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The Study of the Pathology of the Middle One Third of the Small Intestine of the Spontaneously Diabetic Chinese Hamster

Patrick Murray

Western Michigan University

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by

Patrick Murray

A Thesis Submitted to the Faculty of The Graduate College in partial fulfillment of the Degree of Master of Arts

Western Michigan University Kalamazoo, Michigan December 1975
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Patrick Murray.
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Introduction

Diabetes mellitus is one of the most intensively studied human diseases. Even though some of the major symptoms of diabetes were described in ancient times and insulin was first isolated over 50 years ago, there is still no complete picture of the basic biochemical defect(s) in this disease. Furthermore, diabetes is a serious and important health problem, involving 2 percent or more of the population of the United States (1).

Diabetes is a complex disease, displaying different kinds and degrees of pathology. Susceptibility to diabetes has a large genetic component. Physical exercise and the quality of the diet also have an influential effect on the incidence of diabetes.

The primary symptom of acute diabetes mellitus is hyperglycemia, often accompanied by glycosuria and polyuria. Correspondingly, there is considerable hunger and thirst, weight loss, and in more severe cases, ketonemia, ketonuria, and acidosis. A secondary set of symptoms arises in chronic or long-standing diabetes. These include changes in the walls of blood vessels, particularly of capillaries and their basement membrane. Although many different organs are affected by these vascular changes, the eyes and kidneys appear to be most susceptible.

Investigators have developed experimental animal models
for the study of diabetes. It was hoped that these animal models might accurately reflect the human condition. The majority of studies concerning diabetes mellitus in animals was limited to metabolic alterations resulting from (1) pancreatectomy and (2) damage to the islet tissue by alloxan or other drugs. Due to these experimental procedures, the diabetic syndrome produced in these animals may not be similar to the inherited human disease. Diabetes, in general, is a hereditary disease and it is possible that some disorders associated with diabetes were genetically determined. If this was true, the chemically induced diabetic and pancreatectomized diabetic animals may not be an appropriate model to study.

It has been established that the spontaneously diabetic Chinese hamster serves as an appropriate model for the human disease (2). The diabetic Chinese hamster shows morphological, biochemical and physiological changes which are somewhat similar to alterations associated with human diabetes (2). In recent years, numerous biochemical, morphological, and genetic studies have been initiated on most organ systems of this animal. However, only a limited quantity of work has been done on the gastrointestinal tube (3, 4).

Therefore, the purpose of this investigation was to examine histologically the small intestine of the diabetic Chinese hamster for any possible structural disorders. It has been shown that the Chinese hamster displayed elevated
free fatty acid absorption (3), steatorrhea and hyperphagia (4), and hormone imbalances (5), (6), (7). These factors, along with the fact that the pancreas and small intestine have a similar embryonic origin, suggested that morphological changes might be present in the small intestine. Since disorders in the small intestine of diabetic man have been described, it was logical to look for similar pathologies in the intestine of the diabetic hamster.

It is hoped that this structural investigation might establish guidelines for more extensive studies on the digestive and absorptive function of the small intestine of the diabetic Chinese hamster. Since the diabetic hamster resembles some pathologies observed in diabetic man, this current study of observed intestinal pathologies is an attempt to understand these observations and to characterize further the diabetic syndrome(s) in this animal and possibly in man.
A. Pathology of the Diabetic Human Small Intestine

Diabetes mellitus affects most organ systems and the human small intestine is no exception. The structural disorders associated with the small intestine have been thoroughly investigated. However, the etiology of some of these disorders is still unclear. Human biopsy specimens of the small intestine have revealed various types and degrees of structural alterations. These changes appear to correlate with the severity and duration of diabetes.

Gross abnormalities of the intestine of some diabetic patients include thickening of the jejunal wall, marked segmentation, irregularity, and widening of the bowel (8, 9). Variation of the luminal caliber, localized coarseness, and partial obliteration of the small intestine have also been noted (8).

Neurological disorders associated with diabetes in the human small intestine vary considerably. Chromatolysis, vacuolization, and swelling in the ganglion cells of Auerbach's and Meissner's plexuses have been shown (8, 9). Excessive fibrous tissue has been demonstrated in the intestinal tissue adjacent to Auerbach's plexuses (8).

Diabetic diarrhea is frequently related to the presence of visceral neuropathy (8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18). The small bowel mucosa in these patients is usually...
normal despite significant steatorrhea (16). Patients with diabetic diarrhea usually give a history of longstanding, severe, poorly controlled insulin-dependent diabetes, with severe peripheral and autonomic neuropathy (9, 11, 16, 17, 18).

A present hypothesis concerning diabetic diarrhea is that the major functional derangement is not due to autonomic denervation of the gut, but rather to a loss of integrated neuronal activity (17). Evidence has shown that the celiac ganglia of patients with diabetic diarrhea contained more neurons with dendritic swelling than a GSN change. In previous studies, GSN referred to "giant sympathetic neurons" in both the pre- and paravertebral ganglia (17). It was shown that dendritic swelling is morphologically comparable to the process leading to the GSN change (17). GSN has been seen in diabetic patients with and without diarrhea (17). However, dendritic swelling is seen only in diabetics with diabetic diarrhea (17). Morphologic evidence suggests that the function of pluricellular dendritic glomeruli is the integration of activity of postganglionic neurons that participate in the formation of the glomerules. Thus, diseased neurons would lose the function of the specialized receptors, the dendritic glomeruli, and result in a loss of integrated neuronal activity (17).

Severe lesions have been reported in the capillaries, venules, arterioles, and arteries along the gastrointestinal
tract in some diabetics (19). In the external muscular coat
the arterial and capillary lesions were less pronounced (19). Mesenteric vascular insufficiency has led to diabetic hyperos-
molar nonketoacidotic coma in a number of patients (20, 21).

Celiac disease may sometimes coexist with diabetes (16, 22). The two diseases may be genetically related. It is possible that in some individuals "occult" celiac disease may be "uncovered" by the development of diabetic neuropathy just as it has been by partial vagotomy or gastrectomy (16). However, in some children, the symptoms of celiac disease seem to precede the onset of diabetes, whereas in others the two are diagnosed simultaneously (16). Biopsy studies on the diabetic small intestine reveal minimal mucosal damage (18) whereas celiac disease has a profound effect on the intestinal mucosa (16, 22). Evidence to date indicates that the surface epithelial lining is replaced more rapidly in celiac disease than in the normal mucosa. Malabsorption occurs in celiac disease because of the "flat" mucosal layer along with the production of functionally immature epithelia (23). Studies now show that in celiac disease noxious gluten fractions interact with and damage the surface-absorptive cells by some unknown mechanism and that these damaged and dying cells are sloughed rapidly from the mucosal surface into the gut lumen (24). Then, as a compensatory mechanism, cell proliferation increases, the crypts undergo hypertrophy, and cell migration is accelerated to replace the damaged
cells (24). A recent study has shown that normal villus morphology in celiac disease is present and that diagnostic acceptance or rejection of the disease requires multiple biopsy specimens at different time intervals (25). The morphological changes of the mucosal layer observed in patients with diabetes and celiac disease include clubbed, stunted villi, flat mucosal epithelial layer, complete absence, at times, of villi, edema, and considerable lymphocyte infiltration (9, 12).

B. Structural Alterations Associated with Diabetes in the Chinese Hamster

The diabetic Chinese hamster displays Beta cell degranulation, reduced islet volume and Beta cell mass, and glycogen deposits in the Beta cells (2, 26, 27). Ultrastructural alterations of the B-cells include secretory granule depletion, expanded rough endoplasmic reticulum and enlarged Golgi apparatus (28). Increase in the number of nuclear pores, and alterations in the number, size, and distribution of membrane-associated particles in the plasma membrane of Beta cells has also been detected (26). Basement membrane thickening of capillaries in the islets has been reported (2). Long term glycosuric and recent onset ketonuric Chinese hamsters have shown glycogen accumulations in the Alpha, Beta, and Delta cells (29).

The diabetic Chinese hamster has revealed various degrees of retinopathy (27, 29, 30, 31). Abnormal glycogen
deposits have been noted in the Muller cells of the retina (27).

Nephropathy of the diabetic Chinese hamster results in reduction of basement membranes in some areas and thickening in others. Alterations of the mesangial matrix, consisting of an increased number of vesicles, multivesicular bodies, and vacuoles has been observed. Dissociation of the mesangium from the basement membrane, with coalescence and a marked cystic dilatation of capillary loops, has been observed. Renal changes, similar to those that develop with increased age, are characteristic of diabetic glomerulopathy found in the diabetic Chinese hamster (32). Glycogen deposits have also been observed in renal tissues of the diabetic Chinese hamster (27). The distal tubules in the kidney of the ketonuric Chinese hamster display excessive amounts of glycogen (29).

Corresponding to the severity of the disease, diabetic Chinese hamsters showed various degrees of inhibited spermatogenesis, resulting in a reduction of the thickness of the germinal epithelium and widening of the lumina of the seminiferous tubules (31). There has also been a reduction in the number of Leydig cells (31).

Morphologic changes in the aorta of the diabetic Chinese hamster include osmiophilic lipid droplets in the endothelial cell, amorphous material in the extracellular space adjacent to the intima, and calcium deposits in the media.
surrounded by collagen fibers and amorphous substance (33).

Vascular lesions and neuronal degeneration have been observed in the brain of the diabetic Chinese hamster (34). The diabetic Chinese hamster has shown structural changes in the distal peripheral nerves such as segmental demyelination, acute axonal degeneration, decreased and inconsistent internode lengths, and indications of demyelination and remyelination (35).

C. Abnormalities of the Diabetic Chinese Hamster Small Intestine

The pathology of the small intestine of the diabetic Chinese hamster has not been described. However, some studies on absorptive function have been done. Carbohydrate calorie loss via urine and feces and reduced absorption of dietary fat have been displayed in hyperphagic diabetic hamsters (4). Another study has revealed that the intestinal mass of the diabetic is greater than that of the non-diabetic and this has been correlated with an increased uptake of free fatty acids (3).
Materials and Methods

All specimens for this investigation were selected from the Upjohn colony of Chinese hamsters (36, 37). Two types of animals, non-diabetic and nonketotic diabetic, were used in this investigation. A total of 15 pairs of animals were utilized. The nonketotic diabetics were taken from 7 different inbred sublines, whereas the non-diabetics were derived from 3 sublines. Each pair was matched for body weight, sex and age. Age varied from 8 to 18 months and duration of diabetes from 8 to 16 months. Diabetic hamsters displayed continuous glycosuria as measured by consistent TesTape\textsuperscript{R} (Eli Lilly and Company, Indianapolis, Indiana) values of plus 3 to plus 4 (with one exception). Negative Ketostix\textsuperscript{R} (Ames Company, Elkhart, Indiana) values were obtained for all diabetic hamsters. Blood samples from the orbital sinus were drawn prior to termination and analyzed for glucose by the Auto Analyzer technique.

The animals in this study were allowed, ad libitum, access to Purina Mouse Breeder Chow (Ralston Purina Co., St. Louis, Mo.) and water until termination. The Chinese hamsters were raised according to Yerganian (38). None of the diabetic hamsters in this study received insulin therapy at any time.

The Chinese hamsters were sacrificed by exsanguination and decapitation or etherization and cervical dislocation.
and the small intestine was excised. This report concerns itself only with the middle third of the small intestine (Fig. 3). The middle third of the small intestine was then divided into two portions, anterior and posterior, and three pieces of tissue were taken from each portion. About 90 percent of the tissue was utilized. The tissues taken from each portion were then placed into Bouin's (39), Zenker's (39) or cold acetone (39) (four degrees Celsius) fixatives. Tissues fixed in Bouin's stained for general morphological entities such as epithelium, muscle, and connective tissue whereas tissues fixed in Zenker's were stained for goblet cells and mucopolysaccharides. Fixation time in Bouin's fluid was twenty-four hours. Fixation time in Zenker's was twenty-four hours, after which the tissues were placed in running water (tap-water-cold) for five to eight hours in order to remove excess mercuric chloride. Fixation time in cold acetone was twenty-four hours. Tissues fixed in cold acetone were stained for alkaline phosphatase, acid phosphatase and non-specific esterase. Zenker's and Bouin's fixed tissues were embedded in paraffin according to the following scheme:

1. 50 percent ethanol, one hour minimum, three changes, room temperature.

2. 70 percent ethanol, one hour minimum, three changes, room temperature.

3. 80 percent ethanol, thirty minutes, room tempera-
ture.

4. 90 percent ethanol, thirty minutes, room temperature.

5. 95 percent ethanol, thirty minutes, room temperature.

6. 100 percent ethanol, thirty minutes, room temperature.

7. Xylene, fifteen minutes, room temperature.

8. Repeat step 7.

9. Xylene: paraffin 1:1 ratio, one hour, 56 degrees Celcius.

10. Paraffin, forty-five minutes, 56 degrees Celcius.

11. Repeat step 10.

It should be noted that the tissues were placed and kept in one dram vials until the xylene: paraffin procedure. At this time they were transferred into watchglasses. All three types of fixatives employed this technique.

The embedding scheme for acetone fixed tissues was as follows:

1. Acetone, twelve hours, room temperature.

2. Repeat step 1.

3. Xylene, fifteen minutes, room temperature.

4. Repeat step 3.

5. Xylene: paraffin 1:1 ratio, fifteen minutes, 56 degrees Celcius.

6. Paraffin, thirty minutes, 56 degrees Celcius.
After the last step in both preceding paraffin procedures, the tissues were placed and allowed to harden in wax at 4 degrees Celsius. The wax was trimmed and mounted onto wooden blocks. The blocks were then placed on a Spencer rotary microtome 820 and the tissue sectioned at 8 microns. The tissue sections were floated in a Lipshaw electric tissue float to reduce wrinkling and then placed on glass slides coated with Mayer's albumin.

The following stains were employed to reveal specific structures associated with the small intestine:

1. Harris' hematoxylin and eosin (39) to display general morphology.
2. Schorr's modified triple stain (40) to differentiate epithelium, muscle, connective tissue, and blood cells.
3. Periodic Acid-Schiff (41) to stain mucin, glycogen, and other polysaccharides.
4. Acid phosphatase (42) modified to allow for acetone fixation and paraffin embedding. The amount of substrate, sodium alpha naphthyl acid phosphate, was doubled.
5. Alkaline phosphatase (42).
6. Non-Specific Esterase (43) modified in the following manner: (1) tissue sections were not counterstained and (2) a non-aqueous mounting medium was utilized.

After staining was terminated, the tissue sections were covered with non-aqueous mounting media and a coverslip was applied. The slides were dried and then were analyzed using
Wolfe and Leitz binocular light microscopes.

Comparisons in this investigation were done by analyzing both the anterior and posterior portions of the middle third of both diabetic and control intestines.

Several morphological structures were measured in this study such as number of villi per cross section, cross sectional area of the small intestine and cross sectional area of the lumen (determined by the product of the cross sectional length and width measurements), length of villi (ten villi per cross section were analyzed and the number of goblet cells per villus (number of goblet cells of ten villi per cross section were obtained). The student t-test (44) was used to determine any statistical differences between measurements of diabetic and control intestines (Table 1).

Histopathological data was obtained by observing and comparing a number of structures in the diabetic and control intestines. Results were recorded as percent incidence in diabetics (Table 2). Structures which were examined included muscle thickness of the muscular layer, number of Auerbach's plexuses, lymphocyte aggregations, amount of connective tissue in the outer muscle layer, blood vascular disorders, and epithelial sloughing.

The histochemical reactions were analyzed for intensity of enzyme activity between the brush border of diabetic and control intestines. Results were recorded as percent incidence in diabetics (Table 3). The histochemistry included
a study of the Periodic-Acid Schiff positive brush border, and brush border enzyme activity displayed by acid phosphatase, alkaline phosphatase, and non-specific esterase.

Appropriate photomicrographs were processed by the Upjohn Company at Kalamazoo, Michigan, U.S.A.
Observations and Results

A. Gross Anatomy

The small intestine of the Chinese hamster extended from the pylorus of the stomach to the ileocolic valve. The numerous coils of the jejunum and ileum filled the umbilical and hypogastric regions and extended into the cavity of the pelvis minor (Figure 2). The jejunum and ileum were connected to the dorsal wall by the mesentery. This mesentery of the small bowel was fan shaped, composed of two layers, and contained blood vessels, nerves, lymphatic glands, and lymph vessels.

B. Gross Pathology

The small intestine of some diabetic Chinese hamsters displayed a mushy appearance. The diabetic guts also appeared distended, presumably caused by excessive accumulation of partially digested food.

C. Normal Histological Structure

Except for the absence of plicae circulares, Brunner's glands, and a muscularis mucosae, the intestine of the hamster resembled that of the mammalian small bowel.

The mucosal layer of the intestine was comprised of two types of simple columnar cells, absorptive and goblet. The absorptive cells possessed a brush border and the goblet cells were irregularly distributed among the columnar epithel...
Intestinal villi were present in the Chinese hamster intestine (Figure 5). These were fingerlike projections which ranged from 300 to 500 microns or more in length. The essential structures which formed the villi of the Chinese hamster were lacteals, blood vessels, basement membrane, and epithelium. These structures were arranged in the following manner: in the center of each villus was a lacteal, terminating near the summit in a blind pouch; the lacteal was surrounded by a plexus of capillary vessels and nerves; all vessels and nerves were enclosed by a basement membrane upon which rested a simple columnar epithelium. Subjacent to the basement membrane was a layer of reticular tissue which supported and housed the previously described vessels and nerves of the villi.

The epithelium of the villi was continuous and gave rise to tubular depressions or intestinal glands similar to crypts of Lieberkühn (Figure 5). The upper halves of the walls of the crypts were invested with low columnar epithelium which contained absorptive cells, goblet cells, and a few cells resembling basal granular cells. In the lower halves of the crypts the cells were less clearly differentiated and mitosis was evident.

The intestinal blood vessels, having reached the mesenteric border of the small intestine, ramified between the serous and muscular coats (Figure 4). From this location,
the vessels branched and supplied the muscular and submuco-
sal layers and then entered the mucosa to serve the glands
and villi of the mucous membrane (Figures 6 and 11). The
lymphatic system of the small intestine was oriented in the
lacteals as described previously. From this point, the lac-
teals developed into larger and larger lymphatic vessels un-
til they finally emptied into the cisterna chyli at the mid-
dorsal region of the abdomen.

The submucosa of the Chinese hamster intestine consisted
of dense collagenous tissue. Plexuses of nerve fibers and
ganglion cell bodies were present in the submucosal area
(Figure 5). These resembled Meissner's plexuses and were
probably the terminal ganglia of the parasympathetic divi-
sion.

The muscularis externa of the intestine was comprised
of two layers of smooth muscle (Figure 6). The inner layer
had circularly disposed fibers and was somewhat thicker than
the outer longitudinal layer. Situated in connective tissue
islands between the circular and longitudinal layers of the
muscle were the plexuses of Auerbach (Figure 5). These plex-
uses were derived from the parasympathetic division (Figure
5). Nervous supply from sympathetic nerve plexuses around
the superior mesenteric artery also supplied the small intes-
tine.

The serosa contained areolar connective tissue, blood
vessels, and an outermost single layer of squamous mesothelial
cells (Figure 6).

D. Microscopic Measurement of Intestine

Non-fasting blood sugars of 8 out of the 15 pairs of animals were obtained. Mean blood sugar of the diabetics was 244 ± 18 milligrams percent (range 145-320) and the mean for nondiabetics was 104 ± milligrams percent (range 73-125).

Microscopic measurements are presented in Table 1. The number of villi per cross section was significantly increased in both anterior and posterior areas of the middle third of the diabetic intestines. Villi length measurements, however, were not significantly elevated in the diabetics. The width of villi were determined by measuring the base, middle, and tip of each villus. All villus width values were significantly enhanced in the diabetic intestines with the exception of the base measurements in the anterior regions (Table 1).

The cross sectional area of the small intestine was significantly greater in the anterior and posterior regions of the middle third of the diabetic intestines (Table 1). The cross sectional area of the lumen was significantly increased in the posterior portions of the diabetic intestines whereas the anterior portions lacked significance (Table 1).

The number of goblet cells per villus showed no difference between diabetic and control intestines (Table 1).

E. Histopathology
Incidence of pathological observations are recorded in Table 2.

Reduction of the muscular coat (Figures 6 and 7) was observed in the anterior regions of 14 percent of the diabetics. The posterior regions of the diabetic intestines displayed reduction in 20 percent of the animals (Table 2).

Reduction of Auerbach's plexuses was shown in the middle third of the diabetic intestines. The anterior areas displayed a 20 percent decrease whereas the posterior areas revealed a 14 percent diminution (Table 2).

Lymphocyte aggregations were found in only 6 percent of the diabetic intestines. Lymphocyte aggregations were defined as dense massive collections of lymphocytes which thoroughly infiltrated the mucosal and sub-mucosal layers of some diabetic intestines (Figures 8 and 9). Approximately one third of the circumference of the intestinal tissue was invaded by lymphocytic cells. Macrophages were also present among the lymphocytes. The villi associated with the lymphocyte aggregations were usually reduced in size and number. Some of the long, thin fingerlike villi were transformed into blunted or flattened processes. The simple columnar epithelium was usually modified into a pseudostratified or stratified squamous condition.

Blood vessel dilation was observed in the middle third of the diabetic intestines. The diabetic animals displayed a 53 percent incidence of vasodilation in the anterior por-
tions and a 46 percent incidence in the posterior portions (Table 2). Vasodilation was characterized by distention or enlargement of vessels in the submucosal area of the small intestine (Figures 6, 7 and 10). Endothelial cells appeared to be reduced in number or totally absent. The smooth muscle in the walls of the distended vessels was degenerate or totally absent. Connective tissue surrounding these vessels was extremely disorganized and loosely arranged.

Villus atrophy was prevalent in the diabetic intestines. The diabetics showed a 25 percent incidence of villus atrophy in the anterior portions and a 53 percent frequency in the posterior portions (Table 2, Figures 11 and 12). This pathological condition revealed extensive damage to the villi with concomitant loss of epithelial cells and exposure of the tunica propria to the luminal environment. The tunica propria within these villi displayed abnormal blood vessels and connective tissue. The cellular debris, presumably sloughed epithelial cells, was evident near the pathological villi.

F. Histochemistry

Incidence of brush border reactions in diabetics is presented in Table 3.

The diabetic Chinese hamsters displayed reduced acid and alkaline phosphatase activity. The diabetics revealed decreased alkaline phosphatase activity in 66.7 percent of the anterior portions and 33.3 percent of the posterior portions (Figure 17 and 18). Reduced acid phosphatase activity
was shown in 33.3 percent of the anterior areas and 66.7 percent of the posterior areas (Figures 19 and 20).

Esterase activity in the diabetic intestines was also diminished (Table 3). The anterior regions of the diabetic intestines displayed a 66 percent incidence of reduced esterase activity whereas the posterior portion indicated an 84 percent incidence of decreased esterase activity (Figures 16 and 17).

The diabetics displayed a minimal increase of PA/S activity along the brush border (Table 3). The anterior and posterior portions showed a 6 percent incidence of greater PA/S intensity (Figures 13 and 14).
Table 1

Microscopic Measurements of the Middle Third of the Intestine

<table>
<thead>
<tr>
<th>Structures Measured</th>
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<th>Mean and Standard Deviation Values</th>
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<td>Number of Cilli/Cross Section</td>
<td>Anterior</td>
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<td>38.33 ± 3.33</td>
<td>1.879</td>
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<td>Posterior</td>
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<td>41.93 ± 4.93</td>
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<td>3.42 ± .77</td>
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<td>Posterior</td>
<td>4.66 ± 1.22</td>
<td>3.45 ± .62</td>
<td>3.423</td>
<td>99</td>
</tr>
<tr>
<td>Cross Sectional Area of Small Intestine (mm²)</td>
<td>Anterior</td>
<td>4.06 ± .96</td>
<td>3.42 ± .77</td>
<td>1.646</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>4.66 ± 1.22</td>
<td>3.45 ± .62</td>
<td>3.423</td>
<td>99</td>
</tr>
<tr>
<td>Cross Sectional Area of Lumen of Small Intestine (mm²)</td>
<td>Anterior</td>
<td>.73 ± .63</td>
<td>.59 ± .59</td>
<td>.803</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>1.46 ± .86</td>
<td>.87 ± .79</td>
<td>2.11</td>
<td>95</td>
</tr>
<tr>
<td>Length of Villi (u)</td>
<td>Anterior</td>
<td>447.33 ± 86.32</td>
<td>437.93 ± 53.35</td>
<td>.4147</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>357.20 ± 76.15</td>
<td>348.13 ± 62.27</td>
<td>.3774</td>
<td>30</td>
</tr>
<tr>
<td>Villi Width at Base (u)</td>
<td>Anterior</td>
<td>96.73 ± 15.07</td>
<td>95.33 ± 17.67</td>
<td>.2696</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>96.00 ± 22.62</td>
<td>83.73 ± 11.82</td>
<td>2.358</td>
<td>95</td>
</tr>
<tr>
<td>Villi Width in Middle (u)</td>
<td>Anterior</td>
<td>88.67 ± 14.83</td>
<td>79.93 ± 10.42</td>
<td>2.059</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>93.87 ± 19.29</td>
<td>80.53 ± 11.66</td>
<td>3.03</td>
<td>99</td>
</tr>
<tr>
<td>Villi Width at Tip (u)</td>
<td>Anterior</td>
<td>61.40 ± 10.32</td>
<td>55.07 ± 6.77</td>
<td>1.902</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>71.07 ± 16.92</td>
<td>61.20 ± 9.18</td>
<td>2.42</td>
<td>98</td>
</tr>
<tr>
<td>Number of Goblet Cells/Villus</td>
<td>Anterior</td>
<td>11.16 ± 2.47</td>
<td>10.04 ± 1.94</td>
<td>1.409</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>9.99 ± 2.72</td>
<td>9.99 ± 2.63</td>
<td>.1014</td>
<td>10</td>
</tr>
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</table>

A. t-Value  
B. P-Value  
C. Significance Levels in Percent
### Table 2

**Incidence of Pathological Observation in Diabetics**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Percent Incidence</th>
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<tbody>
<tr>
<td></td>
<td>Anterior</td>
</tr>
<tr>
<td>Reduced muscle</td>
<td>14</td>
</tr>
<tr>
<td>Reduced Auerbach's Plexuses</td>
<td>20</td>
</tr>
<tr>
<td>Lymphocyte Aggregations</td>
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<tr>
<td>Vasodilation</td>
<td>53</td>
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<td>Villus Atrophy</td>
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Table 3

Incidence of Brush Border Reactions in Diabetics

<table>
<thead>
<tr>
<th>Enzyme or Reaction</th>
<th>Percent Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Reduced Alkaline Phosphatase Activity</td>
<td>66.7</td>
</tr>
<tr>
<td>Reduced Acid Phosphatase Activity</td>
<td>33.3</td>
</tr>
<tr>
<td>Reduced Esterase Activity</td>
<td>66</td>
</tr>
<tr>
<td>Increased PAS Activity</td>
<td>6</td>
</tr>
</tbody>
</table>
Explanation of Figures

Figure 1. Photograph of Chinese hamster, *Cricetulus griseus* showing its approximate length of 80 millimeters.

Figure 2. Photograph of the anatomy of the viscera in the abdominal cavity. The respective arrows point to the following: 1-Stomach, 2-Large intestine, 3-Small intestine and 4-Bladder (which is distended in this diabetic hamster).
Explanation of Figures

Figure 3. Photograph of the digestive tube from the stomach through the cecum and large intestine. The markers indicated the middle third of the small intestine.

Figure 4. Cross-section of non-diabetic Chinese hamster intestine, middle portion. Photograph shows villi, mesenteric vessels, and food material situated in lumen. Hematoxylin and eosin. 40X
Explanation of Figure

Figure 5. Cross section of the posterior portion of the non-diabetic intestine. The respective arrows point to the following: 1-External muscularis, 2-Auerbach's plexus, 3-Meissner's plexus. Photograph reveals crypts, submucosa, and tunica propria usually seen in control animals. Hematoxylin and eosin. 250X
Explanation of Figures

Figure 6. Cross section of the anterior portion of the non-diabetic Chinese hamster intestine. Arrow points to normal blood vessel located in submucosa between the muscularis external and crypts. Hematoxylin and eosin. 400X

Figure 7. Cross section of the anterior portion of the diabetic Chinese hamster intestine. Arrow shows dilated blood vessel. Also shown is a reduced amount of external muscle layer when compared to the cross section in Figure 6. Hematoxylin and eosin. 400X
Explanation of Figures

Figure 8. Cross section of the nondiabetic intestine. Photograph reveals normal villi and submucosa. Hematoxylin and eosin. 100X

Figure 9. Cross section of the diabetic intestine. Photograph shows lymphocyte infiltration and blunted villi in the mucosa and submucosal area. Hematoxylin and eosin. 100X

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Explanation of Figure

Figure 10. Cross section of diabetic small intestine. Photograph displays: 1-Lymphocyte infiltration of submucosal area, 2-Dilated vessel, and 3-Mucosal glands. Hematoxylin and eosin. 400X
Explanation of Figures

Figure 11. Cross section of anterior portion of nondiabetic Chinese hamster intestine. Normal villous histology is shown. Hematoxylin and eosin. 400X

Figure 12. Cross section of anterior portion of diabetic Chinese hamster intestine. Villous atrophy is present displaying its characteristics. 1-Epithelial sloughing, 2-Tunica propria protrusion, 3-Capillary fusion. Hematoxylin and eosin. 400X
Explanation of Figures

Figure 13. Cross section of anterior portion of nondiabetic Chinese hamster villus. Arrow points to brush border intensity after PA/S stain. Also seen are Goblet cells. Periodic-acid Schiff. 400X

Figure 14. Cross section of anterior portion of diabetic Chinese hamster villus. Photograph demonstrates the intense straining of PAS positive brush border (arrow). Periodic-acid Schiff. 400X
Explanation of Figures

Figure 15. Cross section of posterior portion of nondiabetic Chinese hamster villi. Arrow points to brush border activity with non-specific esterase reaction. Non-specific esterase. 400X

Figure 16. Cross section of posterior portion of diabetic Chinese hamster villi. Arrow points to reduced brush border activity with non-specific esterase reaction. Non-specific esterase. 400X
Explanation of Figures

Figure 17. Cross section of anterior portion of nondiabetic Chinese hamster villi. Alkaline phosphatase activity along the brush border is shown (arrow). Alkaline phosphatase. 400X

Figure 18. Cross section of anterior portion of diabetic Chinese hamster villi. Reduced alkaline phosphatase activity in the brush border is shown (arrow). Alkaline phosphatase. 400X
Explanation of Figures

Figure 19. Cross section of posterior portion of nondiabetic Chinese hamster. Note acid phosphatase activity along brush border (arrow). Acid phosphatase. 400X

Figure 20. Cross section of posterior portion of diabetic Chinese hamster. Note reduced acid phosphatase activity along brush border (arrow). Acid phosphatase. 400X
Discussion

The diabetic intestines displayed an increase in the number of villi compared to control intestines. Most of the length and width measurements of villi also showed the diabetics to have a significant increase over the control groups (Table 1). These data suggested that the diabetic gut exhibited more intestinal surface area than the controls. The diabetic intestines also possessed a greater cross sectional area and lumen (Table 1). These measurements intimated that the diabetics displayed increased intestinal mass. Furthermore, these findings were in agreement with previous studies which reported increased intestinal mass in the diabetic Chinese hamster, diabetic man, alloxan and streptozotocin diabetic induced rats (3, 45, 46). The mechanism for increased mass was uncertain but the hyperphagia presented by the diabetic Chinese hamster may have induced a growth response in the intestine. It has also been shown that elevated food intake was directly related to growth of the gastrointestinal tract in man and experimental animals (45, 46, 47). These data suggested that the diabetic intestines, like those of the alloxan and streptozotocin diabetic induced rats, have increased intestinal mass. The diabetic Chinese hamster has revealed a slight increase in total body weight as compared to the control (4). The alloxan and streptozotocin diabetic induced rats have shown an ample decrease in total
body weight (45). Presently, the possible mechanism for increased intestinal mass in the diabetic Chinese hamster is unknown. Some authors believe that the mechanism in the alloxan and streptozotocin diabetic induced rats is the presence of a hyperphagic condition which stimulates an increase in DNA synthesis that leads to increased intestinal mass (45). Whether this hypothesis can justify itself in the diabetic Chinese hamster, as previously cited, is not known.

Although not significant, there was an increased number of goblet cells per villus in both intestinal regions (Table 1). The diabetic animals displayed a greater mucosal surface area and this was presumably responsible for elevated goblet cell numbers.

Histologically, it was shown that some of the diabetic intestines displayed a reduction of the muscular coat and Auerbach's plexuses (Table 2). The parasympathetic nervous system is responsible for the innervation and subsequent contraction of the muscular coat. Intestinal tone and peristalsis are also controlled by this innervation (48). Decreased numbers of Auerbach's plexuses and reduced muscle thickness could have possibly created intestinal atony along with reduced segmentation and peristaltic contractions. Reduced segmentation and peristaltic contractions may have further diminished the efficiency of digestion and absorption of food material in the small intestine and lead to delayed emptying and excessive food residue. The mushy texture, distention,
and accumulation of excessive food residue in the intestines of some diabetic hamsters could have been the result of delayed emptying and hypomotility. Diabetic man has also been subject to distention, atony, hypomotility, and delayed emptying in the gastrointestinal tract (12).

The variability of myenteric plexus reduction in the diabetic intestines leads to speculation concerning the sympathetic nervous system of the diabetic Chinese hamster. Hyperphagia created excessive food intake in the diabetic animals but there was subsequent loss of dietary fat and carbohydrate calories via urine and feces (4). The loss of these food products might have possibly been the result of dendritic lesions associated with the coeliac ganglion (17). If these dendritic swellings promote effective denervation, this pathology would partially explain the inability to absorb the excessive food material (development of diabetic diarrhea and steatorrhea). Neurological modification in the gastrointestinal reflex and the enterogastric reflex could also have produced irregular states of hyper- and hypomotility (48).

Lymphocyte aggregations were observed in a few of the diabetic animals (Table 2, Figures 8 and 9). Lymphocyte collections were presumably indicative of localized inflammation due to increased chyme passage, vascular disorders and/or intestinal stasis and bacterial overgrowth. Studies on the gastrointestinal tracts of some human diabetic patients have shown bacterial overgrowth due to intestinal stasis and
vascular lesions (10, 49). It was reported that a number of human diabetics exhibited blunted villi and dense round cell infiltration, seemingly due to bacterial contamination of the jejunum (12).

Histologically, it was shown that some diabetic animals displayed villus atrophy (Figures 11 and 12, Table 2). The pathogenesis of this syndrome suggested two hypotheses: (1) Coincidental association of diabetes and the sprue syndrome or (2) A manifestation of diabetes per se resulting from neuropathic, vascular, or metabolic involvement (13).

The histological changes shown in the villi of the diabetic hamster intestine resembled that associated with the sprue syndrome and diabetic diarrhea (8). In some of the diabetic animals which displayed severe villus atrophy the pathology appeared to mimic collagenous sprue syndrome (23). Authors have shown in some diabetic humans an association between sprue and diabetes (13, 22). Development of sprue in diabetic humans has been determined to be genetically related (16). In some children the symptoms of celiac disease seem to precede the onset of diabetes, whereas in others the two are diagnosed simultaneously (16). There is evidence to indicate that the underlying constitutional defect in celiac children is a genetical susceptibility to celiac disease, and that one of the adverse conditions favoring its development is an unfavorable uterine environment (50). Celiac disease has been suggested by a number of stud-
ies to be inherited (50, 51). The repeated occurrence of celiac disease in the diabetic animals was probable, because once developed, their highly inbred mating system would retain the genes needed to consequently develop celiac disease in the offspring. An unfavorable uterine environment has also been suggested in the ketotic Chinese hamster (5). Thus, the repeated development of celiac disease in the diabetic Chinese hamsters was supported by the inheritance factor and the unfavorable uterine environment.

Neurological studies on the small intestine of diabetic humans have shown that minimal mucosal damage is displayed when a neuropathy is present (11, 18, 52). This evidence seemed to eliminate neuropathology as the primary etiology of villus atrophy. It has been shown in dogs that partial ligation of the superior mesenteric arteries can lead to villus atrophy (53). The cases in which partial ligation of the mesenteric artery has been seen in diabetic humans is limited (54, 55). When present, this obstruction results in a high mortality rate. The likelihood of partial ligation occurring in these animals was doubtful. The repeated occurrence of villus atrophy in the intestines of these animals suggested that partial ligation was not a primary factor related to villus atrophy. Alterations in metabolism that govern the mechanism of the normal absorptive process can result in mucosal disorders (53). The effect of diabetes on metabolism that governs the absorptive process in the diabe-
tic Chinese hamster is uncertain.

The current study revealed blood vascular dilation in the intestines of the diabetic animals (Table 2, Figures 6, 7, and 10). The diabetic Chinese hamster has previously shown vascular dilation in the retina and kidney (31, 56). The vessel dilations observed in the diabetic animals varied in degree of severity. Some animals illustrated little or no dilation whereas other hamsters had extensive vascular dilation. Some diabetic humans have also revealed vascular lesions in the gastrointestinal tract (19). The vascular dilation in the intestine of the diabetic Chinese hamster may have been related to several factors: (1) Weakening of blood vessel walls in the Chinese hamster, (2) Impairment of the neurology (17, 48) or (3) Metabolite imbalance (53).

The etiology and ramifications of vasodilation in the diabetic Chinese hamster are yet to be determined. Age, duration of disease, and severity have been noted to have an association with the number and degree of vascular disorder in the diabetic Chinese hamster (27, 31, 56).

The apparent ischemic and necrosis condition of the villi seen in the diabetic hamsters intestine could possibly be the result or cause of vessel dilation. Lesions in the sympathetic system that lead to the integration of these vessels may be responsible for the dilation (17). Imbalances in vasoactive substances due to altered metabolism could also have been possibly as a primary factor in vessel dila-
tion (53). The distention of the intestine in some diabetic hamsters lead to speculation concerning the effect of distention on vessel morphology. In other words, vasodilation might develop as a consequence of the highly distended intestine.

Villus atrophy and vascular dilation possibly caused some form of malabsorption in these animals. The severity and duration of diabetes in these animals is possibly creating or accentuating these pathologies.

Non-specific esterase hydrolyzes the esters of short chain fatty acids (57). This study indicated reduced esterase activity along the intestinal brush border (Table 3, Figures 15 and 16). Furthermore, esterase activity along the brush border of the diabetic hamster with villus atrophy was absent or severely reduced. Investigators have displayed disagreement, perhaps due to methodology, with regard to intestinal fat absorption in the diabetic Chinese hamster (4, 37). The data of the current study supported a previous study which revealed reduced dietary fat absorption (4). Esterase reduction seen in the diabetic animals possibly resulted from a vascular disorder (53), sprue syndrome (16), or secondary effects caused initially by neuropathy.

The Phosphatases split phosphomonoesters at an optimal pH. There is optimal splitting of glycerophosphate at pH 9.4 (Alkaline phosphatase) and also at about pH 5.0 (acid phosphatase). Alkaline and acid phosphatase have been im-
plicated in the maintenance of the intra-cellular concentration of phosphate for the formation of bone and in processes of absorption and transport across intestinal membranes (58). Reduced acid and alkaline phosphatase activity were demonstrated in the intestines of the diabetic Chinese hamster (Table 3, Figures 17, 18, 19, 20). Vascular impairment and sprue syndrome when present have been shown to obstruct and limit absorption (53, 59). These depressed enzymatic activities implied reduced absorption and transport along the brush border of the diabetic intestines but no conclusive evidence exists concerning the etiology of these disorders. The decreased enzymatic activities might partially explain the loss of dietary fat and carbohydrate calories via the feces in the diabetic animals (4).

An increase in the intensity of the PA/S positive brush borders (Table 3) was illustrated along the diabetic guts. Since the diabetics consumed excessive food, the resulting intestinal response would presumably be an increase in mucus and glycoprotein along the epithelial border. Small intestine secretions of mucopolysaccarides have been shown to increase due to greater food quantities and irritative stimuli (48). Chyme presence in the intestine also stimulates intestinal secretion (48).

The pathophysiologic mechanisms of malabsorption occurring in the diabetic Chinese hamster are apparently rather complex. Vascular dilation would imply impaired vascular

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function. Villus atrophy would result in some degree of reduced intestinal absorptive surface, abnormal intestinal flora, and impairment of specific transport mechanisms. Villus atrophy could also reduce in those villi affected the mucosal contact time with substrate material. A possible reduction in intracellular digestive enzymes could also be the result of villus atrophy. Thus overall, the data and speculation on these data suggested a complex interrelated malabsorption syndrome.

These pathologies seen in the diabetic Chinese hamster intestine could possibly be limiting the amount of hormonal action on the beta cells. The human body's normal response to carbohydrate ingestion includes elaboration of an unidentified hormonal gut factor from the upper intestine. This factor sensitizes the beta cells to release more insulin per unit increase in glucose concentration. This amplification appears to optimize the beta-cell response, which apparently serves to reduce glycemic peak and to convert the carbohydrate load rapidly into stored fuel reserves (60, 61).

Recently, an author postulated a GTF (Glucose tolerance factor) compound (62). The mode of action of compounds with GTF activity, namely the potentiation of insulin, is postulated to be mediated through the formation of a ternary complex between chromium, insulin, and insulin receptors of cell membranes. Chromium in its biologically active form resembles a hormone, by being released into the blood in response
to a physiological stimulus (insulin) and being transported to the periphery where it exerts a marked biological action. In response to acute increases of insulin in the blood, GTF is released and exerts its action, the potentiation of insulin at target organs. The site of synthesis of GTF may be the intestinal flora (62). Both of these hormonal type compounds, if present in the Chinese hamster, could possibly be reduced due to pathologies described in the current investigation.

Data indicate variability among the pathological findings in diabetic Chinese hamster. This variability might be related to several factors. This study utilized several highly inbred strains of animals and thus varying degrees and types of pathologies might be expressed due to heterogeneity among the animals in different sublines. There is evidence for heterogeneity of diabetes in both man and Chinese hamster. Phenotypic expression due to similar genotype can vary considerably in man and in Chinese hamster (5). The age, duration of disease, and severity of diabetes in the animals of this study may have an effect on the expression of intestinal pathology (63). Due to the small number of pairs of Chinese hamsters utilized in this study, the duration of diabetes could not be accurately correlated with the severity of the various pathologies. Recent studies have shown a high incidence of retinopathy and nephropathy on the severe long term diabetic Chinese hamster (27). Variability
of intestinal disorders has also been reported in diabetic man (64).
SUMMARY

1. Decreased muscle thickness of the muscularis externus and diminished numbers of Auerbach's plexuses were observed in some diabetic hamsters.

2. Diabetic hamsters displayed increased cross sectional area of the small intestine tube and lumen.

3. Lymphocyte aggregations and blood vessel dilations were found in some diabetics.

4. Increased numbers and size of intestinal villi were showed in some diabetics.

5. Increased numbers of goblet cells and increased PAS positive brush border intensity were found in diabetic hamsters.

6. Villus atrophy was displayed in the diabetic hamsters.

7. Reduced activities of brush border enzymes were displayed by the diabetic hamsters.
References


