to be an alignment on one side headed by Bennett, Hunter, and Vaughan, who admit that celiac disease and non-tropical sprue are identical conditions in different age groups, but insist that tropical sprue, although similar, is definitely a separate entity; and opposed to them is a group, of whom Thaysen is the most vociferous, who maintain that all three are identical.

In his original description, Gee (1888) clearly included all three conditions in the "celiac affection". He wrote: "There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially apt to affect children...Sometimes from India Englishmen return sick with the celiac affection; rarely is it met with in adults who have never left our island."

Since that time, grave doubts have been cast by various writers upon the conclusion which Gee apparently took for granted. No serious objection has been made to uniting celiac disease with non-tropical sprue as a single entity; but many arguments have been raised that tropical sprue does not properly belong in the same category. Those
which require replies are:

(1) Celiac disease is rarely fatal; sprue carries a high mortality (Miller 1923-24).

(2) Shrinkage of the liver is a characteristic post-mortem finding in sprue; celiac disease usually shows a hypertrophy of the liver (Powell 1923-24).

(3) Age of onset is different; celiac disease is much commoner than non-tropical sprue, and even in the latter most cases can be traced back to childhood; while sprue is rarely found in childhood (Bennett, Hunter, and Vaughan 1932).

(4) The stools in tropical sprue are much more gaseous and foamy, the diarrhoea much more severe (Bennett, Hunter, and Vaughan 1932).

(5) Absolute achlorhydria is rather common in sprue; he has never been unable to find free hydrochloric acid in celiac disease (Parsons 1932).

(6) Macrocytic type of anemia is the commonest type found in sprue; in ninety-seven cases of celiac disease, he did not find one macrocytic anemia (Parsons 1932).

(7) Post-mortem examination in sprue shows an atrophic enteritis and a megaloblastic and aplastic condition of the red bone marrow; conditions not found in autopsies on celiac disease (Parsons 1932).

(8) Severe mouth lesions are very common and outstanding in sprue; rare in non-tropical sprue (Bennett 1934).

(9) Tetany, bone changes, and disturbances of calcium meta-
bolism, though they may occur, are rare in tropical sprue, but extremely common in non-tropical sprue (Vaughan 1935).

Each argument will be considered separately and answered, if possible.

(1) Miller (1923-24) claimed that celiac disease is rarely fatal, while sprue carried a high mortality. Yet he himself (1921) reported a fatal case of celiac disease, and reviewed autopsy reports previously reported in the literature. The mortality in celiac disease was estimated by Schaap (1926) at 13 per cent; by Halblutzel-Weber (1923) at 23 per cent. Thaysen (1929) stated that of twenty-three patients with non-tropical sprue five are known to have died. From tropical sprue Manson-Bahr (1924) reported seven deaths in forty-five patients. Miller's point is apparently overruled when these figures are compared.

(2) Powell (1923-24) made a point of difference in that shrinkage of the liver is commonly found in autopsies on tropical sprue. Antedating his objection by some years, Still (1918) writing of celiac disease said: "There is no enlargement of the liver. I have thought, indeed, that the reverse is rather a feature of the disease."

(3) Bennett, Hunter, and Vaughan (1938) placed great emphasis on the statement that tropical sprue is rarely seen in children, while the non-tropical idiopathic steatorrhea has its onset in the large majority of cases sometime in childhood. The difference, however, is not as
great as has been commonly believed. Cases of idiopathic steatorrhea in adults are being more frequently reported every year now, and Thaysen (1933), tabulating the series which he has reviewed, found that the disease commenced after the age of twenty-one in thirty-eight of forty-five cases of non-tropical sprue. And, on the other side, sprue is not unknown in children. In Ashford's (1935) series from Porto Rico of 720 cases of tropical sprue, there were eighty-seven patients — 12 per cent — under the age of ten years, and in 18 per cent more the disease had started between the ages of ten and twenty years. Manson-Bahr (1933) stated that "celiac disease is commonly found in European children brought up in the tropics," and that "I am convinced that sprue does not occur in children." How he differentiates the two is not known, but other observers would probably have diagnosed his "celiac" cases as sprue occurring in children. Still (1918) reported an interesting occurrence along similar lines. A child was born in India, where at the age of nine months she began to suffer with celiac disease, which she still had later when she came under his care; the child was a typical celiac case, and the mother was at the same time ill of sprue — so diagnosed by tropical specialists — also acquired in India. In his opinion (Still 1918) the two diseases are identical.

Evidently, then, the difference in age groups between tropical sprue and the non-tropical idiopathic
steatorrhea has been exaggerated, since both may occur at any age. However, even with a liberal allowance for this exaggeration, it is still a definite fact that the tropical sprue is commoner in adults while the non-tropical idio-pathic steatorrhea is commoner in children - in whom it is known as celiac disease. Whether or not this should hinder acceptance of the three conditions as a unity is a matter of personal judgement, with full knowledge of the actual facts in mind.

(4) The greater severity of the stool symptoms in tropical sprue is pointed out as an important point of differentiation by Bennett, Hunter, and Vaughan (1933). But in the same article they themselves point out that the gas formation and foamingness of the stool is not an essential part of the syndrome - it is due to decomposition of the carbohydrates by the intestinal flora. It is a common observation that diarrheal diseases are more common in the tropics; and in the temperate climates the incidence of diarrhea in the hot summer months is by far the greatest of the year. With these observations in mind, the greater frequency of foamy stools in tropical sprue is not a distinguishing point.

(5) Parsons (1933) maintained that he had never been unable to find free hydrochloric acid in the gastric juice of his patients with celiac disease, while in sprue an absolute achlorhydria is rather common. But he is refuted
by his own allies (Bennett, Hunter, and Vaughan 1932) who stated that gastric achlorhydria is a common, not a constant, finding in idiopathic steatorrhea, and its occurrence is practically in the same percentage of cases as in tropical sprue.

(6) Parsons (1932) says further that the macrocytic type of anemia, which is the commonest in sprue, is not seen in celiac disease. As pointed out in the discussion on anemia, however, a macrocytic anemia is also the commonest in non-tropical sprue, in a percentage comparable to that found in tropical sprue. And Parsons admits the unity of celiac disease and non-tropical sprue! The difference which he found is apparently to be interpreted as a difference in the method of reaction on the part of the juvenile and adult organism respectively (Thayseu 1935). Because, as a matter of fact, a macrocytic anemia from any cause is very rare in childhood.

(7) And Parsons's (1932) third point of differentiation is that post-mortem examination in sprue shows an atrophic enteritis, and a megaloblastic and aplastic condition of the bone marrow; conditions not found in autopsies on celiac disease. Taking the last up first, the condition of the bone marrow is simply the original, of which the blood picture is the image or indicator. In macrocytic anemias that type of bone marrow is to be expected; and the problem of the anemias has already been adequately discussed. Then,
regarding his statement on the presence of atrophic enteritis in sprue, we find in Tice's Medicine that "A study of ten cases that came to autopsy failed to reveal pathognomonic lesions." (Ashford 1923). Evidently, then, the morbid anatomical findings are no more definite in tropical sprue than in non-tropical sprue or in celiac disease.

(8) Bennett (1934) believes that more severe mouth lesions characterize tropical than non-tropical sprue. However, Thayseh (1935) has shown that the incidence of glossitis is no greater in the one than in the other; and the greater severity, if any, may be due to secondary infection, perhaps by the Monilia pseudisia, which Ashford (1933) has so frequently found.

(9) Lastly, we have Vaughan's (1935) objection, that disturbances in calcium metabolism, though they may occur are much less common in tropical than in non-tropical sprue. But, as shown in the discussion on the disordered calcium metabolism, the actual cause of these disturbances is a vitamin D deficiency. And as Parsons (1936) himself has pointed out that the calcium disturbances can be cured by ultra-violet irradiation, surely the solar radiation of the tropics should be a powerful influence in preventing the same disturbances from occurring there.

In summary, celiac disease and non-tropical sprue are one and the same entity, and the only valid difference between them and sprue is that the tropical disease tends
towards a greater frequency in adults and the non-tropical form in children. Weighing against this the fact that all the symptoms discussed in the previous section can be found in either the tropical or the non-tropical form, and that the outstanding features - steatorrhea, disorders of calcium metabolism, anemia, flat glucose tolerance curve, etc. - are common and, with the one exception, of equal frequency in both, the decision is that in all probability we should include in the category "idiopathic steatorrhea" the three conditions Thaysen (1936) had in mind when he first suggested the name - non-tropical sprue, celiac disease, and tropical sprue.
ETIOLOGY

Since the first description of the "celiac affection" theory upon theory has been devised, demolished, and revised and redemolished in an attempt to explain the etiology of the disease; and to date there is not one single theory which can be accepted as the logical and complete explanation.

Gee (1888) frankly admitted that he knew not the why of the "celiac affection", and ventured no guess. Gibbons (1889) thought it was some functional derangement of the liver; Cheadle (1903) interpreted the paleness of the stools as being due to absence of bile, renaming the disease "acholia", and attributing the etiology to some arrest of the chologenetic function of the liver. It was found later that the bile is normally secreted but that hydrobilirubin, which imparts the normal brown color to the stool, is reduced to the colorless form leuko-urobilin (Mackie 1933).

Bramwell (1902) presented a case of infantilism with fatty diarrhea and postulated that the syndrome was due to a pancreatic insufficiency, on the strength of improvement which he noted on feeding pancreatic extract. Still (1918) gives no credence whatsoever to this concept; laboratory investigations in his cases of celiac disease showed no pancreatic deficiency, the fat was normally split,
and treatment with pancreatic extract have completely failed. Bauer (1928) found bile, lipase, trypsin, and amylase all present in normal amounts, and with normal digestive powers. Parsons (1931) stated: "In every instance digestive enzymes were present in normal amounts in the gastric and pancreatic juice". Duodenal ferments were studied in a case of non-tropical sprue at the Mayo Clinic and normal values were found (Snell 1935). From these observations it is obvious that chronic idiopathic steatorrhea is not due to a pancreatic deficiency.

Rerter (1908) believed that his "intestinal infantilism" was essentially a chronic intestinal infection, in which the Gram-positive organisms, Bacillus bifidus and Bacillus infantilis replaced the normal Gram-negative flora, especially B. coli and B. lactis aerogenes. His findings, however, have never been adequately confirmed; Still (1918) reported that bacteriological study showed a preponderance of the B. coli group in the feces; Bauer (1928) made periodic stool examinations for two years on a child with celiac disease, and found the B. coli communis predominating, B. bifidus occasionally recovered — not necessarily coincident with exacerbation — and never B. infantilis. Sauer (1927) denied the infectious nature of celiac disease; he was unable to produce the disease in young Macacus rhesus monkeys by feeding experiments from a fatal case of celiac disease, and reported that none of Koch's postulates had
ever been fulfilled. Haas (1932) gives no credence to the possibility of transmissibility. Apparently, then, the possibility that idiopathic steatorrhea is due to a chronic intestinal infection has no adequate basis.

Observing the frequent occurrence of tetany in his cases of celiac disease, Langmead (1911) conjectured on the possibility of calcium leakage from the body due, perhaps to inefficiency of the parathyroids. Scott (1923) had a similar idea regarding the nature of sprue. He believed that the parathyroid glands had two functions: (1) Regulation of calcium metabolism, and (2) detoxication, especially of the poisons of intestinal origin. Then he theorized that wrong eating habits, especially excess fat in the food, led to excessive intoxication of intestinal origin so that the parathyroid detoxicating function becomes overburdened, with a resultant disorganization of its calcium regulating function. However, the disorders of calcium in idiopathic steatorrhea are definitely not of the parathyroid disturbance type (Aub et al. 1932); and it has been proven beyond a doubt that the primary disorder is malabsorption of fat with the calcium disturbances strictly secondary (Linder and Harris 1930, Bauer and Marble 1932, Bennett, Hunter, and Vaughan 1932, Snell 1935, Thaysen 1935).

Although unwilling to state so definitely, Miller (1920) believed that the fatty diarrhea might be due to a failure in the secretion of bile salts. He based this
belief on the results observed in feeding bile salts to three patients with celiac disease, which results, incidentally, were not at all clear cut. Making observations on the stool while feeding sodium acid phosphate and sodium glycocholate to celiac children, Macrae and Morris (1931) postulated that the etiology consisted of some changes in the physico-chemical constitution of the intestinal contents and probably included a shift of reaction to the alkaline side and a deficiency in the bile salts. This theory has no support from other observers. Examination of duodenal contents has always revealed normal values for biliary as well as for pancreatic constituents (Bauer 1928, Parsons 1931, Snell 1935); bile-salt therapy has failed to produce any significant results; and Parsons (1932), specifically testing this theory, found that the fat balance was not improved by the addition of deoxycholic or dehydroxycholic acids, and that the diffusion rates of the mixtures of bile and fatty acids were the same in a celiac case as in a normal child.

Ryle (1934) reported three cases of fatty stools from obstruction of the lacteals, and suggested that such a condition might be the cause of all cases of idiopathic steatorrhea. In answer to that we have many autopsy reports in which such obstruction could not be demonstrated, and Parsons (1931) went so far as to prove the patency of the lacteal system in one case by injecting methylene blue.
Moncrieff and Payne (1933) suggested that idiopathic steatorrhea is a primary disorder of fat metabolism, analogous to diabetes mellitus, associated with an increase of the fat in the blood and in the feces, where possibly it is being excreted. This idea has been fully discussed and the reasons for its rejection shown in the section on the pathogenesis of the steatorrhea.

Suggestions of lesser import have been recorded in regard to etiology from time to time. Thus, Haas (1932) believes there is a definite familial tendency in celiac disease. On the other hand, Parsons (1932) while admitting that celiac disease has been known in one and both of homologous twins, in sisters, and in cousins, could see no real evidence of any familial predisposition, nor have other observers mentioned it. Another suggestion was made by Einhorn (1933) who thought that celiac disease was caused by diets insufficient in nutritive material or vitamins or both. But it is well known that deficiency symptoms are the results of the primary symptom, steatorrhea; and neither Einhorn (1933) nor any other observer has shown how a deficient diet can cause a steatorrhea; furthermore, in the majority of the cases no deficiency in the intake of these patients can be found.

Castle, Rhoads, Lawson, and Payne (1935) carried out an intensive study on the etiology and treatment of sprue in Porto Rico, and after four years recorded their
observations and conclusions in detail. Their pertinent conclusions are as follows:

(1) "Involvement of the tongue and alimentary tract, the blood, and (rarely) the nervous system was observed in sprue, which thus selects the same systems of the body as does pernicious anemia. Although the characteristic frequency and intensity of the manifestations in these systems are typically different in the two diseases, the condition in certain patients with sprue was found to be indistinguishable clinically from that in patients with pernicious anemia."

(2) "The manifestations of the tongue and alimentary tract as well as the macrocytic anemia of sprue were invariably benefited by adequate doses of a liver extract given by parenteral injection and known to be effective in pernicious anemia."

(3) "Sources of the extrinsic factor...were effective alone in certain patients with sprue...The dietary history of many patients with sprue suggested a deficiency of certain sources of the extrinsic factor."

(4) "The usual absence of the intrinsic factor from the gastric contents of patients with pernicious anemia was paralleled in certain patients
with sprue. In other patients with sprue the intrinsic factor was present in the gastric contents."

(5) "Liver extracts administered orally, as in certain patients with pernicious anemia, were relatively ineffective in many patients with sprue, but on parenteral administration they favorably affected the formation of blood."

Their general conclusion is that sprue, like pernicious anemia, is a "conditioned deficiency" due to one or a combination of the following three mechanisms:

(1) Lack of the extrinsic factor.
(2) Lack of the intrinsic factor.
(3) Difficulty in absorption of the products of the interaction between the two from the intestinal tract.

Porter and Rucker (1929) reported two cases of non-tropical sprue, in both of which liver extract not only cleared up the macrocytic anemias, with strong reticulocyte responses, but also checked the severe diarrheal symptoms almost miraculously. Mackie (1932) described a case of non-tropical sprue in which a low fat diet and liver extract orally had no effect; but when the latter was shifted to the intravenous route, both the macrocytic anemia and the diarrhea cleared up; the anemia became hypochromic in type, so iron was started and liver stopped; then the diarrhea and sore tongue recurred and did not cease until the liver
extract was again given to the patient. These examples apparently uphold the contentions of Castle, Rhoads, et al. (1935). Weir and Adams (1935), on the other hand, could find no positive evidence that liver extract effected any change in the absorption of fat or protein in a patient of theirs.

The final answer on this concept of Castle, Rhoads, et al. (1935) cannot yet be given. Their observations are apparently clear cut and definite. But before accepting their ideas, there are some questions that loom large in the mind:

(1) If pernicious anemia and idiopathic steatorrhea are both due to deficiency of the same factors, why are the common manifestations so different? For example, how can one explain the fact that in a most severe case of steatorrhea, there may be no anemia?

(2) The most pertinent question is, what is the pathogenesis of the steatorrhea in this concept? The diarrheas seen in pernicious anemia are simple diarrheas. Since the deficiency embraces the same factors in both cases, why should pernicious anemia show a simple diarrhea, while sprue is primarily and invariably manifested by a steatorrhea?

Until these questions are answered we must withhold final judgement on the work of Castle, Rhoads, et al. (1935).

One other possibility which has been suggested (Snell
1935) is that non-tropical sprue may not be a specific entity, but may be produced by various diseases which seriously interfere with absorption from the upper portion of the intestinal tract; probably having in mind such cases as Fairley and Kilner's (1931) of the patient with a gastro-jejunocolic fistula simulating sprue, and Radl and Fallon's (1932) with extensive duodenal ulceration. Thaysen (1935), on the other hand, does not believe such cases are non-tropical sprue, and asserts that he can differentiate them by their characteristics. Furthermore, acceptance of the concept that non-tropical sprue is not a specific entity would give little aid in understanding the etiology; because aside from such cases quoted immediately above, the great mass of cases would still be of the "idiopathic" variety, whose etiology is and would still be unexplained.
TREATMENT

Speaking in generalities, treatment should be directed at the underlying etiological factors in any specific disease. In the case of non-tropical sprue, however, where the etiology is, as yet, unknown, the treatment must be entirely symptomatic; especially emphasizing the primary symptom from which springs many secondary disturbances, with the view in mind of preventing their occurrence, if possible, and removing them if present.

Therapy of the steatorrhea, then, becomes the central theme of our treatment, and this revolves, of course, upon a dietary regime. Since fat is poorly absorbed, the basis of the diet must be a low fat content; fortunately, the human organism can do very well with a minimal lipid intake; the only danger in such case being in the development of fat-soluble-vitamin deficiencies. As previously pointed out, however, only vitamin D deficiency is common in non-tropical sprue, hypovitaminosis A being very rare. Therefore the low fat diet should be supplemented with adequate doses of vitamin D, as the second therapeutic measure. This may be supplied by direct irradiation (Parsons 1938), or by oral administration of the vitamin in solid, non-fatty form (Hunter 1935). The carbohydrate content of the diet is preferably high - both for its caloric and its protein-sparing values. If, however,
carbohydrates produce a tendency to flatulence and fermentation, the amount must be decreased and the limit of tolerance found. Then, by gradual addition, the tolerance may be raised considerably; or one may find that certain forms are better tolerated than other — for example, it is claimed that the carbohydrates of the ripe banana are almost always tolerated without limit (Haas 1932).

With both the fat and the carbohydrate intake well controlled, there should then be no diarrhea, and protein absorption will be in no way impaired. Should diarrhea be present, the protein intake must obviously be high, to ensure absorption of an adequate amount; but it should be high, even if the movements are normal, in order to prevent destruction of body protein, which might easily result from the low fat intake.

The dietary measures enumerated above should adequately control the steatorrhea, the diarrhea, and the emaciation, and includes the main step in treatment of the calcium disorders, namely a high vitamin D supply. For the latter an adequate calcium intake is also necessary, but needs be especially high only if definite symptoms of calcium deficiency are present, in which case large doses of calcium lactate or gluconate should be administered. Parathormone is best not used except for the relief of acute tetany, because it merely supplies calcium to the rest of the body by withdrawal from the skeletal reserve.
(Snell 1932). Other hypovitaminosis symptoms should also be prevented and combated by a high vitamin diet, with especial attention being paid towards obtaining an adequate supply of vitamin B, a deficiency of which is the probable cause of most of the neuritic and dermatitic symptoms found in non-tropical sprue.

Treatment of the anemia is dependent on its type. The hypochromic and the erythroblastic anemias respond to large doses of iron; the macrocytic hyperchomic anemias respond well to the same hematopoietic stimulants which produce remissions in pernicious anemia, such as marmite and liver extract. Usually liver extract is much more effective when given parenterally than by oral administration. One must watch the anemia carefully during treatment for change from one type to the other, in which case the therapy is correspondingly changed.

Simply as a personal opinion, it appears at the present time, in view of the reports of Castle, Rhodes, et al. (1935) on the results of liver extract therapy in sprue, that one should at least try the use of liver extract in all cases of idiopathic steatorrhea to determine its value in controlling the gastro-intestinal phenomena - glossitis and diarrhea especially.

Summarizing the present day treatment of non-tropical sprue, it can be outlined as follows:

(1) Fat intake - restricted.
(2) Carbohydrate intake - high.

(3) Protein intake - high.

(4) Vitamin intake - high, with especial emphasis on vitamins D and E.

(5) Minerals -
   (a) Calcium and phosphorus - intake must be adequate; if there is deficiency, intake must be high.
   (b) Iron - large doses if hypochromic anemia is present.

(6) Miscellaneous -
   (a) Liver extract - for macrocytic anemia, and perhaps for glossitis and diarrhea. (This might prove to be the primary point in treatment.)
   (b) Parathormone - only as emergency measure in acute tetany.
   (c) Hydrochloric acid - if achlorhydria is present.
   (d) Other measures symptomatically as needed.
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