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Recent developments in celiac disease

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In 1889 Gee described a chronic nutritional disturbance of children and adults characterized by marked malnutrition, abdominal distention and diarrhea with large, pale, foul-smelling stools containing an excess of fat. A distinction was later made between the diseases in children (celiac disease) and adults (sprue). In 1932, Thaysen recognized these two conditions as an expression of the same disease at different ages.[40] There is still some difference of opinion among various authors as to whether the two are separate processes and should be differentiated, but in general American authors believe the diseases are the same and European authors believe they are entirely different entities. Idiopathic steatorrhea and non-tropical sprue are synonomous terms for the adult form of the disease. The malabsorption syndrome is a common term but includes other causes of malabsorption besides sprue.

Tropical sprue has in the past also been considered a different disease but more recently the consensus of opinion has been that it too is a variant of the non-tropical variety. A group at Mt. Sinai Hospital has recently reported on 23 patients with tropical sprue from Peurto Rico in their hospital during a 25 year period.[7] The majority reported symptoms before coming to the United States and the mean duration of symptoms prior to hospitalization was 2.3 years compared to 8.8 years in their non-tropical sprue patients. Glossitis, paresthesis, and severe anemias were more frequent and macrocytosis and leukocytosis were more common. The response to therapy was better and tetany, hemorrhagic tendencies, and clubbing were rare.

They also had evidence that asymptomatic tropical sprue patients may present objective signs such as malabsorption of carbohydrates and fats, steatorrhea, and x-ray abnormalities of the small bowel, such as has been observed in children with celiac disease and in non-tropical sprue, which they thought suggested that celiac disease, tropical sprue, and non-tropical sprue represented varying manifestations of the same basic disorder. They concluded that tropical sprue was a clinical variety of sprue and that there was a trigger mechanism of sprue in the tropics which might be an impaired nutritional state with multiple dietary inadequacies and an increased incidence of parasites.

Idiopathic celiac disease is characterized by mild chronic ill health, great loss of weight, flatulence, recurrent glossitis and stomatitis, intolerance to dietary fat, greater than normal requirement dietary protein, and in children, marked intolerance to dietary starch.[11,40] It is marked by progressive malnutrition, steatorrhea, hypoproteinuria, and the development of a deficiency state with multiple vitamin and mineral deficiencies, tetany, edema, osteoporosis, osteomalacia, and, at times, rickets may be present. In the fully developed clinical picture there is evidence of impaired fat and carbohydrate absorption and an increase in fecal fat and at times fecal starch. The fecal nitrogen is normal except during periods of acute diarrhea.[40] There is frequently an anemia, usually of a microcytic hypochromic variety in children, and a macrocytic hypochromic in adults. Gastric acidity may be reduced

in all ages and may even be absent in adults.[40] At Mt. Sinai Hospital, 94 patients with idiopathic sprue were studied from 1931 to 1956. The ages ranged from 16 to 73 when first seen and the most frequent symptoms were diarrhea in 94%, weakness in 88%, and weight loss in 84%. Other signs included glossitis in 53%, abdominal flatulence in 34%, emaciation in 65%, abdominal distention in 37%, dependent edema in 36%, an enlarged liver in 31%, and hypotension in 29%. However, the modes of clinical expression are variable. The clinical features in a given patient are determined largely by the inefficient absorption of substances whose supply may be further limited by poor diet, deficient body stores, or increased demands.[2] Thus, the clinical picture may closely resemble other better known disorders such as fibrocystic disease of the pancreas or pernicious anemia or is entirely non-specific. Laboratory tests must be resorted to for demonstration of intestinal malabsorption and definitive diagnosis is possible only by these procedures.

In the past the disease has been considered as either idiopathic steatorrhea with a defect in fat absorption or as a result of chronic infection. Now, with familial occurrence having been frequently reported, it is considered that there is a hereditary constitutional defect in metabolism, which becomes manifest after varied trigger mechanisms are set off.[40] The basic defect may manifest itself at different ages because of inherent differences in the severity of the disease or because of the occurrence of

appropriate trigger mechanisms. These are varied and may consist of emotional upsets, dietary deficiencies, pregnancy, fatigue, and acute tropical and non-tropical infections.[22] Allergy has frequently thought to have been the etiologic factor, but in many series the incidence of allergy was not significantly different than the general population.[40]

Since Dicke in Holland first established in 1950 the relationship between the development of symptoms of celiac disease and the feeding of wheat and rye gluten, much has appeared in the literature concerning this relationship. Dicke had noted that the elimination of wheat and rye from the diet of children having celiac disease was followed by a clinical remission and the addition of either wheat or rye resulted in relapse.[25]

Weijers and Van de Kamer confirmed this in 1953 by feeding experiments using a quantitative biochemical method in the form of a long-term fat balance to determine the appearance and disappearance of steatorrhea.[2] Six other workers independently confirmed the fact that gluten or the protein fraction of wheat flour was the deleterious agent causing symptoms and steatorrhea. Several groups have investigated the possible mechanisms by which gluten acts deleteriously. Some hypotheses have been suggested: 1. Allergic (patient sensitivity to wheat gluten), and 2. Enzyme (alteration in ability of patients to digest and absorb gluten).

Alvey, Anderson, and Freeman tested these hypotheses in 1957 by a series of experiments.[2] First, they discounted the allergy

theory by the observation that only an occasional patient reacted quickly to taking of wheat gluten with diarrhea and vomiting, and in the majority the symptoms appeared slowly and disappeared slowly when gluten was removed from the diet, and stated that this did not clinically resemble allergy. Also there was no asthma, eosinophilia of blood or family history of allergy and also intradermal skin tests were negative. In one experiment they obtained gastric and duodenal fluids and succus entericus by intubation from four celiac patients and allowed this to act on a 2% gluten substrate and the pH adjusted and then incubated. They found that gluten was digested and could not be precipitated by the addition of acetic acid. Digestion with enzymes from normal children produced the same results. They concluded that there was no gross difference in the primary digestion of gluten in normal children and children with celiac disease. In another experiment they tested the effect of the various fractions to different patients and studied the fat excretion in the stools continously during the period of feeding. First phospholipid was extracted and fed. There was no increase in fat excretion in one month but on subsequent feeding of the whole gluten from which the phospholipid was extracted the fat excretion rose within two weeks, showing that the toxic property was still present. Next gluten was digested with trypsin and fed to a patient with celiac disease. By chromatography this was shown to consist of a mixture of peptones and peptides. This caused a recurrence of steatorrhea, and then a recovery after its withdrawal. A dialysate

of this -- a fraction with smaller peptide molecules -- was fed to a patient. At the end of one month there was no increase in fat excretion. Therefore, they concluded complete hydrolysis of gluten removed its toxicity. Fractionation of the tryptic digest was performed by an alcohol concentration of 50 - 95% to isolate peptides. This produced a peptide containing a greater proportion of glutamic acid and proline than the other fractions. Upon feeding to a celiac patient, no increase in fecal fat was demonstrated.

These same workers also made a study of the blood amino acid and peptide pattern in three normal children and in three celiac children. Thirty grams of gluten was given and blood was drawn two hours later and studied by paper chromatography. No difference was noted either before or after acid hydrolysis of the two groups. Fasting blood glutamine levels were done in another experiment and there was no difference in normal children and celiac children. Two hours after a test dose of 700 mg/kg body weight given, there was a rise in blood glutamine in the celiac patients three times that of the controls.

Van de Kamer and Weijers in 1955 also made a study on the deleterious effect of gliadin.[36] They found that gliadin could be separated into various fractions by means of enzymes or chemicals, by which it is completely or partially broken down, or physiochemically, in which the protein as such remains intact. Their investigation focused on glutamine, which is present in gliadin in high proportion (43%). This was fed to two celiac patients in good

condition on a wheat free diet for six weeks. No reaction was found either clinically or chemically -- proving glutamine in the form of a free amino acid is not toxic (but possible that glutamine bound in protein does exert a harmful influence). Therefore, gliadin was treated by boiling it with 1NHCl for 45 minutes so that gliadin was decomposed by deamidation -- 90% dissociated into glutamine acid. This was given to two celiac patients who had shown toxic effects of a wheat diet in three separate periods. Both patients showed clinical improvement and a decrease in steatorrhea. The authors concluded gliadin becomes harmless for patients with celiac disease if it has been boiled with 1NHCl for a short time, which converts glutamine into glutamic acid, and therefore glutamine bound in gliadin, but not as a free amino acid, is probably the toxic factor.

Along the same line Frazer in 1956 also found the complete acid hydrolysate of wheat gluten was harmless and the product of its deamidation with a weak acid was also harmless.[16] He also found that peptic and tryptic digestion appeared normal in celiac children but wheat gluten in vitro subjected to peptic and tryptic digestion was still deleterious in celiac children. Then the enzyme hydrolysate was further fractionated and a water soluble peptide fraction was found to have the toxic properties of the original gluten. With further experimentation, he found that digestion of this with an extract of pigs intestinal mucous membrane caused a disappearance of the toxic effect. Therefore, he concluded the effect of gluten was not dependent on the presence of protein but

was brought about by a glutamine-containing peptide that could be digested by pig intestinal mucous membrane extract. He thought that the enzymes concerned seem to be in the intestinal wall rather than in the juices. Frazer concludes that the faulty handling of certain peptides in the wheat gluten during their absorption is a major fault in celiac disease, and since the children are normal in early infancy and apparently return and remain normal on a gluten free diet, the metabolic defect is revealed only under certain dietary conditions.

Speculation thus is that in celiac disease the patient lacks ability to hydrolyze a glutamine-containing peptide and this is the toxic factor.[3] As the work cited above shows, the digestion of gluten to the peptide stage appears to take place normally and the product of complete digestion to the amino acid stage is harmless, there must be various intermediate fractions which are the harmful substances. The large increase in blood glutamine after a dose of gluten or gliadin further indicates a peptide containing glutamine is the toxic factor, and a specific mucosal peptidase which might deaminate the peptide is absent in the small intestine. But it is also possible that the removal of glutamine peptides from the blood stream by the liver may be impaired and the defect is here.[2]

At the present time, celiac disease or non-tropical sprue can be diagnosed only by exclusion. There are no reliable methods of diagnosis which is specific for the disease. The problem is

twofold: (1) To determine the presence of gastrointestinal malabsorption and (2) to determine its cause.

Since fat appears to be the sole substance in which its absorption is constantly impaired in malabsorption syndromes, the demonstration of steatorrhea is the ideal method of diagnosis.[21] Many observers believe that the presence of steatorrhea can be strongly suspected by the characteristic odor and appearance of the stool, its consistency, and whether they float on water. A typical description of fatty stools is that they are large, bulky, pale, silvery-gray color, and foul smelling. Certainly the amount of fat in the stool affects its appearance and with small amounts of fecal fat excretion, the appearance of the stool would be little altered from normal.

A more reliable indication of steatorrhea is microscopic evidence of increased fat in the stool. One worker found such evidence in 85% of 100 patients.[21] The technique is simple but of value only when done by one person with experience who can establish in his own mind some standard of normal. In the technique of Gibbs, a portion of stool is stained with Sudan IV dye and acetic acid and steamed. The presence of many large round orange globules are indicative of excessive fat.[17]

For precise information as to the degree of steatorrhea, chemical analysis of the stool must be done. Formerly the percentage of fat in dried feces was estimated but this was found to be unsatisfactory.[11] The percentage of dried matter in feces is not constant

and there are technical objections to drying feces. Van de Kamer in 1949 developed a method which estimates total fatty acids against dilute sodium hydroxide with thymol blue as an indicator.[21] Occasionally, fecal chromogens interfer with the accuracy of the titration but in general the test is rapid, simple, and satisfactory. However, a balance technique must be employed in which the diet is of known fat content and collections are adequate. It is now known that rapid dietary controls and measures can be dispensed with as normal mixed diets, such as those containing 50 - 150 grams fat, can be used as normal subjects rarely excrete over 6 grams of fat a day on this diet.[12] It is also known that normal individuals on a fat free diet excrete 1 - 3 grams of fat per day and celiac children can excrete 6 - 10 grams of saturated fatty acids while on a fat free diet.[11]

Oral tolerance tests are the most widely used means of diagnosing intestinal malabsorption. This is because they are easy to perform, rapid, and give a fairly good correlation with the presence or absence of steatorrhea. Most procedures measure blood levels of the test substance after oral administration of a given amount. There is no general agreement concerning the best technique or performance or method of expressing results. There is no correlation with the intensity of steatorrhea and the degree of abnormality of the test. The test substances are affected by variation in gastric emptying, distribution in the blood, lymph, intra- and extracellular fluids, cellular utilization, storage, release, and excretion through

the kidney and liver. Repeat tests may show pronounced intra- and inter-individual variation.[21] Also the tests are not reliable for detection of mild malabsorption.

Probably the best known and most widely used test of absorption is the glucose tolerance test in which blood glucose levels are measured during fasting and at intervals of ½, 1, 2, and 3 hours after ingestion of 50 - 100 grams of sugar. A flat curve is one in which there is less than 40 mg. per 100 cc. difference between fasting and the highest level. In only 6 of 94 patients with severe idiopathic malabsorption did Bossak and associates obtain a normal curve.[7] Gardner, however, found a high percentage of normal subjects with low curves and a high percentage of idiopathic sprue patients with normal curves.[11] Hunter states that 40% of normal persons have a flat curve if 40 mg. per 100 cc. above the fasting level is used and suggests an increase in excess of 25 mg. per 100 cc. be the normal criterion used, but even with this value, 20% of normal persons exhibited a flat curve.[21,5] The test has more disadvantages than most oral absorption tests, since the liver, muscles, and endocrine glands affect glucose metabolism. Also there is an endogenous blood glucose level which is rapidly affected by excretion and metabolism and absorption.[5] The principal value of the test in malabsorption syndromes is, in the absence of family history of diabetes, a diabetic curve in a patient with steatorrhea is strong presumptive evidence of general pancreatic insufficiency.[21,5]

The Vitamin A tolerance test is also a time honored test of intestinal absorption. Usually 75,000 - 180,000 micrograms per kg. of body weight is given and blood levels measured at intervals extending to 9 hours. It is generally agreed that at least a fourfold rise over the fasting level should be present normally and the blood level at 4 to 9 hours should be at least over 125 micrograms per 100 cc. The value of this test is supposed to be an indication of the presence of steatorrhea; however, the results are inconsistent and the test is influenced by other diseases.[21] The Mt. Sinai series of 94 patients showed that 81% has a flat curve.[7] There has been many variations reported on repeat tests on the same individual and the improvement in the general condition of the patient is poorly correlated with this test.

Althusen in 1954 suggested the starch tolerance test as an aid in the diagnosis of pancreatic insufficiency.[21] It consists of comparing the blood sugar curve after oral administration of 100gm. of starch with the glucose tolerance curve. Interpretation of this test is difficult and the presence of diabetes makes it unreliable and it has never gained wide acceptance.

Amino acid tolerance tests evaluate intestinal absorption by evaluating blood amino acid nitrogen levels after administration of amino acids in a protein such as gelatin. Patients with idiopathic malabsorption tend to have flat curves after both are given and those with pancreatic insufficiency have flat curves only after administration of protein.[21] This involves a difficult chemical

technique and so has not been widely used.

In 1953 Gerdwood investigated intestinal absorption by the estimation of folic acid excreted in the urine after intramuscular and oral doses of folic acid.[11,12] The urinary excretion of folic acid 24 hours after 5 mg. of folic acid was injected intramuscularly was compared with the excretion 24 hours after the giving of an oral dose of 5 mg. He found that less than 1.5 mg. excreted after the oral dose (or less than 50% of the excretion following the intramuscular dose) was abnormal. He had no false positive results and only 2 of 30 patients with sprue had a normal test. This test appears to have many merits but nobody has attempted to confirm this test.

The d-xylose absorption test is one of the most valuable of the available absorption tests. Benson measured the urinary excretion of d-xylose in 24 normal subjects and in 28 patients with non-tropical sprue after an oral dose of 25 grams of d-xylose.[5] In the healthy subjects the excretion was 6.5 plus or minus 1.2 gm. in 5 hours and in untreated non-tropical sprue patients the excretion was only about 1 gm. In those patients in remission it was somewhat more. The test was negative in patients with pancreatogenous steatorrhea but tended to reflect deficient absorption after partial gastrectomy or in affection of the small intestine -- hence is not specific for sprue. Blood values after the oral dose showed the same tendency but produced much overlapping. Xylose is neither absorbed against a concentration gradient nor significantly degraded

in the body. It is probably actively absorbed in the small intestine but is not phosphorylated in its passage through the mucosa. It is not normally present in blood and does not undergo selective absorption as does glucose. It is unaltered by the liver and a constant proportion of the amount given -- 40% -- is excreted in the urine. It is a simple test which reflects changes in the clinical status and a good separation has been found between normal and abnormal subjects by all investigators and deserves a wider usage.[21]

Frazer and Stewart in 1937 were the first to perform blood chylomicron counts in healthy persons after ingestion of meals and described a characteristic curve, and since this has been used as a means of diagnosing intestinal malabsorption of fat.[21] This is tedious and the curves are not reproducible, so recently measurement of blood lipids or of serum optical density after oral ingestion of butter has been used. The curves of sprue patients tend to be flat but the overlap with normals is excessive.

I^{131}-labeled triolein is one of the most recent and most promising absorption tests. Labeled triolein is given as a test meal after an overnight fast. Blood and fecal radioactivity are measured at intervals. Iodine is given for 3 or 4 days before the test to block thyroid uptake of radioactive iodine. After ingestion of the labeled triolein there exists in the blood two forms, most of which is inorganic and the remainder bound lipid which is measured.[4] Some investigators, however, measure whole serum and others count whole blood but the curves obtained are similar.[21]

Beres studied I^{131} absorption in 30 patients with functional gastrointestinal symptoms and all had normal fat absorption -- their coefficients of absorption being 95% or higher.[4] In 5 sprue patients the absorption pattern for I^{131} was markedly reduced -- 61 to 65%. Three of these patients were treated with prednisone and after only 3 - 4 days the absorption pattern improved greatly, preceding any measurable decrease in fat excretion by fat balance studies. Measurement of fecal radioactivity for 2 or 3 days after oral administration of the radioactive lipid correlates well with blood curves, blood and stool levels being inversely related. Normally less than 2% of the radioactivity is recovered in the stools. The I^{131} triolein test is simple and easy to interpret and relatively reproducible and is a prompt and accurate indication of the efficiency of therapy. The fecal counting procedure holds even greater promise and may be the means by which steatorrhea can be detected with a high degree of accuracy. There is also an I^{131}-labeled oleic acid test which is said to differentiate pancreatic malabsorption from other types of malabsorption, as oleic acid does not require digestion before absorption.[21]

The ability to absorb Vitamin B_{12} with radioactive Co^{60} and the detection of poor absorption by increased radioactivity in the stools collected over a 7-10 day period was first reported in 1952.[21] The Schilling 24 hour urinary excretion test is the most popular method to detect absorption of radioactive B_{12}. Recently

Glass and Bond reported an accelerated method of measurement of hepatic uptake of Co^{60}, with use of castor oil and an enema to rid the intestines of unabsorbed radioactivity so that liver counting may be perfomred in 48 hours.[19] They found the hepatic uptake to be normal in anemia due to blood loss, hemolytic anemias, and nutritional macrocytic anemias due to dietary deficiency of Folic Acid or B_{12}; was entirely abolished (or traces) in pernicious anemia in relapse, remission, or preanemic stage, but can be corrected by addition of Intrinsic Factor. In 4 cases of sprue the uptake was also zero but couldn't be corrected by IF. These tests allow one to rule out pernicious anemia in 48 hours or to make diagnosis of pernicious anemia or sprue within 4 days without regard to previous therapy or stage of disease. This pattern was demonstrated also by Oxenhorn[30] and other workers. Kaufman and his coworkers did not find this, however.[23] In 5 patients with sprue, three showed impaired abosrption and two were in the normal range. Of two who received prednisone, one showed a significant rise in absorption of Vitamin B_{12} and the other a decrease. One patient treated with a gluten-free diet showed marked improvement radiologically and clinically despite a decrease in B_{12} absorption at 4 and 8 weeks. They concluded that the Vitamin B_{12} absorption test was not a diagnostic test of malabsorption. Thus it appears the radioactive Vitamin B_{12} absorption tests are of great value in differentiating the various types of megaloblastic anemias but their use as a screening procedure for presence of intestinal

malabsorption of fat is limited.[23]

Low blood carotene levels were found in celiac disease patients 15 years ago. Wenger in a recent study of 110 patients without any organic gastrointestinal disease but all having gastrointestinal complaints, the mean range of serum carotene was 123 mg/100 cc.[38] In 30 patients with sprue all had levels in the severely depleted range -- below 30 mg/100 cc. They concluded that fasting serum carotene levels were a good screening test for steatorrhea, but had certain limitations as poor diet, liver disease, and certain febrile states can give low levels. However, if low levels are due to dietary deficiency, it can be reversed by giving oral carotene.

Weijers and Van de Kamer in 1955, presuming the deleterious effect in celiac disease was caused by a bound form of glutamine, thought there would be an increase of blood glutamine after oral administration of gliadin.[35,37] To study this a gliadin tolerance curve was made in celiac patients with healty children as controls. They tested 15 patients with wheat in their diet and 14 patients on gluten-free diets and 13 normal children. They found both groups having celiac disease had an increase of more than 50% of blood glutamine and this was indicative of a sensitivity to wheat, as the 13 normals did not have an increase of more than 40%. Payne and Jenkinson recently attempted to determine the value of this test with 33 patients in all stages of celiac disease and therapy.[31] Their controls came from convalescent patients who had disease with no alimentary tract involvement and also from four convalescents from

disorders of the alimentary tract from causes other than celiac disease. The patients to be tested were fasted for 12 hours and blood drawn and then given 350 mg/kg of body weight. Hourly samples of blood were drawn for five hours and plasma glutamine estimated as glutamic acid. They found that the mean maximum increment of apparent plasma glutamine of children with celiac disease was significantly greater than that of normal children, but the control group of four convalescent patients recovering from disorders of the alimentary tract other than celiac disease showed a mean percentage rise which was intermediate between normal children and children with celiac disease, and the mean percentage was not significantly different from either normal or celiac children. Their results also showed there was no relation between age and magnitude of increase of apparent plasma glutamine levels. Also there was no correlation between magnitude of rise of plasma glutamine and the phase of the disease whether symptoms were active or controlled by treatment. Also diet had no influence on the test. They concluded that their results confirmed that there is a greater rise of plasma glutamine after ingestion of gliadin. The intermediate position of children convalescent from gastrointestinal disorders other than celiac disease suggested that the abnormal increase in plasma glutamine may be a non-specific effect common to other gastrointestinal disorders. However, the number of children tested was too small to show conclusive evidence. This, they state, probably reflects the unreliability of a test dependent on the rate of absorption in children

where absorption is disturbed. The overlap of range of results from controls and celiac patients was considerable and the authors do not recommend the test as a diagnostic one.

The presence of anemia has been underemphasized as a screening procedure in the diagnosis of idiopathic intestinal malabsorption.[21] Most authors regard a persistently normal blood count as strong evidence against idiopathic steatorrhea. Frequently, the only clinical manifestation of malabsorption is megaloblastic anemia. Two-thirds of the patients at Mt. Sinai Hospital had a macrocytosis.[14] Although macrocytic normochromic is the usual type of anemia which develops in intestinal malabsorption, microcytic, hypochromic anemia due to malabsorption of iron is not uncommon.[11] Absorption of iron may be investigated by measuring radioactivity in blood or feces after radioactive iron is given orally or by measuring levels of iron in the serum at intervals after oral administration of iron. Many patients with sprue who are not demonstrably iron deficient have flat blood curves, but there is much overlap with normals.

Electrolyte malabsorption is common in idiopathic steatorrhea even without diarrhea, but normal serum electrolyte values are also not uncommon.[21] Hypocalcemia traditionally is a diagnostic finding, but this is due to diarrhea and when found there is also evidence of water and electrolyte depletion.[11] The secretin test is the most specific and accurate test of pancreatic insufficiency. Dreiling had great success in differentiating by this test the

normal response of patients with idiopathic steatorrhea from that of patients with pancreatic insufficiency.[13] Estimation of sweat electrolytes is a sensitive and reliable means of diagnosing fibrocystic disease of the pancreas, as is the determination of the ability of fecal enzymes to digest the gelatin film from an x-ray plate.

More than 20 years ago it was observed that there was an abnormal roentgenographic appearance of the small intestine in patients with the sprue syndrome.[37] This consisted of dilation and smoothing of jejunal contour, segmentation and clumping and flocculation of barium, reduced motility and an increased intestinal transport time. These changes were recognized at the time, however, as being non-specific. In one of the most recent studies, Marshak and his associates observed dilation of the mid and distal jejunum in 40 of 46 cases and considered this an important radiologic finding.[29] Another important finding according to this report was segmentation of the barium column in the small intestine. This was seen, however, only in cases of severe steatorrhea in which the lipid content is due to a large amount of fatty acids, and also neutral fats. Patients with pancreatic steatorrhea have a normal small intestine pattern as the steatorrhea is due only to neutral fats. They state the most important single factor in the production of the segmentation pattern in sprue was the abnormal quality and quantity of the secretions in the intestine caused by the increased fatty acids.

The mucosa of the gastrointestinal tract of sprue patients is unusually susceptible to postmortem autolytic changes, and thus true interpretation of changes are difficult at autopsy. For this reason pathologic changes in the small intestine have previously been minimized or reported as normal. In 1957 a method of small intestinal biopsy by the oral route was devised by Shiner.[21] The biopsy is obtained from the jejunum by the use of a knife cylinder at the end of a flexible plastic tube introduced similarly to that of intestinal intubation. It has been found to be quite safe and agonal changes and postmortem autolysis is eliminated. Himes and Adlersberg recently had 15 cases in which the pathology of the small bowel was studied.[20] The age range was 16 years to 67 and included both men and women. Eleven cases were at autopsy and four by oral biopsy. The most consistent gross change at autopsy was atrophy and thinning of the wall of the small bowel in 7 of the 11 cases. Four were normal. All of the seven had flattening and thickening (clubbing) of the villi and an increase in the mucosal cellularity -- mainly chronic inflammatory cells.

The mucosa of the colon was not atrophic. In the four oral biopsy cases all had pronounced mucosal changes consisting of various degrees of thickening of the villi, progressing from clubbing to complete fusion. Alterations were more advanced near the periphery and the deeper structures (crypts and glands) were normal. The surface epithelium, instead of tall columnar cells, was lower and cuboidal in some areas. The nuclei were irregular in size and

position. In all the goblet cells were choked with mucus and in some there was a moderate increase in goblet cells. There was also an increase in cellular exudate, mainly lymphocytic and plasma cells with occasional eosinophils. The earliest changes were found to occur at the tips of the villi and consisted of clubbing with progression to fusion of the villous tips with complete obliteration of the normal pattern resulting in a flat surface with a marked decrease in area available for absorption. Some of the changes were noted in patients who were asymptomatic on corticosteroid therapy.

The authors concluded that these changes and the absorptive defect may be related to each other as cause and effect or the changes may be a result of alteration of small intestinal motility, changes in intestinal flora, or lack of specific nutritional or enzymatic factors, or the result of toxic degeneration or inflammation. Another group has performed 110 suction biopsies of the small intestine in 65 patients comprising idiopathic steatorrhea, suitably aged controls, and active, latent and adult celiac disease.[32] They found changes similar to that described above in both idiopathic steatorrhea patients and those with celiac disease. This also offers further proof that the two processes are similar. Intestinal biopsy holds great promise as a menas of diagnosing sprue and may well provide the long sought for firm basis for diagnosis.[21] More information is needed as to microscopic findings in unrelated disease states, especially those associated with

poor nutrition.

The importance of diet in the treatment of celiac disease has been realized since Gee first described the disease in 1888. Clinical experience led gradually to the use of a low fat and high protein diet, and that monosacchorides were more beneficial than polysacchorides.[9] Interest in a gluten-free diet was aroused in 1950 by the observation of Dicke that celiac children had clinical remission upon the elimination of wheat and rye from their diet, and the addition of either resulted in relapse.[25] Conflicting reports have appeared in the literature since but most patients do well on the gluten-free diet.[25] It has been of little help, however, in patients with the tropical variety of sprue. In 28 patients at Duke Hospital treated with a gluten-free diet, 7 with sprue had clinical recovery; 2 with Whipples disease improved somewhat; 4 with irritable colon syndrome, 4 with regional enteritis, and 11 with gastric resections remained unchanged.[25] Poor results reported may be due to failure to follow the diet strictly, inadequate trial, or mistaken diagnosis. Strict avoidance of any food with gluten, even in minute amounts, is essential for at least 3 months before discarding it as of no value.

At the present time the value of a wheat and rye gluten-free diet in the treatment of children with celiac disease is well established.[8,34,37] There is, however, no agreement amongst investigators as to the value of such a diet in the treatment of idiopathic steatorrhea in adults. Formerly little success had been achieved

in older patients by exclusion of wheat or rye. McIver in England reported the first case of non-tropical sprue in whom a remission followed the use of the gluten-free diet in 1952. Two years later Ruffin subsequently reported clinical improvement in 3 patients with the adult form of the disorder on a wheat free diet in this country.[34] French and his colleagues have had the greatest experience in the treatment of adults and in 1957 reported a study of 22 adults and the effect of wheat-gluten free diet.[39] Twenty-two patients were placed on the diet alone and of these, 16 made a complete recovery. Six patients failed to respond. Complete recovery was characterized by disappearance of symptoms of diarrhea, glossitis, stomatitis, and return of normal appetite, energy and blood picture and normal fat absorption and weight increase. They concluded the gluten-free diet was advantageous to adults but took a much longer feeding trial. The fact that not all recovered on the diet they thought indicated the possible existence of other etiologic factors.

In another report of 6 patients with non-tropical sprue all had dramatic clinical and laboratory improvement with the gluten-free diet and this improvement has been maintained for 8 months to 3 years.[34] Two of the patients underwent detailed metabolic balance studies before instituting the gluten-free regimen and at various periods afterwords. In both patients fat absorption returned to normal, positive nitrogen balances decreased with repletion of protein stores, and absorption of sodium, potassium, magnesium and

phosphorus returned to normal, as did blood levels of calcium, albumin, and prothrombin. All 6 patients made complete rehabilitation and undesirable side effects were absent.

Another study by a Canadian group has recently been reported.[8] Nine patients with the malabsorption syndrome who had no clinical or laboratory evidence of hepatic, pancreatic, or intrinsic small bowel disease were studied. All had chronic or recurrent diarrhea over periods ranging from 2 months to 18 years and some had been previously given adrenocortical steroids, Vitamin B_{12}, folic acid and various dietary regimens, but with no benefit. The gluten-free diet was the only form of treatment given to five of the patients; the others were given additional vitamins. All were re-examined 2 to 18 months later. It was found that all gained weight, ranging from 20 to 46 pounds, and in all the number of stools decreased from 3 to 10 per day to one per day and were no longer bulky, greasy, and foul-smelling as they were previously. All showed a fall in fecal fat excretion from a mean of 28 grams per day to a mean of 7.3 grams per day. Whereas 7 of the 9 had flat glucose tolerance curves before treatment, only 4 still had flat curves when re-examined after treatment. Five patients had serum calcium levels below 4.5 mEq/L when first seen and all had normal levels when examined after treatment. The serum albumin levels rose from below 3.5 gm% to above this figure after treatment in all. Also all the patients had dilated small bowels on x-ray before treatment and all showed improvement after a period on the diet, although

their response was slow. All showed subjective improvement, such as an increase in appetite, sense of well-being, and an increase in strength. Although 2 responded dramatically to the change in diet, in the others the improvement was gradual and the return to more normal gastrointestinal function took many months. The author felt that from the result of this study, dietary treatment over a prolonged period should form the basis of treatment in all cases of the malabsorption syndrome.

Thus it appears that the majority of patients with non-tropical sprue will respond to a diet free of gluten, but the fact remains that some have an intractable form of the disease which fails to respond to this therapy. The possibility then exists that non-tropical sprue is a disorder of multiple causalities.[34] To those who do not respond to the gluten-free diet, adrenocortical steroids have proven useful. Almy in 1950 was the first to use ACTH in sprue patients with good results. Early experience has shown that ACTH and cortisone were beneficial but relapses occurred when they were discontinued, which was done because of fear of complication. A recent report was published concerning 6 cases in which small oral maintenance dosage of adrenal steroids was given for periods ranging from 1 to 6 years.[28] Rapid response was obtained in all 6 with an increase in stamina and appetite, cessation of diarrhea, increased weight gain, decrease in tetany, better absorption of fat from the intestine, and a good improvement in x-ray appearance of the small bowel. There were no adverse affects in any of the

6 patients. All the patients suffered relapses when the therapy was stopped but improved upon reinstitution of the steroids. The daily amount required for maintenance was fairly constant and did not exceed 50 mg. of cortisone, 40 mg. of hydrocortisone, or 10 mg. of prednisone. The authors felt that steroid therapy should be reserved for cases of intractable sprue who fail to respond to gluten-free therapy, vitamins, folic acid and Vitamin B_{12} or liver extract. The mechanism of effect of the steroids is obscure. There has never been any evidence reported of adrenal cortical disease on autopsy of patients with non-tropical sprue. The theory of adrenal cortical insufficiency is inadequate as one would expect sprue in patients with Addisons disease. The mechanism may be that these hormones in some unknown manner influence the absorption of various substances from the small intestine. Or perhaps their efficiency lies in the interference with the intestinal reaction to gluten.[34] Also, because of the acuteness and violence of gluten-induced symtpoms which has occasionally been reported, the effect of adrenal steroids may be due to interference with an allergic reaction.[28]

Gibbs in 1954 published a report concerning the use of hog duodenum in the treatment of celiac disease in children.[17,18] He had thought that perhaps the disease might involve deficiency of some specific substance which could be provided by administration of normal intestinal mucosa. A preparation of defatted and desicated pig duodenum was available (Viodenum) which consisted largely of

protein and was rich in phosphatase and enterokinase and presumably contained other physioactive principles. At the time of his report he had a series of 10 infants with celiac disease who had been fed the powdered duodenum. In each case there had been an observed control period prior to a period of trial with the ingredient. In most instances the routine dietary celiac regime was withheld or given only in partial form during these experimental periods. In all cases the patients had done well with respect to weight gain and decrease in the number of stools. A dosage of 0.5 to 2.0 grams was tolerated well by the patients and resulted in prompt recovery. In all cases except one the recovery persisted after discontinuance of the medication. Since this report he has added 10 more cases to his series. The age range in this series was from a newborn to 17 years. When first seen, all presented various degrees of diarrhea, weight loss, emaciation, and abdominal distention, and most were anemic. The diagnosis of celiac disease was made in all instances by the demonstration microscopically of excess fat in the stools and exclusion of other causes of malabsorption and failure to do well on standard anti-allergenic formulas. Pancreatic insufficiency was ruled out by normal secretin tests, normal stool trypsin and normal sweat chlorides. Glucose, Vitamin A and starch tolerance tests were also done. After trial therapy consisting of anti-diarrheal agents, allergic regimes, low fat and high protein and monosacchoride diets, and antibiotics without relief, Viodenum was tried. In all cases the patients almost immediately started gaining

weight and the number of stools decreased down to 1 - 2 per day and became normal in appearance. A follow up of these patients is not available.

There is apparently no other mention in the literature of clinical therapy trial with the use of animal intestinal mucosa, although Frazer in his experiments in 1956 used an extract of pigs intestinal mucous membrane to digest a toxic peptide fraction of gluten and thus rendered it harmless.[16] The good results obtained in Gibbs series of 20 patients certainly deserves further trial and evaluation.

SUMMARY

Celiac disease and sprue are considered by most authorities as an expression of the same disease at different ages. Tropical sprue also is considered as a variant of the non-tropical variety.

The most frequent symptoms and signs of idiopathic steatorrhea in a large series were diarrhea, weakness, weight loss, glossitis, abdominal distention, and emaciation. The etiology of the disease is now considered to be a hereditary constitutional defect in metabolism, which becomes manifest after varied trigger mechanisms are set off.

The relationship between celiac disease and wheat and rye gluten has been the subject of many experiments and writings. Several of these experiments have confirmed that the protein fraction of wheat flour was the deleterious agent. With further experimentation a glutamine-containing peptide was found to be the toxic factor. The digestion of gluten to the peptide stage appears to take place normally and the complete digestion to the amino acid stage is harmless, and so various intermediate fractions must be the harmful substances.

At the present time celiac disease can be diagnosed only by exclusion. There are no diagnostic methods which are specific for the disease. The demonstration of fat in the stool is an ideal method but requires trained observers for microscopic examination or prolonged chemical analysis.

Oral tolerance tests are the most widely used means of

diagnosing intestinal malabsorption. Most of these tests, such as the glucose, Vitamin A, starch, and amino acid tolerance tests give inconsistent results and show many variations which greatly reduce their effectiveness. The folic acid absorption test appears to have many merits but needs confirmation by further usage. The d-xylose absorption test is one of the most valuable of the available absorption tests. Although not specific, it is a simple test which reflects changes in the clinical status and has a wide range between normal and abnormal subjects. I^{131}-labeled triolein is another recent and promising test. It is simple and gives a prompt and accurate indication of the efficiency of therapy. Measurement of fecal radioactivity after oral administration of the lipid holds even greater promise in accuracy of detecting steatorrhea. Radioactive Vitamin B_{12} absorption tests are of great value in differentiating the various types of megaloblastic anemias but their use as a screening procedure for the presence of intestinal malabsorption of fat is apparently limited. Fasting serum carotene levels is a good screening test for steatorrhea, but has certain limitations. Recent experiments on blood glutamine levels has shown a significantly greater difference between celiac children and normal children but the mean percentage rise between children convalescing from gastrointestinal disorders other than celiac disease was not significantly different from either normal or celiac children, although the number of children tested was too small to show

conclusive evidence.

Dilation of the mid and distal jejunum and segmentation of the barium column in the small intestine appear to be important radiologic findings. The recent development of intestinal biopsy by the oral route has shown rather specific mucosal changes, consisting of various degrees of thickening of the villi, epithelial changes, and an increase in cellular exudate. This method holds great promise as a means of diagnosing sprue and may provide a firm basis for diagnosis.

Most authorities agree as to the value of a gluten-free diet in the treatment of both the children and adult form of the disease and recommend the diet be tried before other measures. Poor results may be due to failure to follow the diet strictly, inadequate trial or mistaken diagnosis. Intractability to this form of treatment necessitates treatment with adrenocortical steroids which can be maintained in small doses for prolonged periods according to a recent report. Hog duodenal extract fed to celiac children has resulted in a prompt weight gain and a cessation of diarrhea in a series of 20 cases.

CONCLUSIONS

Celiac disease, non-tropical sprue, and tropical sprue are clinical variations of the same basic disorder.

There is a hereditary constitutional defect in metabolism and the basic defect manifests itself because of the occurrence of appropriate trigger mechanisms, and clinical variations are due to inherent differences in the severity of the disease.

The basic metabolic defect is probably an inability to hydrolyze a glutamine containing peptide because of a lack of specific mucoasl enzymes in the small intestine, and this peptide thus acts in some way as a toxic factor.

There are no diagnostic methods specific for the disease; along with the detection of excessive fat in the stool the d-xylose absorption test, the I^{131} labeled triolein absorption test, the glutamine tolerance test, and intestinal mucosal biopsy by the oral route are the most reliable means of diagnosing the disease.

As soon as the diagnosis of sprue is made all patients should be given trial therapy on a strict gluten-free diet for a prolonged period of time.

Adrenal steroid therapy is indicated for cases intractable to the gluten-free diet and should probably be maintained on small doses indefinitely.

Powdered hog duodenal extract appears to be a satisfactory therapeutic agent and should be used more often.

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