Lesions of the Gastrointestinal Tract of Pigs Infected with Transmissible Gastroenteritis

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SUMMARY

Gross, subgross and histological lesions were studied in 103 pigs infected with transmissible gastroenteritis virus and killed at daily intervals for 14 days. Twenty-three pigs served as controls. Thirty-six pigs were given colchicine four hours prior to being killed in order to determine the mitotic activity in the gastrointestinal tract. The gross lesions consisted of dehydration, excessive milk curd in the stomach, focal hemorrhage in the submucosa of the diverticulum ventriculi of the stomach, fundic and pyloric congestion in severely dehydrated animals and thinning of the small intestinal wall. The major subgross lesion was a marked shortening of the villi in the lower duodenum, jejunum and ileum within 24 hours after exposure to the virus. Regrowth of the villi became evident on about the sixth day after infection. Histological examination of the small intestine revealed that the villus-height/crypt-depth ratio in the jejunum was reduced from 7:1 in normal pigs to less than 1:1 in infected pigs. Villous atrophy was less severe in the proximal duodenum and ileum. Cells covering the atrophic villi were flattened or cuboidal and did not have well defined brush borders. Inflammatory changes in the gastrointestinal tract were minimal at all stages of infection. Goblet cell numbers increased slightly in the recovery stage of the disease and small numbers of mononuclear cells accumulated in the lamina propria during regrowth of the villi. The number of metaphase nuclei in the small intestinal crypts of infected pigs was greater than in normal pigs.

INTRODUCTION

The sequential changes in the digestive tract of baby pigs infected with transmissible gastroenteritis (TGE) virus have not been reported. Published reports of the gross and histopathological lesions of the digestive tract do not agree on either the nature or the severity of lesions to be expected in infected pigs (2, 6, 7, 8, 11, 12, 15, 22, 23). This lack of agreement appears to be related to variation in the age of the pig and the stage of infection when examined, confusion of post-mortem autolytic changes with ante-mortem lesions, and more recently, variation in virulence of the virus associated with its attenuation in tissue culture. The studies reported here were undertaken to identify the sequential changes in the gastrointestinal tract of young pigs infected with a virulent strain of TGE virus which had been maintained by pig passage at Purdue University since its original isolation in 1945.

MATERIALS AND METHODS

PIGS

Pigs used in these experiments were of mixed Chester White, Yorkshire and Tamworth breeding. They were from a herd established using pigs taken by cesarean section and maintained in a secluded area of the Veterinary Research Farm. All of the pigs were farrowed naturally. They were placed in individual isolation units at three to five days of age and fed cow's milk twice daily. Pigs were separated from their excretions in the isolation unit by an expanded metal floor. All pigs were between one and two weeks of age at the time they were infected.

TGE VIRUS

The virus used in these experiments represented the sixth pig passage of material obtained from Dr. W. W. Bay in 1952 by Dr. Haelterman. The sixth pig passage virus pool was prepared from small intestinal mucosa taken from three pigs killed 48 hours after exposure to fifth pig passage material. A 20 per cent suspension of

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intestinal mucosa was prepared in Hanks' balanced salt solution containing 10 per cent reconstituted dried skim milk by homogenization in a VerTis grinder. Th esupernatant fluid was quick frozen in screw cap vials and stored at -30°C. Twenty-five pigs were used to determine the titer of the virus pool. The dilution which would produce infection in 50 per cent of the pigs as calculated by the Reed-Muench formula was found to be $10^{6.4}$. The standard dose of virus used to infect pigs in these experiments was 1,000 pig infectious doses.

Nine additional isolates of TGE virus were used to compare the lesions obtained with those produced by the Purdue strain. Seven virus isolates were obtained from field outbreaks of TGE in Indiana, one isolate was obtained from a field outbreak in Iowa and the Cornell strain of TGE virus was obtained from Dr. J. A. Baker. Each of these isolates were used to inoculate two or more pigs held in isolation. One of these pigs was killed two days after exposure and its intestinal tract examined in the same manner as other experimental pigs. The second pig was allowed to recover and then given the Purdue strain of TGE virus to determine if resistance had been induced by the initial infection.

Pathological Examination

Pigs were stunned by a blow on the head and exsanguinated. Subgross observation of the small intestinal mucosa was accomplished within 15 minutes after death by trimming the small intestine from its mesentery, opening the intestine and examining it under a thin layer of water through a dissecting microscope. Tissue specimens were taken from the center of the greater curvature of the stomach, the duodenum at the beginning of the mesenteric border, the approximate middle of the jejunum, the ileum 5 cm anterior to the ileocecal valve and at the apex of the spiral colon. These were fixed in neutral buffered formalin and processed in a routine manner. Sections were stained with hemotoxylin and eosin and with mucicarmine-mentanil yellow-hematoxylin. Average villous lengths and crypt depths were determined in selected areas in which the villi and crypts were continuous and sectioned through their entire length. At that point the mean length of the three longest villi and mean depths of three adjacent crypts were determined using an occular micrometer.

Mitotic Activity

Thirty-six pigs maintained in isolation were used to determine the effect of TGE infection on the mitotic activity of the gastrointestinal tract. Six normal pigs were used as controls and six pigs were killed on each of the first five days after infection. Each pig was given a feeding of milk at 8 a.m. and two to three hours later an intraperitoneal injection of 0.25 mg colchicine/kg body weight (17). They were killed exactly four hours after the injection and tissues were fixed immediately in neutral buffered formalin. The average number of mitotic figures in crypts included in a single high power field was determined in each section.

RESULTS

Gross Lesions

The degree of dehydration in pigs dying or killed after exposure to TGE virus was related to the length of life after the onset of vomition and diarrhea. Following the onset of diarrhea, dehydration was rapid and most pigs infected at one to two weeks of age lost ¼ to ⅓ of their body weight within a few days. The consistency of the fecal material was related to the degree of hydration with more profuse watery diarrhea being observed in the early stages of the disease. As dehydration became more marked, the stool became thicker and more homogeneous. The nature of the stomach contents changed little during the course of the disease, being a fairly solid caseous curd at all times. In the later stages of the disease, the curd was often bile stained. The fluidity of the intestinal contents was directly related to the degree of hydration so that in most pigs dying of the disease, the small and large intestine contained a thick bile stained chyme. This chyme was not, however, catarrhal in nature and thus different than the mucoid chyme seen in some other enteric diseases of young pigs.

Congestion of the mesenteric vessels was commonly seen in pigs that died of the disease, but in pigs killed at daily intervals after infection the degree of congestion was directly related to the degree of dehydration. Marked congestion occurred in the region of the greater curvature of the stomach in some pigs which were severely dehydrated.

Hemorrhage was not a constant feature

and when encountered in these experiments, it was confined to a focal area at the border of the diverticulum ventriculi on the diaphragmatic side of the stomach. Fifty per cent of the pigs killed on the first and second day after infection had this lesion which ranged in size from pinpoint to 2 cm in diameter. The hemorrhage occurred primarily in the submucosa and was apparently readily reabsorbed since hemorrhage or evidence of previous hemorrhage was not observed in pigs killed after the eighth day of infection. Free blood was never observed in the stomach or intestinal contents.

One of the striking features was the absence of chyle in the subserosal and mesenteric lymphatics and the mesenteric nodes. In normal pigs sucking the sow or being fed cow's milk chyle was always seen in the lymphatics of upper ½ to ⅔ and frequently throughout the length of the small intestine. At 24 hours or more after infection, chyle was not observed except in the lymphatics of the first part of the duodenum.

Subgross Lesions of the Small Intestine

Lesions of the small intestinal mucosa could be observed readily when examined under water with a dissecting microscope. With experience these changes could be recognized with the unaided eye or with a hand lens. It was important that the mucosa be held just beneath the surface of the water since this allowed free separation of the villi.

The normal villi of the small intestine were long narrow finger-like extensions of the mucosa toward the luminal surface. Infection with TGE caused a marked shortening of these villi to a point where only small protusions of a relatively flat mucosal surface were observed. A comparison of normal (bottom) and TGE infected (top) small intestine is shown in (Fig. 1). The presence or absence of chyle in the lymphatics of the villi could also be readily detected when viewed with low power magnification.

Variation in the degree of villous atrophy was found. Within one day after infection most of the villi were atrophied to a maximal degree. However, the villi in the first few centimeters of the duodenum usually remained normal throughout the course of the disease, and there was then a gradual shortening of villi in the next several centimeters. The villi over Peyer's patches

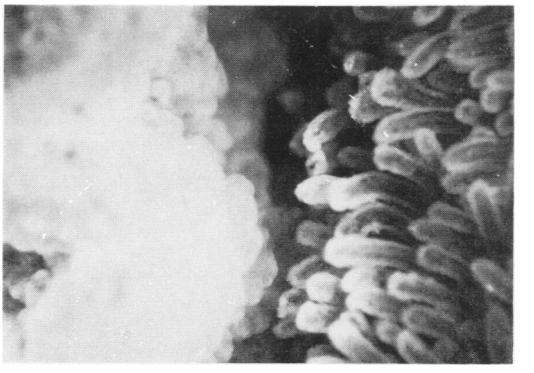

Fig. 1. Subgross appearance of normal finger-like villi in the jejunum of one pig and atrophic jejunal villi of a second pig 48 hours after infection with transmissible gastroenteritis virus.

did not generally decrease in size to the same degree as those villi immediately adjacent. The greater portion of the small intestine did, however, undergo a fairly uniform villous atrophy within one day post-exposure.

Beginning on the sixth day, regrowth of the villi became apparent. This was seen first as areas of increased villous length in the jejunum and was not uniform until the eighth day after exposure. Beginning on the seventh day chyle was found in the lacteals where regrowth of villi had occurred.

In several pigs killed on the ninth and tenth day after infection, there were focal accumulations of mucus in the small intestine. These never occurred in the first 30 centimeters or last meter of the intestine and while several were sometimes present in a single small intestine, the length of the individual mucus-covered areas was only 25 to 40 cm. The villi in such areas were completely covered by a tenacious mucus. When the mucus was teased away, the villi were as long as adjacent villi but appeared thinner and chyle was not visible in the lacteals.

One pig killed on the 14th day after infection had villi shorter than other recovered pigs and in addition to the shortening there was a marked leaf formation of the villi. In all other pigs examined in the recovery stages of TGE, the regenerating villi were round or slightly elliptical and resembled normal villi except for length.

Histological Lesions of the Stomach

The mucosa of the stomach in pigs infected with TGE was slightly thinner than that of normal pigs. Thinning of the mucosa was noted by the second day after

TABLE I Length of Villi and Crypts in the Small Intestines of Pigs Infected with TGE. The Mean and One Standard Deviation are Given in Microns

Day After Infection	No. Pigs	Duodenum Villi	Duodenum Crypt	Jejunum Villi	Jejunum Crypt	Ileum Villi[a]	Ileum Villi[b]	Ileum Crypt
Normal	23	641 ± 268	124 ± 27	795 ± 260	110 ± 26	384 ± 122	456 ± 194	121 ± 31
1	23	272 ± 182	176 ± 48	180 ± 83	157 ± 27	274 ± 105	209 ± 140	138 ± 22
2	19	231 ± 175	169 ± 38	122 ± 48	150 ± 23	212 ± 59	125 ± 44	146 ± 25
3	11	252 ± 210	169 ± 23	150 ± 48	170 ± 23	218 ± 93	159 ± 65	142 ± 20
4	12	525 ± 203	182 ± 37	174 ± 57	193 ± 34	267 ± 95	190 ± 66	147 ± 23
5	13	520 ± 268	174 ± 39	157 ± 46	195 ± 37	263 ± 131	195 ± 121	166 ± 27
6 - 7	6	464 ± 310	173 ± 25	332 ± 156	175 ± 22	250 ± 130	230 ± 99	154 ± 18
8 - 10	7	707 ± 235	159 ± 25	467 ± 179	156 ± 25	282 ± 102	267 ± 90	139 ± 21
11	6	559 ± 233	192 ± 34	502 ± 175	169 ± 40	472 ± 84	418 ± 109	129 ± 27
12 - 14	6	574 ± 176	155 ± 39	431 ± 111	145 ± 22	336 ± 62	299 ± 77	134 ± 27

[a]Villi measured over the Peyer's patches
[b]Villi measured over the area where no lymphoid tissue was present in the submucosa

infection and did not return to normal until after the seventh day. The thinning was not due to erosion or ulceration, but could be attributed to stretching of the stomach wall associated with retention of ingesta.

Within three days after infection there was a depletion in the amount of stainable mucus in the cells on the luminal surface and in the gastric pits in about one-half of the stomachs examined. The cells were shorter and had less cytoplasmic mass. These changes were seldom observed after the seventh day of infection and were not of sufficient severity or consistency to be considered a highly significant change

A slight increase in the number of mononuclear cells in the lamina propria of the stomach was observed in five of 13 pigs within 24 hours after infection. Slightly more cells were seen by the second day after infection in seven of 13 pigs. This lesion was found throughout the 14 day period of this study, but in a lesser number of animals and to a lesser degree after the seventh day of infection.

Slight mucosal edema and more pronounced submucosal edema was present in a few stomach sections taken after the first day of infection. Congestion was most marked on the fourth day after infection. Not all stomachs on any given day of infection were congested and those with the greatest degree of congestion were from pigs which were most dehydrated. Thrombi were found in the gastric vessels only once.

Sections through hemorrhagic foci in the region of diverticulum ventriculi revealed that the hemorrhage was primarily in the submucosal tissue. Some hemorrhage was present in the lamina propria of the overlying mucosa but this was minimal.

Histological Lesions of the Small Intestine

The variability in intestinal lesions observed at the subgross level was confirmed on histological examination. The greatest variability was found in the mucosa of sections taken at the beginning of the mesenteric border of the small intestine. The mucosa at that point was in the area of variable atrophy and in only a few pigs was the atrophy observed to be as complete in the duodenal area as in the jejunal area. There was little difference between jejunal villi and ileal villi not located over lymphoid tissue. However, those villi in the ileum which overlaid lymphoid tissue did not atrophy to the same degree even though infection with TGE did reduce them to about one-half their normal length. Table I lists dimensions of villi and crypts in the small intestines of pigs killed at various intervals after infection with TGE. There it can be seen that atrophy of the villi and increased depth of the crypt of Liberkuhn was marked within 24 hours after infection. Variability in the length of duodenal villi was evidenced by the large standard deviation. Regrowth in the jejunal area was apparent after the fifth day of infection supporting the subgross observations. The histological appearance of a normal and typically affected intestine are shown in Figs. 2 and 3.

Villous atrophy was associated with a failure of the cells migrating from the crypt

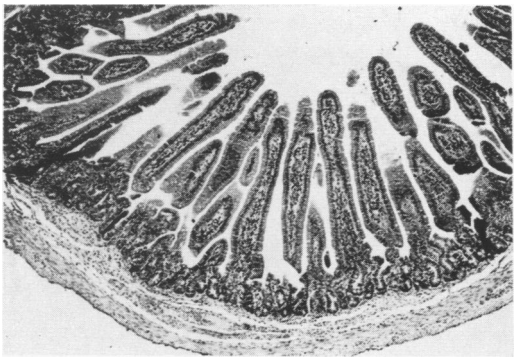

Fig. 2. Normal jejunal mucosa of a five day old pig. Note the appearance of the epithelial cells covering the villi.

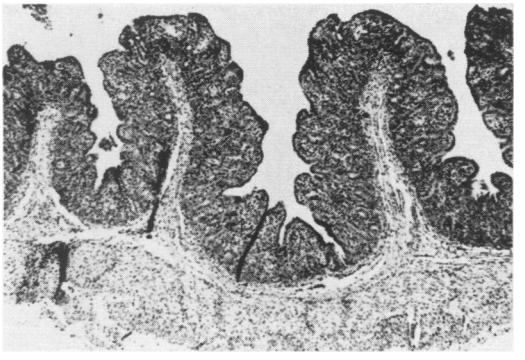

Fig. 3. Jejunal mucosa of a pig two days after infection with transmissible gastroenteritis virus. Note the shortened and clubbed stubs of villi and the increase in depth of the crypts of Lieberkuhn. There is a marked reduction in number of villi, and epithelial cells covering the villi are flattened.

to undergo normal differentiation to columnar epithelium. Typical villous epithelial cells in the intestines of TGE-infected pigs were flat to cuboidal in shape, had a vacuolated cytoplasm, indistinct cytoplasmic borders and short poorly defined microvilli. The appearance of these cells is shown in Fig. 3. Vacuolation was observed in the epithelial cells of normal pigs, but rarely. When it occurred it was mostly in the cells at the tip of the villus. In the jejunum, vacuolation was present in a large number of intestines one day after infection and was present in almost all jejunal sections from the second through the fifth day after infection. In pigs which were recovering from TGE the vacuolated cells were found primarily in tissues where villus atrophy was still marked. Epithelial cells in the ileum appeared less degenerate than those in the jejunum with cells located on villi over lymphoid tissue having the least degenerate appearance.

Undifferentiated cells covering villous stubs had alterations in the structural and staining properties of their nucleoli. The nucleoli were large, sometimes paired, and more esoinophilic than normal. Cells containing such nucleoli were more numerous near the throats of crypts and their relative number was related to the degree of non-differentiation.

Only minimal inflammatory changes were associated with TGE infection even though large numbers of bacteria were obvious in the lumen of many sections prepared from animals infected one or more days. In a few sections taken 24 hours post-infection, epithelial cells had clearly sloughed and small focal neutrophile accumulations were present. Beginning on the fifth day after infection accumulations of mononuclear cells appeared in the lamina propria. These cells collected first, and in the greatest numbers, at the base of the mucosa.

Congestion and edema of the lamina propria were present in varying degrees in some of the sections taken from pigs killed during the first few days of the disease. However, the low number of tissues containing this lesion indicated that it was relatively unimportant.

There was some depletion of lymphocytes in the follicles of Peyer's patches as early as the second day after infection. This depletion was most marked on the third through the fifth day after infection when the follicles also appeared reduced in size.

The amount of stainable mucus in goblet cells was decreased during the first and second day of infection and then returned to normal. The mean number of goblet cells per given area of crypt tissue increased slightly during the recovery stages of the disease. The production of mucin and movement of the goblet cells was apparently not influenced by infection with TGE.

Regeneration and differentiation of normal appearing epithelial cells were closely associated with regeneration of the villous structure. In the duodenum most sections of tissue had nearly normal epithelial cells within four days after infection but it is possible that this represented lack of initial destruction rather than regeneration. In the jejunum there was some improvement in the appearance of cells by the fourth day after infection, but entirely normal appearing cells were not observed until the seventh day after infection. It may be noticed in Table I that within eight to ten days after infection, villi had attained

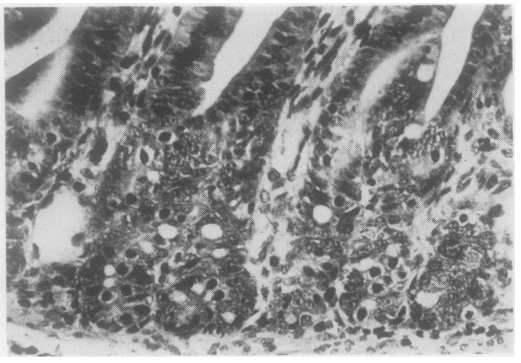

Fig. 4. Mitotic activity in the crypts of normal jejunum. Mitotic figures are the dark solid structures located near the crypt lumen.

a length considered normal for adult swine (21).

Histological Lesions of the Colon

Grossly apparent inflammatory changes were absent in the colonic mucosa at all stages of infection. Histological changes were so minimal as to be insignificant in relation to those of the small intestine. Epithelial cells bordering the lumen appeared slightly shorter on the fourth and fifth day of infection. Focal mucosal necrosis was present in only one section of colon. Slight edema and congestion were present in a few sections from pigs killed the first few days after infection. A moderate mononuclear cell infiltration of the lamina propria was observed to occur after the fifth day of infection. Infection with TGE virus did not produce detectable effects on the colonic diverticuli or lymphoid tissue of the colon.

Mitotic Activity in the Gastrointestinal Mucosa

Mitotic activity of the stomach mucosa appeared to decrease during infection with TGE while both large and small intestinal mucosa had apparent increases in mitotic activity. Comparison of Figs. 4 and 5 will indicate the appearance of mitotic figures in tissue collected four hours after colchicine administration. In Fig. 5 the failure of normal cell differentiation described above is also apparent.

Lesions in Pigs Infected with Field Isolates of TGE Virus

All pigs killed on the second day after infection with field isolates and the Cornell

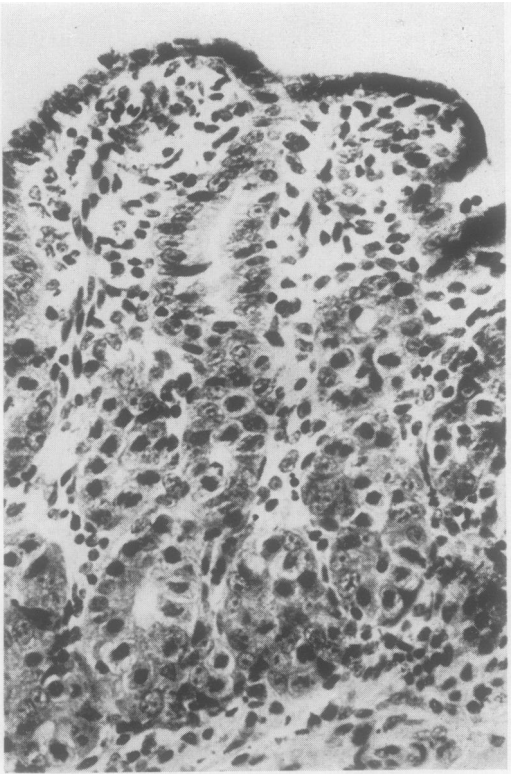

Fig. 5. Mitotic activity in the crypts of the jejunum from a pig killed two days after infection with transmissible gastroenteritis virus. There is an increased number of mitotic fgures as well as a failure of normal cell differentiation on villi.

strain of TGE virus had lesions similar to those pigs infected with the Purdue strain and killed at a comparable time. Pigs infected with field isolates or the Cornell strain failed to develop signs of infection when subsequently exposed to the Purdue strain of TGE virus indicating that cross protection occurred.

DISCUSSION

The primary gross lesions associated with TGE infection in baby pigs were dehydration, accumulation of milk curd in the stomach and congestion of the gastrointestinal tract. These observations have been widely reported and are present in most baby pigs in the advanced stages of the disease. The only gross lesion about which there is disagreement is occurrence of hemorrhage in the stomach and small intestine. Grossly evident hemorrhage was found only in the submucosa of the diverticulum ventriculi of the stomach in the infected pigs in this study and its presence

was associated with vascular rupture caused by vomition, a constant early clinical feature of TGE, rather than by degenerative changes in the stomach mucosa. Microscopic evidence of hemorrhage was not found in the fundic portion of the stomach or in the intestinal tract.

There is widespread disagreement on the nature of the histopathological changes in the small intestine of TGE infected pigs. Lee, Moro and Baker (11) and Feenstra, *et al* (7) failed to find any significant microscopic changes. Others (2, 8) reported focal necrosis of the small intestinal mucosa with loss of up to one-half of the individual villus which was associated with sloughing of the epithelium and infiltration of polymorphonuclear leukocytes. Wallace and Whitehair (23) reported similar epithelial sloughing, necrosis, and cellular infiltration and included photographs which revealed marked villous atrophy in the jejunum of affected pigs. They also reported a reduction in the height of the mucosal epithelium. Okaniwa and Maeda (15) considered the essential lesion to be a serous catarrhal inflammation throughout the small intestine with slight desquamation of epithelium, but with exudative and cellular reaction in the tunica propria. They also published photographs indicating villous atrophy and failure of normal cell differentiation. Trapp, Sanger, and Stalnaker (22) infected germ free pigs with TGE virus and reported that there was destruction of the villi in the jejunum and ileum and that epithelial cells covering the villi were vacuolated and appeared squamous like. Maronpot and Whitehair (12) reported both villous atrophy and poor differentiation of epithelial cells in three pigs infected at three weeks of age.

The most significant lesions in the small intestine of pigs used in the present studies were marked villous atrophy and temporary failure of epithelial cells to differentiate to normal columnar epithelium. The reason for lack of atrophy in the proximal portion of the duodenum in many of the intestines is not known. We reported that virus will replicate in the upper duodenum (9). However, in using isolated duodenal loops to demonstrate virus replication, bile was prevented from entering the loop. Since TGE virus is sensitive to ether (13, 19, 25), there may be some protective effect on the upper duodenum by continuous secretion of bile in the intact animal. This conjecture has yet to be tested however. Relative resistance of ileal villi overlying lymphoid tissue may be due to the amount of mucus and goblet cells present at those sites since approximately twice the number of goblet cells are present there as can be found in other areas of small intestinal mucosa. Lymphoid tissue may also contribute some protective factor to the mucosa.

Villous atrophy was a consistent finding in all infected pigs. This suggests that it is a typical lesion of the disease and not related specifically to the Purdue strain of TGE virus. Uniformity of this lesion in the disease is supported by reports and published photographs of several other investigators (12, 15, 22, 23). Report of similar lesions in gnotobiotic pigs also indicates that the lesion is caused by virus rather than by secondary bacterial infection (22).

The exact pathogenesis of the villous atrophy is not certain although it is assumed that it occurs because of destruction of the epithelium covering the villi. Atrophic lesions can be produced by several infectious and chemical agents. Biggers, Kraft and Sprinz (4) reported marked villous atrophy and giant cell formation in lethal intestinal virus infection of mice. Partial villous atrophy was reported in man during infection with infectious hepatitis (18). Abrams, *et al* (1) reported alteration in the villous-height crypt-depth ratio, abnormal differentiation of epithelial cells and increased mitotic activity in focal areas of mouse ileum infected with *Salmonella typhimurium.* Prolonged disruption of normal mitotic activity will also produce villous atrophy as shown in mice given 5-fluoruracil (14) and in rats given colchicine (5). Gluten enteropathy in humans is characterized by villous atrophy, relative and absolute increase in the depth of crypts, inflammatory cell increase in the lamina propria and alterations in surface epithelial cells (16). The accelerated mitotic activity found in TGE infected animals suggests that villous atrophy is caused by a destructive effect on the differentiated epithelial cells on the villi rather than by inhibiting cellular replication in the crypts.

The temporary failure of differentiation of cells covering the stubs of villi after the initial loss of functional epithelium is probably as significant in the pathogenesis of the disease as is the decrease in length of villi. Most of the hydrolytic enzymes associated with digestive activity of the small intestine develop during the migration of

the cell up the villus and are absent or present in only low levels in the crypts in normal animals (24). Therefore cellular loss would be expected to reduce the amount of digestive enzymes accordingly. Maronpot and Whitehair (12) used six histochemical tests on the small intestine and found the concentration of all were lower in infected than in normal pigs. It has been shown that the nature of the epithelial cell is more important in relation to clinical signs of gluten enteropathy than is villous atrophy (3). Histochemical techniques have also shown that some of the hydrolytic enzymes are localized at the brush border of the cell (24) so that failure of cellular differentiation and brush border development in pigs infected with TGE would further reduce the digestive capability of the small intestine.

With the degree of mucosal destruction and cellular alteration observed in pigs with TGE, it is interesting to speculate on the relationship these changes might have to the clinical signs observed in the disease. Onset of diarrhea was closely correlated with destruction of villous epithelium and would seem to be directly related. Rapid weight loss and associated dehydration of baby pigs affected with TGE indicates that loss of fluids from the body is greater than that absorbed from dietary intake. Kalser, *et al.* (10) have concluded that in man, ingestion of either an isotonic or hypertonic solution caused a dilution of the meal in the stomach and duodenum and absorption in the jejunum. If this concept holds true in the pig, body fluids may be lost into the lumen of the digestive tract in an effort to dilute ingesta to an isotonic solution. Because of digestive and absorptive failure due to the loss of functional epithelium, fluid (saliva, stomach secretions, pancreatic secretions, bile, and ingesta) would remain in the intestinal lumen and be lost in the feces. There is no indication that the function of bile or pancreatic secretions are altered in TGE. If these secretions function normally there would be some breakdown of ingesta which would combine with the bacterial metabolites to increase the osmotic pressure of chyme over that of the ingesta. This explanation fits well with the observation that clinical signs and mucosal changes in the small intestine are closely related to one another both at the onset and during the recovery stages of TGE.

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