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THE UNIVERSITY OF ALBERTA

SURGICAL TREATMENT OF SHORT BOWEL SYNDROME: THE BIANCHI PROCEDURE

BY

© W. DONALD BUIE, MD

A THESIS

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William Donald Buie

William Donald Buie
1401, 8210 - 111 Street
Edmonton, Alberta
T6G 2C7

Date: June 9, 1990.

QUOTATION

YOU SEE ONLY WHAT YOU LOOK FOR;

YOU RECOGNIZE ONLY WHAT YOU KNOW.

- Merril C. Sosman

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **SURGICAL TREATMENT OF SHORT BOWEL SYNDROME: THE BIANCHI PROCEDURE**, submitted by W Donald Buie in partial fulfillment of the requirements for the degree of MASTER OF SCIENCE in EXPERIMENTAL SURGERY.

Dr O G Thurston

Dr R N Fedorak

Dr F X Aherne

Dr J C Russell

Date: 6 June 1990

DEDICATION

To my wife, Kathleen

ABSTRACT

The Bianchi bowel lengthening procedure is effective in treatment of Short Bowel Syndrome (SBS). The object of this experiment was to compare the efficacy of a Bianchi bowel lengthening procedure performed in residual ileum and jejunum of a 75% short bowel model. Eighteen female piglets weighing 14-17 kg underwent a 75% mid small bowel resection. After a six week post-operative period, animal weights were similar and pigs were randomly assigned to one of three treatment groups: a control group receiving no further therapy, a group receiving a Bianchi procedure in the residual jejunal segment and a group receiving a Bianchi procedure in the residual ileal segment. The animals were followed for a further twelve weeks. Six additional animals underwent sham operations and were followed for 18 weeks. Jejunal Bianchi-treated short bowel demonstrated a greater weight gain (78.8$\pm$4.9 kg) compared to short bowel control (63.0$\pm$6.6 kg) and ileal (69.3$\pm$6.9 kg) groups. The rate of weight gain for the jejunal Bianchi group was significantly greater (5.0$\pm$0.3 kg/wk) vs short bowel controls (3.4$\pm$0.4 kg/wk) ($p < 0.05$). The increase in weight gain in the jejunal Bianchi group was not a consequence of initial bowel

length, changes in bowel length or diameter, digestibility of fat, or nutritional status. Kinetic constants for the effects of D-glucose on short circuit current following 18 weeks of SBS demonstrated a lowered glucose V_{max} in animals with short bowel compared to sham-operated controls. Furthermore, ileal V_{max} was further lowered in the presence of a Bianchi procedure. Glucose Kd was similar in all groups.

We conclude that: 1) during SBS, weight gain was significantly higher in animals when the Bianchi bowel lengthening was performed in jejunum, 2) the effect of the procedure is not due to bowel lengthening, 3) SBS in swine decreases intestinal glucose V_{max} and impairs glucose transport and 4) the Bianchi segment has no intrinsic adaptive ability with respect to glucose transport.

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CHAPTER I

INTRODUCTION

Short Bowel Syndrome is the clinical consequence of massive resection for many different intestinal diseases (1,2). Until the advent of total parenteral nutrition (TPN) and specialized nutritional support, survival was uncommon. Total parenteral nutrition has increased the prevalence of this condition, however, it has created its own set of problems (3). It is not a cure and the clinician is still largely dependent on the intrinsic adaptability of the residual intestine for ultimate patient survival.

Medical and surgical intervention is primarily supportive until adaptation can take place. Most surgical therapy has been relegated to those patients whose adaptation has been inadequate even with maximal medical support.

The Bianchi procedure is relatively new, having been described in 1980 (5). It has been shown both experimentally and clinically to be effective in the treatment of Short Bowel Syndrome (5-9). One study has

compared the Bianchi procedure to medical therapy and to other conventional surgical procedures in the treatment of short bowel in a swine model (10). The procedure was as effective as medical therapy and better than colon interposition in promoting adaptation. The Bianchi procedure, however, has never been critically evaluated with respect to the importance of location or length of the Bianchi segment nor has the mechanism of action been revealed.

The pig is an appropriate model for human gastrointestinal function (11). The anatomy, both macroscopic and microscopic (12), the physiology of digestion and absorption (12,13), and the nutritional requirements of humans and pigs are very similar (14). A 75% short bowel pig model has been previously described and was adopted for this experiment (5).

In this thesis, Chapter II focuses on the mechanisms of intestinal adaptation to Short Bowel Syndrome. It reviews the morphological and functional adaptation of residual small bowel after massive intestinal resection and the factors which influence adaptation along with the three basic pathophysiological defects. The latter will serve as

a basis for the discussion of medical therapy of Short Bowel Syndrome.

Chapter III is concerned with surgical therapy and is again organized around the basic pathophysiological defects of Short Bowel Syndrome.

Chapter IV is the experimental portion of the thesis and examines the Bianchi bowel lengthening procedure as it pertains to the surgical treatment of Short Bowel Syndrome. The study compares the efficacy of a jejunal versus an ileal Bianchi procedure in the treatment of a 75% short bowel pig model. Our hypothesis is that there is no difference between an ileal and a jejunal procedure in promoting adaptation in the 75% short bowel swine. The study also investigates possible mechanisms of action of the Bianchi procedure comparing glucose transport capabilities of jejunal and ileal Bianchi segments.

The final chapter is a general discussion of the results relating them to other short bowel models and to the clinical situation in humans.

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CHAPTER II

SHORT BOWEL SYNDROME:

INTESTINAL ADAPTATION AND MEDICAL THERAPY[1]

Surgical treatment of many gastrointestinal diseases necessitates resection of segments of small intestine. This is well tolerated in most cases due to the intrinsic reserve of the gastrointestinal tract. However, massive intestinal resection can lead to a variable clinical picture of diarrhoea, steatorrhoea, malabsorption and weight loss. This constellation of clinical events has been termed the Short Bowel Syndrome and has been recently reviewed (1,2).

The disease states which predispose to massive intestinal resection are determined primarily by the age of the patient. The infant population must contend with necrotizing enterocolitis, atresias, volvuli and abdominal wall defects with resultant herniation and vascular compromise (3,4). The adult is more likely to be faced with

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1 A version of this chapter has been published. Buie WD, Thurston OG, Fedorak RN. Can J Gastroenterol 1990;4:70-8.

repeated resection as a consequence of Crohn's disease (5) while in the elderly, resection is most likely due to a mesenteric infarct (6).

In the past, there has been a high mortality rate associated with short bowel and, thus, Short Bowel Syndrome was an extremely rare entity (7,8). Development of improved supportive care and total parenteral nutrition have prolonged survival and made this condition prevalent (4,9-11). Parenteral nutrition has allowed continued intravenous feeding during intolerance to oral nutrition, and patients with extremely short bowel can now exist entirely on home total parenteral nutrition (12,13).

Although it is well known that residual small bowel length below 50 cm makes maintenance of adequate nutrition difficult, the minimal length of small intestine that is compatible with life (without nutritional support) is poorly defined. In the early 1950's, it was believed that survival with less than one half of the small bowel length was improbable (7,8). This was quickly challenged by reports of patients surviving with shorter and shorter length of bowel (14-16). The first comprehensive study of Short Bowel Syndrome in children was published in 1972 by Wilmore in which he reviewed the outcome of 50 infants (17). He found

that survival depended to a large extend on the presence or absence of the ileocaecal valve in addition to residual intestinal length. Infants with greater than 38 cm of small bowel and an ileocaecal valve had 100% long-term survival while those with 15-38 cm had only a 50% survival. Infants with less than 15 cm of bowel had a 100% mortality regardless of the status of the ileocaecal valve. In the absence of an ileocaecal valve, 40 cm of residual bowel was the lower limit for any degree of survival.

The next most important determinant of the clinical picture following small bowel resection is intrinsic intestinal adaptation (18). Intestinal adaptation is felt to be influenced by three factors:

1) the type of intestine that remains;

2) the disease state for which the resection was necessary, and

3) the condition of the residual intestine (1,2).

Presently, treatment of the Short Bowel Syndrome can be divided into two general categories: supportive therapy or therapy to enhance intestinal adaptation. Most treatment measures, whether medical or surgical, are supportive in nature while awaiting intrinsic intestinal adaptation to

take place. Recent developments suggest some modes of therapy may enhance or accelerate intestinal adaptation.

This review will first examine intestinal adaptation following the stimulus of small bowel resection. It will then examine medical therapy (and finally surgical therapy) for the Short Bowel Syndrome. For the purpose of this discussion, a strict definition of Short Bowel Syndrome as defined by length or percent of bowel resected will be avoided. This is because of the extreme variation in function of patients with similar residual lengths (2). The definition used will be a clinical one in which the signs and symptoms as outlined above are present.

INTESTINAL ADAPTATION

Intrinsic intestinal adaptation may be the single most important variable affecting the eventual outcome of a patient with Short Bowel Syndrome. It, in turn, is dependent on four factors: (a) the length of residual intestine, (b) the type of residual intestine, (c) the functional state of the residual intestine and, (d) concomitant colonic and ileocaecal valve resection, both of which are detrimental to adaptation (1).

It has been clearly shown by Hanson et al that the adaptive intestinal response is directly related to the amount of intestine that is resected (19) and clinical studies have confirmed this (4,14,17,20). This adaptive response can be overwhelmed by massive intestinal resection (18). Residual ileum is much more efficient and effective at intestinal adaptation than jejunum although the mechanism(s) involved are not entirely clear (18,21,22). If the residual intestine is affected by an active disease process such as Crohn's disease or diffuse arteriosclerosis, intestinal adaptation may also be inhibited.

Adaptation is also a function of time and in humans, it is generally accepted to continue to occur up to two years following small bowel resection (1,2,23). The definitive effects of medical or supportive therapy can not be evaluated until after this time.

Intestinal adaptation can now be discussed from two viewpoints: morphological and functional adaptation. Original descriptive studies of intestinal adaptation were from a morphological viewpoint only and it has been only in the last 20 years that functional studies have been performed to complement them.

MORPHOLOGICAL ADAPTATION

Macroscopic changes following intestinal resection have been recognized since the classical experiments of Senn in 1888 and Flint in 1912 (24,25) and have been confirmed by many subsequent studies (26-31). Residual intestine undergoes dilation and thickening of all of its layers (29). However, whether or not there is a true increase in bowel length is controversial and may, in part, be attributed to different animal models examined. Most authors believe that an increase in intestinal length is not part of the morphological adaptive response in man (18,21,32).

The microscopic picture of intestinal adaptation has also been well described. Flint in his classic paper, demonstrated that the intestinal villi doubled in height and while he calculated a four-fold increase in mucosal surface area, he correctly observed that the number of villi remained constant and that crypt depth increased. Subsequent studies have confirmed these observations (26-34).

Mucosal hypertrophy is maximal just distal to the post-resectional anastomotic site and decreases further downstream (28). Although distinct mucosal hyperplasia occurs proximal to the anastomosis, it is far less

pronounced. Jejunal resection produces a 70-100% increase in structural and functional measurements in the residual ileum whereas ileal resection produces only 20-30% increases in structural and functional measurements in residual jejunum (27,28,32-35).

FUNCTIONAL ADAPTATION

The morphological adaptations that are observed likely contribute to functional adaptation. These functional alterations can be separated into changes in absorption and changes in motility.

The loss of mucosal surface area reduces the absorption sites of almost all nutrients and, as a consequence, functional adaptation is seen involving the absorption of most nutrients (21,33). There is increased segmental absorption of fluid and electrolytes (36). Oligo saccharides and monosaccharides are absorbed at increasing rates when absorption is expressed per length of intestine (21,31,37). Thus it appears that absorption can be induced suggesting the possibility of receptor recruitment (38,39).

Brush border enzymes also show adaptive changes with increase in total activity per segment, however, specific activity of the enzymes is not altered and may even decrease

in vitro (38,40). It has been suggested that brush border membrane enzymes may be induced earlier along the villus such that enterocytes are functional at an earlier stage of development (29,41). Recently, however, studies by Menge and Chaves on disaccharidase activity in post-resectional rat mucosa show maintenance of the normal enzymatic gradient along the villus and stress that the cells are probably not functional immature cells (42). The function of individual enzymes may be more dependent on the total enzyme activity levels in the residual segments prior to resection as specific enzyme systems are not uniformly distributed throughout the bowel. Despite these changes in brush border enzymes, the lipid composition (total free fatty acids, total bile acids, total cholesterol, total and individual phospholipids, and the ratio of total phospholipids to total cholesterol) of brush border membrane was found to be similar in control resected intestine (43).

Adaptation to the absorption of amino acids and peptides also occurs following intestinal resection. The brush border becomes much more efficient at protein utilization increasing both absorption and peptidase activity as expressed per unit length (21,33,38). Again this is probably secondary to mucosal hyperplasia (41).

Adaptation to lipid digestion and absorption is more difficult to assess due to the compounding problem of bile acid pool losses. It appears that there is an increase in the absorption of free fatty acids, mono and diglycerides per unit length of residual intestine (21).

As is seen with the morphological adaptive response to intestinal resection, the functional adaptive response of the ileum is greater than that of the jejunum. In the normal intestine, jejunal absorption of nutrients is greater than the ileum. With jejunal resection, the ileum adapts to absorb nutrients at nearly the same rate or an increased rate relative to normal jejunum (44). Following ileal resection, residual jejunum undergoes a small degree of adaptation. The increase in absorptive function is not as marked and it cannot assume the specialized ileal functions of bile salt and Vitamin B_{12} absorption (21,33). Interestingly, as ileal enterocytes undergo adaptive hyperplasia, there is a supranormal absorption of both Vitamin B_{12} and bile acids as expressed per unit length of intestine, although this appears to be of little clinical consequence (21).

As the major cause for malabsorption in the Short Bowel Syndrome is the loss of mucosal surface area, the

morphological changes of adaptation to increase the residual surface area are understandable. Similarly, maintaining the functional capacity of the short gut requires that the intestine absorb more per unit length. Clinically, functional adaptation is observed as the patient with Short Bowel Syndrome slowly recovers tolerance to oral feeds with diminishing diarrhoea and steatorrhoea (1,2,18).

The second functional adaptation involves intestinal motility. Transection of the proximal bowel separates the duodenal pacemaker from the residual intestine (45). Uncoordinated peristalsis, combined with dilation of the intestine leads to ineffective forward propulsion and mixing. This results in bacterial overgrowth, impaired mixing of chyme, poor digestion and alteration in transit time.

There is recent evidence that the ileum acts as a brake on proximal intestinal transit. Initial studies by Snell first described the association between steatorrhoea and small bowel hypomotility (46). In a recent experiment, Spiller et al demonstrated that the instillation of fat into the ileum caused a delay in transit time of jejunal contents (47). The effect was not seen with the instillation of either carbohydrate or protein solutions. This may further

explain why jejunal resection is clinically better tolerated than ileal resection as a residual ileal segment can still exert this braking effect on intestinal transit.

MECHANISMS OF ADAPTATION

How does intestinal adaptation occur? There is no single theory which explains all experimental evidence. Three major factors proposed include: (a) luminal nutrition, (b) hormonal or systemic factors, and (c) pancreatico-biliary secretions.

Luminal nutrition

Evidence for the importance of luminal nutrition in the adaptive response following resection is best illustrated in three situations. When luminal nutrition is withheld by starvation, with or without maintenance of parenteral nutrition, the intestinal mucosa atrophies (48,49). This intestinal atrophy can be reversed by the reinstitution of oral nutrition (50). Secondly, exclusion of the intestine from the luminal stream by creation of Thiry-Vella fistulas or with intestinal bypass causes atrophy in the defunctioned intestine (44,51). Furthermore, Jacobs et al showed that the institution of elemental Vivonex^{R} solution into a Thiry-Vella fistula not only prevented atrophy but induced mucosal

hypertrophy (51). Thirdly, transplantation of the ileum to a more proximal position in the gut exposes the ileum to a greater volume of luminal nutrients with a resultant ileal mucosal hypertrophy and functional adaptation. The jejunum which is now lying downstream from the ileum undergoes slight hypoplasia (52).

The relative importance of luminal nutrients in the adaptive response to resection is unknown. Studies by Morin in rats showed that the oral infusion of only 20% of the total daily caloric requirements as long chain triglyceride fat prevented intestinal atrophy in rats maintained on parenteral nutrition. Protein and carbohydrate when infused in a similar manner had only a partial sparing effect (53).

Whether the effect of luminal nutrients on intestinal adaptation is mediated directly or indirectly through paracrine or endocrine responses remains to be determined (71).

Hormonal factors

Not all facets of intestinal adaptation are adequately explained by the effects of luminal nutrition. Mucosal hyperplasia proximal to an anastomosis and the hypertrophic effect of intestinal resection on a previously constructed

Thiry-Vella loop suggests that other mechanisms must be present (28,55).

Perhaps the strongest evidence for the existence of humoral factors is the parabiotic rat studies and the cross circulation experiments in pigs. In these experiments, paired animals are either cross-circulated with each other's blood on a continual (the rat) or an intermittent (the pig) basis. When one animal in the pairing undergoes a small bowel resection, mucosal adaptation is seen in both the resected animal and its partner (56,57).

The search for the elusive humoral factor has lead through a number of hormones from the gut and elsewhere. Initial investigations centred around the hormone gastrin as many authors felt that this was the trophic hormone of the gut (58,59). The observation of elevated gastrin levels in animal models of Short Bowel Syndrome suggested an indirect association (60). Yet gastric hypersecretion and hypergastrinemia were not found universally and several studies demonstrated a lack of correlation between levels of serum gastrin and observed intestinal adaptation (61,62). Furthermore, there was no hyperplasia observed in patients with Zollinger-Ellison Syndrome or pernicious aenemia, conditions which have high serum gastrin levels. It is now

felt that the trophic effects of gastrin are limited to gastric and duodenal mucosal growth with little or no effect on small intestinal adaptation (62,63).

Cholecystokinin and secretin have also been postulated as possible intestinal trophic factors (21,33). Unfortunately, it is difficult to separate the direct effects of these hormones from those of pancreatico-biliary secretions which they stimulate. Exogenous cholecystokinin and secretin given to dogs maintained on total parenteral nutrition prevented the intestinal hypoplasia which normally occurs on total parenteral nutrition (64). Weser et al in trying to delineate which hormone was more important found that cholecystokinin given alone in parenterally fed rats was the trophic hormone in the cholecystokinin-secretin mixture (65). However, in another experiment, Hughs gave synthetic cholecystokinin octapeptide to rats in a high and low dosage scheme only to find that there was no effect on the intestinal mucosa in either case but a marked effect on pancreatic growth (66). The divergent results with cholecystokinin may relate to differences in amino acid sequence between synthetic and natural fragments examined.

Prolactin has also been investigated as a prospective agent due to the mucosal hyperplasia seen with lactating

rats. Muller used two models of hyperprolactinemia and, in the face of mammary hyperplasia and documented hyperprolactinemia found no change in the villus height, crypt depth, mucosal wet weight or DNA content per unit length of intestine (67).

Hormone profiles in models of intestinal adaptation have consistently shown elevation of the hormone enteroglucagon (68,69,70). Enteroglucagon though structurally similar to pancreatic glucagon is produced in the intestine with maximal concentrations in the ileum and the colon (54,71). A classic case report by Gleeson et al in 1971 demonstrated intestinal mucosal hyperplasia in a patient with a renal cell enteroglucagon secreting tumor. Following surgical removal of the tumor and return to normal enteroglucagon levels, the patient's intestinal mucosa reverted to normal (72,73). Experiments by Bloom and Dowling in rats with extracts made from the tumor confirmed that the tumor products caused mucosal hypertrophy (21). Jacobs et al examined enteroglucagon levels in three models of rat intestinal adaptation: resection, lactation and cold-induced hyperphagia. In all cases the concentration of enteroglucagon was greatest in the ileal mucosa. When enteroglucagon concentration was expressed as quantity per

unit weight of mucosa, there was also a marked increase (74). This suggests that either there was more enteroglucagon producing cells in the intestine or that they were making enteroglucagon at an increased rate.

The definitive proof for a trophic effect of enteroglucagon resides in the ability of pharmacological doses to promote intestinal adaptation. Several experiments have been performed thus far with singularly disappointing results (75). It may be that enteroglucagon is not the trophic hormone but has a permissive effect on the adaptive process.

Other hormones examined as potential mediators of adaptation include epidermal growth factor, vasoactive intestinal peptide, peptide YY and the trophic peptides polyamines: putrescine, spermidine and spermine (76-78). Only the latter family of compounds have been shown to correlate with the adaptive phenomena. The enzyme ornithine decarboxylase seems to be activated by adaptation and is the rate limiting step in the synthesis of polyamines. The role and importance of these peptides in intestinal adaptation is unknown at the present time.

Pancreatico-biliary secretions

Some of the effects of pancreatico-biliary secretion have been outlined in the previous section on the hormones cholecystokinin and secretin. It is not known whether the effect of pancreatico-biliary secretion is separate from the effect of these hormones themselves (79). Original studies by Altman and Leblond in which bile and pancreatic secretions were diverted to isolated loops of ileum demonstrated mucosal hyperplasia with increases in villus size (80). Later experiments with the intraluminal infusion of previously isolated pancreatic juice showed a trophic mucosal effect (81). The adaptation seen in these early experiments are now felt to be due to the protein load given intraluminally and are explained by the effects of luminal nutrition.

Experiments with pancreatico-biliary diversion in rats showed that post resectional ileal hyperplasia could be further enhanced by pancreatico-biliary diversion to the midpoint in the intestine (80,81). Unfortunately, the expected hypoplasia of the proximal jejunum did not happen and, in fact, the mucosa became somewhat hyperplastic with increases in villus height, mucosal mass and absorptive surface area. These latter observations have cast some

doubt as to the relative importance of pancreatico-biliary secretion in the adaptive process. Most authors feel that although there is no question as to the trophic effects of pancreatico-biliary secretion on the pancreas, the effects on the intestine are minimal and of little consequence in intestinal adaptation (79,82-84).

Other factors

Several other factors have been looked into as possible additional mediators of adaptation (21). Changes in mucosal blood flow may be the final common pathway to all the changes of adaptation. Laplace demonstrated the abolishment of the adaptive response to partial bowel resection after vagotomy in a pig model, but little else is known of the role neural factors play (85). Also of interest is the effect of changing luminal bacterial flora, and additional trophic factors from the saliva, the stomach and duodenum (33). Further investigation is needed to determine the relative importance of these factors.

TREATMENT

Aside from malnutrition and weight loss there are many metabolic complications which may arise from the Short Bowel Syndrome. These include: gastric hypersecretion (86),

watery diarrhoea, malabsorption of fat and the fat soluble vitamins with accompanying steatorrhoea, hypokalemia and renal and oxalate stone formation (87,88,89), divalent cation deficiencies (calcium, magnesium and zinc) (90), formation of lithogenic bile with cholesterol gallstone formation (91-93), essential fatty acid deficiency (1) and Vitamin B_{12} deficiency. The individual clinical picture is, therefore, variable both in its form and severity.

Both medical and surgical treatment of Short Bowel Syndrome have been designed to control or improve three basic pathophysiological defects: (a) decreased mucosal absorptive surface area, (b) gastric hypersecretion, and (c) decreased intestinal transit time. Most forms of treatment are supportive while the process of intestinal adaptation is occurring. Nevertheless, recent forms of treatment are being developed to enhance intestinal adaptation as well.

Medical treatment

Medical treatment is designed to directly address gastric hypersecretion and decreased intestinal transit time. Indirectly, it addresses the loss of intestinal absorptive

surface area by the addition of ancillary nutritional support.

Increasing effective absorption

The loss of effective mucosal absorptive surface area underlies most of the signs and symptoms of Short Bowel Syndrome.

Perhaps the greatest advance in supportive therapy of Short Bowel Syndrome has been the introduction of total parenteral nutrition (10-12,94). Total parenteral nutrition allows provision of calories to a patient unable to tolerate oral feeding and is responsible for the increase in patient survival with Short Bowel Syndrome. It provides time while intestinal adaptation occurs and in the case of extreme short bowel can provide all calories and nutrients indefinitely (94,95). Total parenteral nutrition is not without its problems. Venous access on a long-term basis may be difficult due to recurrent sepsis and venous obstruction (94). Also, long term total parenteral nutrition especially in the paediatric population leads to liver failure from cholestasis (96,97). At present, the main causes of death in the paediatric short bowel population are sepsis and liver failure secondary to total parenteral nutrition (97).

The recognition that luminal nutrition is necessary for the adaptive response to resection has made the use of low residue, partially hydrolyzed, high caloric oral feeds an integral part of the treatment of Short Bowel Syndrome. This is one of the few treatments which can be classified as both supportive and enhancing intestinal adaptation. To effect maximal adaptation, patients should be started on oral feeds as soon as they can be tolerated, even if only a small part of the total caloric intake is consumed in this manner. There is no agreement as to the actual composition of the oral diet. A high carbohydrate and protein diet has generally been recommended due to the severe malabsorption of complex dietary fats.

Unfortunately, much of the early work was done in uncontrolled situations and the osmotic effect of high carbohydrate diets was not appreciated. Some authors have recently shown that the restriction of fat may not be as important as once believed (98,99). Studies by Woolf et al on eight patients with Short Bowel Syndrome comparing a high carbohydrate and a high fat diet showed no difference in the absorption of fluid, electrolytes, divalent cations or calories (100). In an extension of this work, they demonstrated that patients stabilized for one year on an

oral diet do not need to restrict fat intake. There was virtually no difference in the malabsorption of fat, carbohydrate, protein or total calories on a controlled test diet containing 46% of the total calories as fat (90). They do suggest, however, that oral intake should be increased to 35-40 kcal/kg of body weight and that the divalent cations (calcium, magnesium and zinc), require oral supplementation due to increased intestinal losses. Lactose intolerance is common in Short Bowel Syndrome and patients should be advised to limit exposure to milk products. Mineral and vitamin supplements are required in nearly all cases (87). Recently, it has been demonstrated that both jejunal and colonic uptake of hexoses and lipids can be modified by variations in the fat content of the diet (101-103). Whether these dietary manipulations will prove of benefit in humans with Short Bowel Syndrome remain to be determined.

When there has been a significant loss of ileal length, bile acids cannot be re-absorbed in the distal ileum and thus are lost to the colon. This loss of bile acids has two consequences. First, if an increased bile acid synthesis in the liver cannot compensate for bile acid loss, then a decrease in luminal concentration of bile acids results in impaired micellular formation and subsequent diminished fat

absorption. In this case, oral bile acid supplementation may increase the size of the bile salt pool (87). Secondly, the presence of bile acids in the colon has a direct stimulatory effect on water secretion by colonic mucosa. This choleretic diarrhoea can be treated with cholestyramine which binds bile acids in the lumen decreasing their secretory activity in the colon (104-107).

Decreasing gastric hypersecretion

The increase in gastric secretion after extensive intestinal resection has been described for many years in animal models and man. Initial observations in man came from the surgical literature where patients with previous vagotomies and gastrectomies for ulcers did better than others after extensive bowel resection (108,109). Subsequently, gastric hypersecretion has not been shown in man universally and many authors doubt its existence or feel that it is only a temporary problem (86,107). Certainly, the high levels of gastrin seen postoperatively do not correlate with levels of gastric secretion (110,111).

The introduction of Histamine-2 receptor antagonists has made surgical treatment of gastric hypersecretion obsolete. Studies have shown both cimetidine (112-115) and ranitidine

(116) to be effective in controlling gastric hypersecretion associated with Short Bowel Syndrome.

Cimetidine may also have an effect on intestinal adaptation completely separate from its effect on gastric secretion. Studies by Cortot et al show an increase in nutrient absorption with cimetidine in patients with Short Bowel Syndrome (117). Cimetidine has also been shown to increase villus length and reduce steatorrhoea (118). It has been postulated that the effects of cimetidine are a consequence of enhanced crypt cell production rate (CCPR) or a direct trophic effect on the bowel, however, neither theory has been proven conclusively (119,120).

Slowing intestinal transit

The decrease in intestinal transit time associated with Short Bowel Syndrome is due both to a loss of intestinal length and an alteration in intestinal motility. The resultant loss of contact time with the absorptive mucosal surfaces and the digestive enzymes causes further compromise of intestinal digestion and absorption of nutrients. Medical therapy designed to decrease intestinal motility has, in the past, been based on narcotics or narcotic analogues such as codeine and diphenoxylate. These drugs act directly on intestinal smooth muscle to decrease

peristalsis. Recently, loperamide has been shown to be as effective as codeine in altering intestinal transit with far fewer side effects. It appears to act by increasing non-propulsive motor activity in both the fasting and the postprandial state enhancing retention of chyme within the small bowel (121-123).

Somatostatin is one of the major inhibitory hormones of the gut and has a marked effect on gastric secretion through direct inhibition of both gastrin and intestinal motility (124). Long-acting synthetic somatostatin analogues have been shown to increase intestinal transit time and have been used to decrease diarrhoea and ileostomy outputs (125,126). Unfortunately, the effect of somatostatin analogues appears to be only transient (127). Furthermore, a study by Holmes in rats demonstrated that somatostatin has an inhibitory effect on the hyperplastic response to ileal resection and inhibits nutrient absorption (128). For these reasons, somatostatin has limited use in Short Bowel Syndrome at present.

CONCLUSIONS

Although the factors which influence intestinal adaptation after massive intestinal resection are well known, their relative contributions to the final clinical picture are not clear. Furthermore, no single theory adequately explains the mechanism of intestinal adaptation. More than likely, several mechanisms are at work. With this gap in knowledge, it is not surprising that medical therapy to this point has been relatively ineffective in manipulating intestinal adaptation. Present therapy is supportive controlling symptoms which arise from the basic pathophysiologic defects of Short Bowel Syndrome; decreased intestinal transit time, gastric hypersecretion and reduced mucosal surface area. Until there is better understanding of the mechanisms of intestinal adaptation in Short Bowel Syndrome allowing active intervention, the clinician will be forced to rely largely on the intrinsic ability of the residual intestine to adapt.

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CHAPTER III

SHORT BOWEL SYNDROME: SURGICAL THERAPY[2]

As a common cause of Short Bowel Syndrome is surgical resection, it is not surprising that many surgical solutions to Short Bowel Syndrome have been proposed. Although none have been uniformly successful, some have proved to have merit when used in conjunction with medical therapy and often represent the patients only chance to become independent from parenteral nutrition.

The best form of surgical treatment still remains that of prevention with conservative resections (1). Even the retention of a few extra centimetres of bowel can have a profound influence on the intestine's ability to adapt and thus the eventual prognosis. Many authors have advocated construction of multiple ostomies with a second look procedure for all marginal bowel which may be viable (1-3).

Surgical treatment can be classified into three categories based on pathophysiologic processes: (1) slowing transit

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2 A version of this chapter is in press. Buie WD, Thurston OG, Fedorak RN. Can J Gastroenterol 1990.

time; (2) decreasing gastric secretions; and (3) increasing the effective mucosal surface area (4).

Slowing intestinal transit Surgical therapy to decrease intestinal transit time is based on the construction of a partial small bowel obstruction. Many different methods have been devised, however, all are unpredictable in their eventual effect. Most of the complications which arise from each method are due to bowel obstruction.

Antiperistaltic segments. Reversal of intestinal segments to create antiperistaltic regions was originally described by Mall in 1896. He reversed variable segments of small bowel in three dogs, two of which died of bowel obstruction while the third lived for three months. At laparotomy two months later, the segment showed retention of reversed peristalsis. Through the use of glass beads as markers, Mall also demonstrated a delay in intestinal transit time (5). The procedure was viewed as impossible until the 1950's when Hammer demonstrated that the duodenum could be reversed successfully resulting in an increase in intestinal transit time (6). Later in 1955, Hammer demonstrated that an 80% small bowel resection in the dog could be tolerated with the addition of a reversed ileal segment as short as two inches. In a controlled follow-up experiment, he demonstrated that

dogs could survive a 90% resection for up to two years with the reversal of a small segment of intestine (7).

The first human report of segmental reversal was by Gibson in a lady with Short Bowel Syndrome from a mesenteric infarction. She recovered following the reversal of a 7.5 cm segment of jejunum (8). Subsequently, Stahlgren demonstrated that the fecal output of fat and, to a lesser degree, nitrogen decreased with the insertion of an antiperistaltic segment in the jejunum of dogs (9). Using 3-4 cm paired proximal and distal reversed segments Keller proposed that the mechanism by which intestinal reversal worked was by prolongation of intestinal transit with an increase in the contact time of mucosa and luminal contents (10). Venables in 1966 in the first human study of absorption showed a 50% decrease in fecal fat absorption with the insertion of a reversed segment (11).

There are two critical factors in creating antiperistaltic segments: (1) the length of the segment and (2) its location. If the segment is too short there will be no benefit whereas a long segment will cause a bowel obstruction. Fink and Olson favoured a 10 cm segment located proximally to retard gastric emptying (12), however, the weight of evidence is now for distal placement. Wilmore

failed in his attempt to treat ileostomy diarrhoea over the long term with a distal 10 cm segment, however, there was a small short term decrease in ileostomy volume (13). Persemlidis also felt that the segment should be placed as distal as possible and used a 14 cm segment 12 cm proximal to the ostomy to prevent stagnant loop syndrome and bacterial overgrowth (14). Warden in 1978 reported five babies with a 3 cm reversal placed as distally as possible with survival in four (15).

In summary, intestinal reversal to create an antiperistaltic region and delay transit is one of the more common surgical interventions used in the treatment of Short Bowel Syndrome. The ideal length in the adult seems to be 10 - 15 cm with placement as distal as possible. Nevertheless, inconsistent results and difficulty in predicting those patients likely to respond have consistently dampened enthusiasm for this approach.

Recirculating loops. The recirculating loop is an extension of intestinal reversal and was first suggested by Stafford et al in 1959 (16). Mackby in 1965 showed an improved survival in dogs when a recirculating loop was combined with a separate antiperistaltic segment (17). Altman in a controlled experiment on 20 dogs found that animals with

recirculating loops had better fat absorption but lost more weight and often died due to anorexia when compared to controls (18). In a separate study comparing recirculating loops to segmental reversals, the latter were more often technically successful and had fewer complications (19). Although a further report of successful clinical application of the recirculating loop was submitted in 1975, the procedure has fallen into general disfavour due to the strong evidence against its being superior to a simple reversal and to the fact that the procedure is complicated, uses long lengths of bowel and is fraught with complications causing a high mortality rate (20).

Colon interposition. Colon interposition has also been used in the treatment of Short Bowel Syndrome. Use of the colon has three main advantages: (1) an intrinsically slow peristalsis, (2) decreased likelihood of causing obstruction due to the fact that it can be placed isoperistaltically, and (3) it does not require the use of small bowel which is already compromised in residual length. Initially, antiperistaltic colonic segments were used and shown to be of benefit in a dog model (21). In 1967, Trinkle and Bryant placed a 5 cm antiperistaltic segment of transverse colon in a three week old infant after massive

resection for a mid gut volvulus. Although the patient died, she initially gained weight and had an increase in transit time with a decrease in stool frequency (22). Later isoperistaltic colon interposition was investigated by Hutcher. In a series of experiments with beagle puppies, he showed increased survival with the interposition of a 15 cm segment of isoperistaltic colon both pre-ileal and pre-jejunal after a 90% small bowel resection. The animals in both cases attained approximately 70% of their expected growth with a decrease in mortality and morbidity when compared to controls (23-24). In a case report, Garcia et al interposed a 24 cm segment of isoperistaltic colon to a 15 cm length of small bowel with an intact ileo-caecal valve. After an adaptive period, intestinal transit time increased from 10 min to 105 min and the patient was able to maintain adequate nutrition by oral feeding. In this patient, the development of a D-lactic acidemia was postulated to be due to bacterial overgrowth (25). Comparison of iso- and antiperistaltic colonic interposition was examined by Lloyd using a 90% small bowel resection in the rat. In a series of experiments, he found that antiperistaltic colonic interposition effectively prolonged transit time but had other unpredictable effects. Some

animals acquired a small bowel obstruction and had, on average, lower body weights with only a slight increase in the absorption of albumin and no change in the absorption of fat compared to controls (26,27). He concluded that there was no advantage to antiperistaltic interposition over isoperistaltic and, indeed, there may be disadvantages. Further studies in dogs by Carner showed that the insertion of a 20 cm length of antiperistaltic colon made no difference in xylose absorption, 24 hr fat excretion, bowel transit time or average weight loss. Although his numbers were small, he concluded that antiperistaltic colonic interposition was of no benefit (28).

Glick et al in 1984 published a series on six infants in which a proximal isoperistaltic segment of colon had been used to treat Short Bowel Syndrome (29). The segments were 11 - 15 cm in length and three of the infants survived while the others died of sepsis and total parenteral nutrition-induced liver failure. His conclusions were that survival was associated with greater residual small bowel length, colon interposition at a younger age and a shorter duration of medical management. Unfortunately, the average residual bowel length in the survivors was 86 cm and these patients may well have adapted on their own with time. Brolin

published a case report of a 34 yr old female with 12 cm of residual length of small bowel in whom an isoperistaltic colonic interposition was done. Post-operatively, she did well in the short term, however, no nutritional studies were done (30).

Isoperistaltic colonic interposition is a viable alternative in the treatment of Short Bowel Syndrome. Proximal placement seems to be best, however, the optimal length of the segment has yet to be determined. The range in the literature is from 8 - 24 cm. All these length are reported to prolong intestinal transit time. Whether or not the segment has the ability to absorb nutrients has not been established. The actual mechanism of improved absorption is presumed to be through prolonged intestinal transit time and greater mucosal contact time of luminal contents. There appear to be no short term difficulties with the procedure. In the long term, bacterial overgrowth due to stasis with resultant D-lactic acidemia and possible encephalopathy may prove to be a problem especially in the infant population.

Experimental valves. The recognition that the presence of an ileo-caecal valve has a positive effect in the residual intestine's ability to adapt to resection has led to attempts to create an "artificial" ileo-caecal valve.

Experimental valves have been looked at as another means of slowing intestinal transit time. Intestinal valves of many different types have been used including the ablation of the outer longitudinal muscle layer (31,32), the reverse intussuception valve (33), and several other valves of similar construction (34-38).

The valves have all increased transit time but the effects have not always been predictable. Schiller attempted to show that the outer muscle ablating sphincter was better than intestinal reversal in promoting survival after a 90% resection, however, his numbers were very small (31). Waddell presented three patients with an intussuception valve; one patient having marked success, one satisfactory and the third eventually acquiring a bowel obstruction such that the valve had to be taken down (33). Vinograd published a study of the submucosally tunnelled valve constructed much like the re-implantation of a ureter into the bladder. He found the optimal length to be 4 - 6 cm and in a dog model in prolonged intestinal transit time with no demonstrable reflux (36). Chardavoyne et al examined the efficacy of a surgically created nipple valve in a dog by introducing labelled bacteria below the valve. The occurrence of bacteria above the valve was no different

than with an intact ileo-caecal valve (39).

It is not surprising that clinical series examining intestinal valves are very few in number. The unpredictability, the occurrence of bowel obstruction and the loss of further intestinal length to construct the valves are all major deterrents to their routine use.

Retrograde luminal pacing. It has been known for some time that the propagation of peristalsis distally in the intestine is through electrical impulses from a pacemaker in the duodenum. Phillips et al, in a series of experiments in dogs, demonstrated that retrograde electrical pacing of intact jejunum enhances absorption of glucose, water and sodium (40). When the bowel was transected to eliminate the proximal pacemaker retrograde pacing had a profound effect on absorption such that it was greater than the absorption from intact jejunum with or without retrograde pacing. It appears that retrograde pacing slowed transit time and in some cases reversed the flow of luminal contents (41,42). Layzell later demonstrated that dogs with retrograde luminal pacing showed an increase in body weight and a decrease in fecal fat and nitrogen excretion (43).

Investigation into the mechanism of action has shown that the effect of pacing can be inhibited by an α-adrenergic

blockade and thus the effect must be mediated, at least in part, by an adrenergic mechanism (44).

This therapy has remained experimental since entrainment requires transection of the duodenum to eliminate the intrinsic pacemaker, prolonged function of the electrodes has been difficult, and the electrodes must be implanted surgically and need to be removed surgically when they fail.

Decreasing gastric hypersecretion. As mentioned previously, gastric hypersecretion has been recognized as a component of the Short Bowel Syndrome for some time. This was felt to be detrimental for a number of reasons: (1) there would be an increase in the volume of intestinal secretions presented to an already compromised absorptive system, (2) the acidification of the lumen of the intestine would hinder the action of the digestive enzymes, and (3) the resultant osmotic and volume load would further compound the fluid, electrolyte and nutrient losses already occurring in the compromised bowel.

The realization that patients with previous vagotomies and gastrectomies were more tolerant of massive resection lead to the use of these procedures for the control of gastric hypersecretion in Short Bowel Syndrome. Today with the emergence of the histamine$_2$ receptor antagonists and the

realization that gastric hypersecretion is probably temporary, there is no place for the surgical treatment of gastric hypersecretion.

Increasing the effective mucosal surface area. Attempts at increasing the effective mucosal surface area has lead to three completely different approaches: (1) the growth of neomucosa, (2) bowel lengthening and tapering procedures, and (3) small bowel transplantation.

Neomucosa. Neomucosa was originally investigated in 1968 by Cywes (45) and by Binnington in 1974 (46). They observed that the serosa of neighbouring bowel could be used as a bed to stimulate the growth of a mucosal covering. In a series of experiments on dogs and pigs, respectively, they found that if the small bowel was opened along its antimesenteric border and sutured to the serosa of a neighbouring piece of bowel in a longitudinal intestinal patch, the intervening serosa would be covered with mucosa. This was proven to contain enzyme levels similar to normal mucosa (46). The functional nutrient absorptive ability of this mucosa, however, was not known.

An exhaustive series of experiments by Thompson (47-50) culminated in a paper in 1988 which seemed to summarize neomucosa (51). He observed that intestinal patching had an

inhibitory effect on intestinal adaptation in dogs subjected to a 75% intestinal resection and intestinal patching. His data showed a decrease in the overall growth of the intestine and in the villus height. Transit time was prolonged but the animals lost weight and had lower albumin levels. Furthermore, the increase in intestinal mucosal surface area was insignificant. It would seem that neomucosa has little if anything to offer in the treatment of Short Bowel Syndrome at the present time.

Tapering and lengthening procedures. Intestinal tapering and lengthening procedures have met with much more success. Tapering was originally proposed when it was noted that bowel proximal to an atretic segment always became markedly dilated such that re-anastomosis was difficult. Peristalsis was felt to be functionally ineffective. Initially, the antimesenteric border was opened and a longitudinal strip of bowel was removed before re-approximating the bowel. The calibre of the remaining bowel was reduced such that anastomosis was easier and peristalsis was aided due to apposition of the bowel wall during peristalsis. Patients treated in this way did, indeed, gain weight and many were able to come off total parenteral nutrition (52). The major drawback to this procedure was that it necessitated the loss

of valuable mucosal surface area. A modification of this technique called plication (internal infolding) performed along the antimesenteric border was compared to antimesenteric excision by Ramanujan (53). He found that plicated bowel was eventually incorporated into the bowel wall and was better structurally and functionally after artificially induced bowel dilation in a dog model.

In 1980 Bianchi described in a pig model an elegant procedure called intestinal lengthening (54). The procedure is based on the premise that the blood supply to the small bowel runs in an alternating fashion around each side of the bowel. This allows an avascular plane to be developed between the two leaves of the mesentery such that a GIA stapler can be passed down the centre dividing the bowel into two parallel tubes. These can be approximated end to end in an isoperistaltic fashion to give a segment which is twice as long but only half the diametre of the original bowel. The procedure was first used clinically by Boeckman and Traylor on a child with Short Bowel Syndrome from a gastroschisis with bowel necrosis (55). The child was left with 39 cm of small bowel anastomosed to the transverse colon. This grew to a length of 50 cm over the ensuing years, however, the child weighed only 9.2 kg at four years.

Following a Bianchi procedure, the patient required total parenteral nutrition for a further 10 wk but was progressed to a full diet and did not require further artificial nutrition after this time.

Aigrain in 1985 published a report of another infant with Short Bowel Syndrome who had an intestinal lengthening procedure done (56). Post-operatively, she remained on total parenteral nutrition for 4 wk but was then able to progress to regular diet. He modified the procedure to some extent by re-anastomosing the lengthened bowel in a helical formation to prevent traction on the mesenteric vessels. The problems encountered post-operatively included bacterial overgrowth proximal to the lengthened loop, nutritional intolerance and gastroesophageal reflux. Bacterial overgrowth was felt to be due to poor peristalsis in the proximal dilated duodenum which was not tapered. Oral tolerance of feed was complete by eight months although continuous tube feed supplementation still maintained a large proportion of the caloric intake. Urecholine was used to combat the reflux with complete success.

Thompson et al in 1985 were unsuccessful in their attempt to apply the Bianchi procedure to a child with the Short Bowel Syndrome (57). After dividing the bowel they re-

anastomosed it only to have one segment of the lengthened bowel become non-viable. Interestingly, the patient apparently improved clinically and the authors attributed this to the resultant tapering of the remaining segment of bowel.

A direct comparison of the efficacy of intestinal lengthening relative to other surgical treatments of Short Bowel Syndrome has been performed in a pig model by Sigalet et al (unpublished data). They compared isoperistaltic colon interposition to intestinal lengthening. While both groups showed superior weight gain to control animals receiving no treatment, intestinal lengthening was found to be superior to isoperistaltic colon interpositioning.

Intestinal lengthening appears to be a viable alternative in the surgical treatment of Short Bowel Syndrome. Application of this procedure seems to be tailored to the subset of the population in which the residual bowel has dilated markedly such that peristalsis is relatively ineffective (58). The advantages include the fact that no mucosal surface area need be sacrificed, a slowing of transit time is obtained without causing a functional obstruction, and normal peristalsis is restored to a previously dilated segment.

Small bowel transplantation. Successful small bowel transplantation may be the ultimate treatment for Short Bowel Syndrome. The technical feasibility was first established experimentally in the late 1960's by Lillihei in a dog model (59). His procedure consisted of transplanting the entire small intestine with vascular anastomosis between the respective mesenteric vessels of the graft and host. His autografts survived indefinitely but the allografts all rejected in a matter of days. At present, the major obstacle is still rejection as the large amount of lymphoid tissue present in the transplanted organ makes it extremely immunogenic (60,61). Control of rejection can be approached by either general immunosuppression of the host or by alteration of the immunogenicity of the donor organ. Numerous methods of temporary control of rejection have been accomplished in the dog model using conventional host immunosuppressive therapy. Unfortunately, both azathioprine and prednisone interfere with mucosal cell replication and thus the function of the graft (60). Anti-lymphocyte serum alone has been shown to the insufficient in averting rejection in dogs (62).

The development of the immunosuppressive agent, cyclosporine (CsA), attracted new interest. Mono drug

therapy with CsA in a rat model (15 mg/kg/d) given for 4 wks post-operatively can prevent rejection (63). Recently, low dose CsA (5 mg/kg/d) given over 2 wks has also prevented rejection in rats (64). Unfortunately, the results in large animal models have not been as successful. Reznick et al in 1982 demonstrated that intramuscular CsA (25 mg/kg/d) would prolong survival in a transplanted dog from a mean of 12.5 d to a mean of 103.8 d (65). The importance of parenteral administration of the drug was underlined in an extension of this work by Craddock et al who demonstrated that dogs with incontinuity grafts given oral cyclosporine survived for less than one month (66). This emphasized the fact that absorptive function of an allograft is initially suboptimal and immunosuppressive therapy should be accomplished parenterally. Further studies by Ricour (67) and Grant (68) in pigs confirm these findings. The addition of prednisone to CsA therapy has been shown in dogs to improve survival over CsA alone (69), however, these results have not consistently been reproduced. High dose CsA therapy may not be without its own problems for a reversible impairment of intestinal absorption with a protein losing enteropathy has been described in dogs (70). Experimental attempts at passive immune enhancement (anti-donor antibody) have been

entirely unsuccessful in prolonging survival (61).

Attempts at reducing the immunogenicity of the graft tissue have met with failure. Schraut irradiated the graft tissue prior to transplantation in rats with no increase in graft survival (60). When lymph nodes from the graft were examined microscopically there was considerable lymphocyte depletion but many lymphocytes were still present. This failure to eradicate all lymph tissue may explain the lack of success. Much of the immunogenicity of the graft is felt to be due to the class II antigen-bearing cells. A new approach using pre-transplant administration of monoclonal antibodies to class II antigens is being investigated. This method has already been shown to prolong graft survival of pancreatic islet transplants (71). Other approaches include pre-transplant blood transfusions and segmental grafts (72,73). The latter is a direct attempt to decrease the immunogenic load which, in turn, has resulted in lower CsA doses necessary to prevent rejection. Another complicating factor in intestinal transplants is that one of the first functions to fail with rejection is the mucosal barrier. This enables the translocation of bacteria into the submucosa and, eventually, the blood stream with resultant

sepsis. If the rejection process proceeds to this point, it is irreversible.

Small bowel grafts contain large amounts of lymphoid tissue which creates the potential for graft-versus-host disease (GVHD). Some authors feel that this is a laboratory phenomenon due to the heavy immunosuppression of the host immune system. Most, however, feel that rejection and GVHD are not mutually exclusive and can co-exist (74). Graft-versus-host disease can manifest itself even if rejection is prevented by CsA (75). This is contrary to other organ system models in which GVHD can be prevented by large doses of immunosuppressive agents. The use of anti-lymphocyte serum to pretreat the donor along with CsA treatment to the recipient has been shown to uniformly prevent GVHD in rats (76).

In addition, there remain technical problems associated with small bowel transplantation at the present time. Most early graft failures are due to arterial and venous thrombosis of the graft and intestinal volvulus (65,77). The incidence of the latter can be decreased by ensuring proper orientation of the transplanted bowel. Monitoring the <u>in vivo</u> function of the graft to ensure early detection of rejection is difficult. Functional tests of water,

sodium and sugar absorption with repeated small bowel biopsy have been proposed as the most reliable methods (78). A recent study by Banner at al suggests that sub-clinical rejection can persist in the intestinal wall in the submucosa and muscle undetectable by mucosal biopsy alone (79). Additional technical problems centre around short term graft preservation. Presently, intravascular flushing with a balanced salt solution containing fructose in combination with hypothermia will provide up to 18 hr of preservation (61). This has also been shown to decrease graft immunogenicity (80).

At the present time, small bowel transplantation remains an experimental alternative in the treatment of Short Bowel Syndrome (61,62). Control of rejection is still the major obstacle to successful transplants. Clinical experience with small bowel transplantation and cyclosporine therapy remains limited. Nine patients (including four children with multivisceral grafts) have undergone small bowel transplantation under cyclosporine coverage. Four patients have survived although three have had their grafts removed. The remaining five have all died due to sepsis, haemorrhage and unknown causes (81).

CONCLUSIONS

Management of the Short Bowel Syndrome continues to be a difficult clinical problem. Over the long term, the clinician depends on intrinsic adaptation of the residual intestine and this, in turn, is dependent on length, type and functional state of the residual bowel along with the presence or absence of an ileo-caecal valve and colon. The mechanisms of adaptation are not entirely understood thus preventing active interventional therapy to accelerate adaptation. As the most common cause of Short Bowel Syndrome is surgical resection, the best therapy is prevention using conservative resections and second-look procedures in the case of bowel of questionable viability. Present therapy, whether medical or surgical, is purely supportive while the adaptive process is occurring and is directed at controlling or improving three pathophysiologic problems: (1) decreased intestinal transit time, (2) gastric hypersecretion, and (3) reduced functional mucosal surface area. Initial therapy should be medical with consideration of surgical intervention only after therapeutic failure. Patience is very important as clinical improvement due to adaptation can be expected for up to two years.

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CHAPTER IV

SURGICAL TREATMENT OF SHORT BOWEL SYNDROME: THE BIANCHI PROCEDURE

INTRODUCTION

Surgical removal of large segments of the small bowel results in diarrhoea, steatorrhoea, malnutrition and weight loss. This clinical condition has been termed the Short Bowel Syndrome. Massive resection of the small intestine may become necessary in many pathological situations which vary with the age of the patient. Thrombotic or embolic occlusive disease of the superior mesenteric artery, abdominal trauma, internal adhesions or volvulus may necessitate small bowel resection in the adult population (1). Crohn's disease may also precipitate Short Bowel Syndrome due to repeated small bowel resections (2). Neonates have a different spectrum of disease necessitating small bowel resection including atresias, exomphalos, gastroschisis, long segment aganglionosis and necrotizing enterocolitis (3).

There has been a high mortality rate associated with Short Bowel Syndrome in the past. The development of total

parenteral nutrition (TPN) has made this condition more prevalent due to prolonged survival (4). This is not a complete solution for, after three to four months of TPN, the resulting liver failure, especially in infants can lead to death (5).

REVIEW

The treatment of Short Bowel Syndrome, both medical and surgical, is designed to control or improve three basic pathophysiological problems: (a) Gastric hypersecretion; (b) Decreased intestinal transit time; and (c) Decreased effective absorptive surface area (6).

The ultimate solution to Short Bowel Syndrome may be intestinal transplantation (7,8); however, at present this remains largely an experimental procedure due to the continued problems of rejection (7,9). Gastric hypersecretion during Short Bowel Syndrome (10-12) has been controlled in the past by vagotomy with some degree of success (13-15). Presently, the addition of H_2 blocking agents has made vagotomy obsolete in the treatment of gastric hypersecretion and hyperacidity (16-19).

Increased intestinal transit time has been dealt with medically and surgically. Opiates and related drugs have

been used to slow intestinal transit with some success. From the surgical viewpoint, antiperistaltic segments (20-23), recirculating loops (24-26), colon interpositioning (27-29), intestinal valve reconstruction (30-33), and intestinal pacing (34-36) have all been used experimentally and, in some cases, clinically with variable success. Mechanistically, these surgical therapies cause a partial small bowel obstruction, slowing down the movement of chyme with the consequence of enteropooling and enhanced absorption.

An alternative surgical approach is the recently described Bianchi procedure which attempts to save all viable intestinal mucosa and redistribute it such that dilated bowel is tapered and lengthened (37-41). This procedure increases the effective absorptive surface area and has been reported in eight infants with good therapeutic results (41).

Our interest in this procedure arises from the present inadequacies in treatment of Short Bowel Syndrome. In most cases, it is the intrinsic ability of the bowel to adapt with enhanced absorption, irrespective of any surgical or medical intervention, which determines the clinical outcome. This intrinsic ability is, in turn, dependent on the type of

residual intestine, the total residual length, the presence of the ileocaecal valve and concomitant disease or resection of the colon (42). A small proportion of the population with short bowel will be unable to adapt for a variety of reasons. In this population, adjunctive measures to aid adaptation such as the Bianchi procedure, may be of benefit.

Ileum has been shown to adapt more effectively than other segments of the intestine (43,44). The Bianchi procedure should, therefore, be more effective when performed on residual ileum and, thus, a subset of the Short Bowel population may exist which will respond best to a bowel lengthening procedure.

Although the efficacy of the Bianchi procedure has been demonstrated both clinically and experimentally, the actual mechanism of action is not understood. Speculation has arisen as to whether the procedure causes a partial mechanical small bowel obstruction. Others feel that it may improve the effectiveness of peristalsis in dilated segments of bowel much like tapering (6,40).

The swine gut closely resembles the human in structure and function, and its use as a model for human gastrointestinal physiology is well documented (45). A 75% small bowel resection is well tolerated by young piglets

and, although they continue to grow, it is at a much slower rate due to malabsorption. Indeed, this model is felt to be representative of the human infant with Short Bowel Syndrome (46).

Previous studies have shown the Bianchi procedure to improve weight gain in the short bowel swine model as compared to control short bowel animals (46). In this study, we examined, using in vivo and in vitro techniques, the effect of a Bianchi intestinal lengthening procedure in swine with a 75% small bowel resection. The Bianchi procedure was performed in either jejunum or ileum and results compared to non-treated short bowel animals and sham-operated controls.

Our final hypothesis is that there is no difference between a short bowel pig treated with a jejunal or an ileal Bianchi procedure in terms of the weight change over 12 weeks.

MATERIALS AND METHODS

Animals and Study Outline

Twenty-four female domestic swine (Sus scrofa: Pig Improvement Canada strain), 8 weeks of age and 16± 0.6 kg in weight were used in the study. At time zero, 18 animals underwent a 75% mid small bowel resection. After a post-operative recovery period of 72 h, the animals were housed at the University of Alberta Swine Unit in individual pens with free access to swine chow (standard grower diet: 18% protein, 4% fat, 4% fibre, 70% carbohydrate) and water. Six weeks later, the short bowel animals were randomly assigned to one of three groups: (1) a control group receiving no further therapy (non-treated short bowel); (2) a group receiving a jejunal bowel lengthening procedure (jejunal Bianchi-treated short bowel); and (3) a group receiving an ileal bowel lengthening procedure (ileal Bianchi-treated short bowel). An additional six animals underwent two sham operative procedures consisting of a bowel transection with immediate re-anastomosis at time zero and again at six weeks (sham-operated control). The sham-operated control group was pair fed with the non-treated short bowel group through the entire experiment to control for differences in feed intake. After the second post-operative recovery period of

72 h, animals were, once again, returned to the University of Alberta Swine Unit for a further 12 weeks with free access to swine chow (standard grower diet) and water. Eighteen weeks after the onset of the study (12 wks after the Bianchi procedure), all animals underwent a terminal laparotomy and were given a lethal injection of KCl under general halothane oxygen anaesthesia.

Operative Procedures

All surgery was performed at the Surgical Medical Research Institute on the University of Alberta campus.

1. Small Bowel Resection (two hour procedure)

The animals were brought in from the University of Alberta Swine Unit the day before surgery, fasted for 12 h and given an IM injection of penicillin 10,000 units/kg and streptomycin 10 mg/kg one hour pre-operatively. Each pig was anaesthetized with halothane (1.5% by volume) and oxygen (2 L/min) administered by mask. The animal was placed on her back on a "v" operating table with all four legs individually secured. A 20 gauge angiocatheter was inserted in a dorsal ear vein and Ringer's lactate solution run at 10 mL/kg/h. When required, blood samples were taken from the superior vena cava with a 20 gauge needle on a syringe using a right-sided suprasternal approach.

The abdomen was shaved, cleaned with betadine, draped sterilely, and opened through a midline incision centered around the umbilicus. Cautery was used for haemostasis. The total small bowel length was measured along its antimesenteric border using a precut 150 cm length of umbilical tape from the Ligament of Treitz to the ileo-caecal valve. The middle 75% of the small bowel was identified and resected. The remaining lengths of jejunum and ileum were anastomosed with a single layer of interrupted sero-muscular stitches of 4-0 silk. The mesenteric defect was closed using a running 2-0 dexon^{R} (Davis & Geck, Manati PR, USA). After covering the anastomosis with loops of small bowel, the incision was closed with interrupted figure of eight stitches of 1 dexon. The skin was approximated with a running subcuticular stitch of 3-0 dexon.

Post-operatively, the animals were given 30 mL/kg/h of Ringer's lactate solution for 12 h. On the first post-operative day, the intravenous was removed and the animals offered water ad libitum. On the second day, they were progressed to feed mixed with water and by the third day, were given free access to standard grower diet. All animals experienced diarrhoea which lasted 3 - 7 days. They

were returned to the Swine Unit in satisfactory, stable condition by Day 6.

2. Small Bowel Lengthening (four hour procedure)(37)

The animals were brought in from the University of Alberta Swine Unit the day prior to surgery, fasted for 12 h and 1 h pre-operatively, were given penicillin 10,000 units/kg and streptomycin 10 mg/kg IM. General anaesthesia was administered by mask as described above. An intravenous was started in an ear vein and Ringer's lactate solution was run at 10 mg/kg/h. Cephalothin 500 mg was given IV by bolus injection pre-operatively, immediately post-operatively and 8 hr post-operatively.

The abdomen was shaved, cleaned with betadine, draped sterilely and opened through the old scar. All adhesions were taken down and the small bowel was measured along its antimesenteric border with umbilical tape. A 30 cm length of bowel was then isolated either 20 cm distal from the Ligament of Treitz for a jejunal bowel lengthening procedure or 30 cm proximal to the ileo-caecal valve for an ileal bowel lengthening procedure.

The bowel segment was marked off with silk stay sutures and divided along with its mesentery as close to the mesenteric base as possible. Bleeding from the cut edge was

allowed to stop spontaneously with direct pressure. Cautery was used sparingly. An avascular plane was developed between the leaves of the mesentery separating the vasa recti in an undulating fashion to their appropriate sides. The mesentery was separated in 5 cm lengths with a small Penrose drain drawn back through the leaves to maintain the intramesenteric tunnel (38). The procedure was repeated until the entire mesenteric segment had been separated in this fashion. After a final check to ensure that all vessels had been assigned to the appropriate mesenteric side, the Penrose was used to guide the placement of the GIA 50 stapler anvil^{R} (Auto Suture, Ville St Laurent, Quebec, Canada) through the tunnel. The antimesenteric border was opened at each end of the segment for a distance of 3 cm to take up the extra length along the antimesenteric side. The bowel was evenly distributed on both sides of the anvil and the cartridge assembly closed and fired. The procedure was then repeated until the bowel segment was completely divided into two parallel tubes of bowel, half the original diameter, each with half the mesenteric blood supply.

At this point, the two segments were arranged in a spiral (after Agrain) (39), to ensure minimal vascular torsion and allow the bowel to be anastomosed in an isoperistaltic

direction. The anastomoses were performed in a single layer with interrupted inverting 4-0 silk stitches. The two large mesenteric defects were closed with 2-0 dexon. After a final inspection for patency and viability, the segment was placed under loops of small bowel away from the incision. Next, a 20 French Foley catheter was used as a stamm gastrostomy and was brought out through a separate stab wound placed in the left upper quadrant.

The abdomen was then closed in a single layer mass closure with interrupted figure-of-eight stitches of 1 dexon. The skin was re-approximated with a running subcuticular stitch of 3-0 dexon. At this point, the animal was placed on her right side and the gastrostomy tube was tunnelled subcutaneously to the mid-scapular region (47). The skin at the primary stab wound was closed with 3-0 dexon.

Post-operatively, the animals were recovered in the operating room covered with a warming blanket and receiving oxygen by mask. The intravenous site was heparin locked with 3 mL of 100 units/mL solution. Once the animal had voided and was awake and able to protect her airway, she was taken to her own pen and placed under heat lamps. Analgesic

was given in the form of intramuscular morphine (0.2 mg/kg q8 hr for 48 hr).

The animals were all checked on an 8 hr schedule personally by the investigator for the administration of fluids, antibiotics and analgesics for the first 48 hours. An animal technician was available from 0700 to 1600 daily to ensure that the investigator was aware of any problems that arose throughout the day. If a surgical problem arose post-operatively, the animal was brought back down to the operating room for re-exploration within the hour.

The animals were kept NPO for 48 hr post-operatively receiving 5% dextrose in Ringer's lactate at 50 mL/kg/d divided into three bolus doses (approximately 450-500 mL). The gastrostomy tube was decompressed at the same time by suction with a syringe. On post-operative Day 3, the animals were given free access to water. On Day 5, they were started on 500 mL half strength Vital HN^{R} (Ross Laboratories, Columbus, Ohio, USA) and given an additional 1000 cc on Day 6. If the post-operative course to this point had been uneventful, they were started on solid food mixed into a soft paste with water on Day 7. Over the next 3 - 5 d, the diet was progressed to a full diet ad libitum and when intake returned to normal, the gastrostomy tube and

heparin lock were removed. All animals returned to the Swine Unit by post-operative Day 15.

Measurements

Measurements were recorded in five general areas:

1. Weekly weights and feed intakes of all animals. The end point of the experiment was maximal weight gain over the experimental time period.
2. Bowel morphology. At each laparotomy, the entire small bowel was measured for changes in length and diameter.
3. General nutritional studies. Bloodwork was drawn at time 0, 6 and 18 weeks. This included a CBC and differential, albumin, total protein, calcium and phosphorus.
4. In vivo nutrient utilization. This portion consisted of two parts: a Dysprosium analysis to obtain digestibility co-efficients of dry matter and analysis of the relative digestibility of protein and fat. Dysprosium is an inert rare earth metal which is not absorbed in the intestine and, as such, has been used as a marker for swine digestibility studies (48). A known quantity of Dysprosium was added evenly to a general feed mixture. Following a period of 5-7 d to allow the distribution of labelled feed throughout the gut, a

stool sample was taken. This was freeze-dried, ground into a fine powder and a small amount of known weight was sent for neutron activation analysis at the Slow Poke Reactor facility (University of Alberta). The relative change in the concentration of Dysprosium in the feces compared to the feed gives an estimate of the digestibility co-efficient for the animal. Stool samples were taken at 6 and 18 weeks from all animals. Stool samples were also taken at 6 and 18 weeks for analysis of protein, fat and energy. Protein analysis was done using the Kjeldahl method (49). Proteins in the samples were reduced to ammonia using strong acid. The ammonia was then captured by distillation in a boric acid solution and titrated with a strong acid to give an accurate measure of the protein content of the sample. Lipid content was obtained using the ether extraction technique and energy content of the samples was obtained using bomb calorimetry (50).

5. In vitro electrical studies. After removal, the segment of small bowel was rinsed clear of mucous and chyme with normal saline, opened along its antimesenteric border and kept in iced saline. The serosa along with the inner and outer muscle layers, were removed by blunt

dissection. Before use, all tissues were maintained in ice cold normal Ringer's solution gassed with 5% CO_2 and 95% O_2. Tissues were then clamped in Ussing-type chambers and bathed on both sides by normal Ringer's solution (in mM/L: Na, 144; K, 5; Ca, 1.25; Mg, 1.1; Cl, 117.5; HCO_3, 25; H_2PO_4, 0.35; HPO_4, 1.65), gassed with 5% CO_2 and 95% O_2 (pH 7.4), and maintained at 37°C. Transepithelial electrical potential difference (PD), electrical resistance (R), and short circuit current (Isc) were determined. A chloride and bicarbonate-free Ringer solution, in which these ions were replaced by gluconate and 10 mM TRIS/HEPES (pH 7.4), gassed with 100% O_2 was used to determine the anion dependence of glucose due to changes in Isc. In all experiments, 20 mM fructose was added to the serosal mucosal bathing medium to ensure sufficient substrate for energy metabolism. Tissue for experimentation was obtained from: 1) jejunum, 50 cm from the Ligament of Treitz; 2) ileum, 60 cm from the ileo-caecal valve; and, 3) the centre of the respective Bianchi segment.

Statistical Methods

All laboratory data was coded and entered into the computer. Information from the data base was edited for

analysis by the SPSS statistical package on the University of Alberta computer. Descriptive statistics and frequencies were determined for each treatment group. Comparisons among groups were performed at baseline, 6 weeks and 18 weeks. The average weight for all 18 weeks was plotted for each of the 4 groups. The data was complete for all 18 weeks with the exception of week 7 in which the weights for the jejunal Bianchi and ileal Bianchi groups were not recorded as the animals were fasting. A first order regression fit line into each plot and an analysis of co-variance was used to compare the groups. The level of significance was taken as $p < 0.05$. All results are expressed as the mean $\pm$ the standard error of the mean (SEM).

RESULTS

Animal Profile

A total of 24 pigs underwent a 75% mid small bowel resection with a total of 6 deaths (Table I). The most common cause of death in this group was secondary to strangulated small bowel obstruction from adhesions. Additional deaths resulted from acute gastric dilatation, anastomotic perforation, and a case of sudden unexplained death. Six animals underwent sham operations with one death

due to an intussusception. In total, 23 animals completed the study; three resected groups of 6 animals each (non-treated short bowel controls; jejunal Bianchi-treated short bowel; ileal Bianchi-treated short bowel) and one sham-operated group (sham-operated control) of 5 animals.

General non-fatal complications included two cases of pneumonia (successfully treated with antibiotics), a case of acute gastric dilatation (treated with decompression) and two ventral hernias. Spontaneous ventral hernias are not uncommon in swine as they gain weight and neither animal was adversely affected. Complications directly attributable to the Bianchi procedure included one fistula, two strictures and one internal hernia causing a partial bowel obstruction. The fistula was approximately 4 mm in largest diameter while the neighbouring bowel was 2.5 cm suggesting that very little chyme bypassed through the fistula tract. One of the strictures occurred at an anastomotic site presumably secondary to ischemia and required anastomotic revision on post-operative Day 6. The sham-operated control animals had no internal complications.

At time zero all four groups were essentially similar with respect to initial weight as outlined in Table II. The post resectional residual bowel lengths for the non-treated

short bowel control, the jejunal Bianchi-treated short bowel and the ileal Bianchi-treated short bowel groups were also similar.

Weight Gain

Figure 1 shows the swine weights for the first 7 wk of the study prior to treatment randomization. Although all four groups gained weight, the sham-operated control animals gained significantly more weight when compared to all short bowel groups ($p < 0.05$). The three short bowel groups showed relatively flat weight gain curves which were not significantly different when compared to each other.

Figure 2 demonstrates the weight gain of each group from weeks 8-18 following treatment randomization. The sham-operated control group gained significantly more weight when compared to the non-treated short bowel animals at all time periods. In contrast, when the sham-operated control group is compared to the jejunal Bianchi-treated and the ileal Bianchi-treated groups, significance of differences in animal weight is lost at weeks 14 and 16, respectively. In addition, both the jejunal Bianchi-treated and ileal Bianchi-treated short bowel groups showed greater weight gain when compared to the short bowel control animals;

however, in neither case is the final weight significantly different.

When the rate of weight gain over the study was examined (Table III), the sham-operated control group, the jejunal Bianchi-treated and the ileal Bianchi-treated short bowel groups gained 4.5 kg/wk, 5.0 kg/wk and 4.4 kg/wk, respectively. When these values are compared to the non-treated short bowel group (3.4 kg/wk), only the jejunal Bianchi-treated short bowel group showed statistical significance ($p < 0.05$).

Feed Intake and Efficiency

There was no significant difference in the average feed intake (kg/d) over the experimental period between the four groups (Table III). The sham-operated control animals and the non-treated short bowel controls were pair fed by definition and consumed an identical amount of food. Although the trend was for the jejunal Bianchi-treated group to eat more food on a daily basis than all other groups, direct comparison between the groups can be made using the feed-to-weight-gain conversion efficiency. This is an estimate of the cost in kilograms of food of a kilogram of live weight gain. The sham-operated and the non-treated short bowel animals had an efficiency of 2.6 and 3.3,

respectively. This was significant at a p value of < 0.05 and implies that to gain 1 kg of weight, an animal with 25% of its small bowel must eat 18% more food by weight when compared to a normal animal. Both the jejunal Bianchi-treated and ileal Bianchi-treated groups showed an intermediate efficiency of 3.0 and were not statistically significant when compared to the non-treated short bowel animals.

Gross Bowel Morphology

Gross bowel morphology showed some dramatic changes (Table IVa). The short bowel control, the ileal Bianchi-treated and the jejunal Bianchi-treated groups all underwent an approximate 50% increase in length over the course of the study. In absolute values, this ranged from 206 and 234 cm. The sham-operated control group showed an absolute increase in length of only 169 cm. Of interest was the fact that the short bowel animals, regardless of their group, had attained approximately 90-95% of their final length by 6 wks. The jejunal and ileal Bianchi segments comprised 7.7 and 8.5% of the final length respectively.

All short bowel groups demonstrated the ability of the residual bowel to dilate (Table IVb). While the sham-operated control animals on average doubled the diameter of

the bowel, the short bowel groups showed a markedly greater increase in bowel diameter ranging from 2.5 to 4-fold. The jejunum from the non-treated short bowel controls and the jejunal Bianchi-treated group was significantly larger when compared to the sham-operated control group while only ileum from the jejunal and ileal Bianchi-treated groups was significantly larger when compared to the sham-operated control group. There was no significant difference between the pre- and post-Bianchi segments in either the jejunal or ileal groups.

Looking at the relative growth potential of residual jejunum and ileum to increase in length, it appears to be equal at 6 wks (Table IVc). Furthermore, at 18 wks, the non-treated short bowel group demonstrated that residual bowel which was not surgically manipulated retained this equivalent potential.

Nutritional bloodwork

Table V shows the bloodwork for the respective groups at time 0, 6 and 18 wks. There is no statistically significant difference between the groups when compared at time 0 and at time 18 either intra- or inter-group. When specific values of albumin are examined, there is a definite downward trend for all three short bowel groups suggesting that they are

not as nutritionally balanced as the sham-operated control group. At 18 weeks, both the jejunal Bianchi-treated and ileal Bianchi groups demonstrated intermediate values of albumin between the sham-operated group and the non-treated short bowel group.

Digestibility in vivo

The results of the digestibility studies are shown in Table VI. At 6 wks, there was no significant difference between the animals with respect to their ability to digest dry matter, nitrogen, lipid or energy although the non-treated short bowel animals showed a decreased ability to digest fat (25.9%). At 18 weeks, there was no significant improvement within any group with respect to the animals' ability to digest dry matter, nitrogen, lipid or energy. Again, the non-treated short bowel animals demonstrated a decreased ability to digest fat, however, this was not significant when compared to the other groups.

In vitro kinetic studies

Maximal transport capacity (Vmax) and changes in carrier affinity ($K_{0.5}$) were determined by Eadie-Hofstee plots of the data using microcomputer program Sigmaplot, version 3.1, Jandel Scientific, Sausolito, CA. In addition, V_{max} and Km were calculated using best fit regression curves. Eadie-

Hofstee plots of the data (data not shown) mirrored the results shown with the best regression curves.

Short circuit current changes produced by D-glucose proved to be independent of anions in solution. Thus, glucose-induced short circuit changes in all groups were the same in magnitude when the Ringer's solution contained chloride and bicarbonate as when these ions were replaced with glucose and HEPES, respectively (data not shown).

To assess whether alterations in absorption of D-glucose were due to changes in maximal transport capacity (V_{max}), changes in carrier affinity ($K_{0.5}$), or both, we determined the Isc responses to varying concentrations of D-glucose (concentration range of D-glucose, 0.5 - 70 mM). Measurements were made in jejunum, ileum and from within the Bianchi-lengthened segment of each animal group. Results, plotted as the rate of D-glucose-stimulated sodium transport (change in Isc/cm^2) vs concentration of D-glucose, can be fit by a rectangular hyperbole for the solute.

As shown in Table VII, the pair-fed control animals at Time 0, demonstrated an enhanced V_{max} in both the jejunum (three-fold) and ileum (two-fold) which fell within 6 wks to a level which remained constant thereafter. Carrier

affinity remained constant in both jejunum and ileum throughout all time periods.

Table VIII examined the kinetic constants for effects of D-glucose on Isc in swine intestine following 18 wks of short bowel and compares these results to sham-operated controls. Animals with a 75% mid small bowel resection demonstrated a significantly lower V_{max} in both jejunum and ileum as compared to sham-operated controls. In short bowel animals treated with a jejunal Bianchi procedure, jejunal V_{max} remained constant compared to non-treated short bowel. Furthermore, V_{max} within the jejunal Bianchi segment was significantly lower than adjacent jejunal tissue and resembled values seen in the ileum in this group. In short bowel animals treated with an ileal Bianchi procedure, jejunal V_{max} was unchanged while ileal V_{max} fell up to 50% of short bowel control values. V_{max} in the ileal Bianchi segment was significantly lower than short bowel control ileum but was similar to adjacent ileal tissue from the ileal Bianchi group.

DISCUSSION

The Bianchi procedure has been shown both clinically and experimentally to be a useful adjunct to adaptation in the

Short Bowel Syndrome (37-41). In this study, both the jejunal Bianchi-treated and the ileal Bianchi-treated groups demonstrated greater rate of weight gain when compared to non-treated short bowel animals. Only the jejunal Bianchi-treated group showed significantly greater weight gain at 5.0 kg/wk vs 3.4 kg/wk for the non-treated short bowel animals ($p < 0.05$). Although there was no significant difference between the final weight of either the jejunal or ileal groups when compared to the non-treated short bowel group, the jejunal Bianchi-treated group approached significance at weeks 17 and 18 ($p < 0.07$) suggesting that if the study had been extended or a larger number of animals had been used, it may have reached significance.

The morphological changes of adaptation are well documented (51-55). The residual intestine underwent thickening of all layers and dilation consistent with observations in rats, dogs, pigs, and humans (53-57). These changes have been most consistently shown following proximal or mid small bowel resection. An increase in residual intestinal length has also been demonstrated in the literature in many different animals models of Short Bowel Syndrome, however, growth potential seems to be species dependent. Shin et al working with dogs showed a 30%

increase in length following resection (58) and Nygaard demonstrated a 139% increase in rats (54). He felt that the hypertrophy was a response to a loss of function as opposed to a loss of intestinal tissue as an equivalent bypass resulted in an equivalent amount of measured hypertrophy. Our own data shows close to a 50% increase in bowel length post-resection almost identical to that demonstrated previously by Sigalet in this model (59). The only large study of Short Bowel Syndrome in mini-pigs by Bahr demonstrated a 100% increase in length from three weeks to six months of age (60).

Many of the short bowel experiments have been performed on young animals, such as puppies (53) and piglets (60). The increase in gross morphological measurements is felt to be a combination of growth potential of the residual intestine and growth due to resectional stimulation. In these experimental situations, younger animals appear to adapt better, which is consistent with the human experience and in fact, hinge on the growth potential of the residual intestine. In this experiment, both the residual jejunum and ileum demonstrated equal potential for growth suggesting that the most important stimulus for longitudinal growth was not resection in these young animals but their

intrinsic growth potential. This may also explain why many authors do not believe that increased residual length is part of the adaptive response in man (44,61,62).

The ileum adapts better than the jejunum both morphologically and functionally. Jejunal resection results in a 70-100% increase in structure and function, while ileal resection only results in a 20-30% increase (54,62-66). As the jejunum is capable of less functional adaptation (44,55), we expected that an ileal Bianchi segment would allow greater morphological and functional adaptation; however, this was not observed. Surgical manipulation appears to partially inhibit both the morphological and functional adaptation of the segment irrespective of the parent bowel type.

Pair feeding of the sham-operated control animals and the non-treated short bowel animals caused the sham-operated control animals to be held back with respect to their growth potential due to the poor appetite of the non-treated short bowel animals. This is consistent with the results from Sigalet who noted that massive intestinal resection in this swine model was associated with a decrease in food intake (59). Why was the intake of the non-treated short bowel animals so poor? Although the average intake over weeks 8

to 18 was not significantly different from other groups, a weekly breakdown shows that from weeks 14 to 18, they ate significantly less than the jejunal Bianchi-treated group. The intake of the ileal Bianchi-treated group was never significantly greater when compared to the non-treated short bowel animals. Our results suggest that the loss of appetite after massive intestinal resection was partly reversed by a jejunal Bianchi or that a jejunal Bianchi provided a stimulus to the appetite of the short bowel animal. Presumably, maintenance costs of the short bowel animals are higher than sham-operated control animals and this loss of efficiency should mean an increase in feed consumption as in rat models, however, this was not observed (67).

The Bianchi procedure, whether performed in the jejunum or the ileum, had the ability to increase the efficiency of the resected animals; however, this was not significant when compared to the non-treated short bowel animals. Again, this may be a function of the small numbers of animals used in each group for a change in efficiency from 3.3 to 3.0 represents a 9% increase in the feed conversion efficiency. As the experimental groups both showed increased and equal efficiency, the demonstrated differences

in weight gain could be due to the differences in feed intake alone. Although there was no statistical difference in feed intake over the experimental period between the different groups, the trend was for the jejunal group to consume a greater amount of food as mentioned above. This could be explained by a sampling error in that the animals assigned to the jejunal group could have had intrinsically greater appetites. As the animals were randomly assigned to each experimental group, this would seem unlikely and we are left again with the possibility that the procedure itself has an effect on appetite. By pair feeding the non-treated short bowel animals and the sham-operated control animals, the calculated relative loss of efficiency of a 75% small bowel resection is about 20%. In other words, an animal with 25% of its bowel needs to consume approximately 20% more food by weight to maintain the same rate of weight gain. The Bianchi procedure cut the loss in efficiency of short bowel animals in half.

While a 75% small bowel resection is a severe stress to the animals, it caused no significant changes in their nutritional bloodwork over the course of the study. This demonstrates the extreme adaptability and reserve of the pig from a nutritional standpoint. Part of this reserve may be

due to the fact that the domestic swine is known to possess more than 1.4 times the length of intestine of the wild pig, due to selective breeding by man. Interestingly, all four groups showed a drop in their albumin levels at six weeks but showed some degree of recovery to normal levels by 18 weeks. The non-treated short bowel animals demonstrated the least improvement suggesting that a 75% resection is near the limit of the animals' ability to compensate and that more extensive resection could bring about significant changes.

The fact that digestibility of dry matter, protein and energy was not altered by resection or surgical treatment is not surprising. Previous experiments by Sigalet have shown similar data and are perhaps further proof of the adaptability and reserve of the swine gut (59). Much of the carbohydrate ingested by swine on a grain diet is starch and greater than 50% of digestion and absorption occurs in the stomach and duodenum (68). Fat is the nutrient whose absorption is most affected by loss of bowel length as it is absorbed uniformly throughout the entire small bowel (69). Although there was a trend towards improved fat absorption in the short bowel jejunal and ileal Bianchi groups, this was not significant. This is in contrast to the results

shown by Sigalet who found that the jejunal Bianchi procedure improved fat absorption when compared to non-treated short bowel animals (59). The reason for this discrepancy is unknown, however, because the fat content of the diet was only 4.5%, malabsorption may have been difficult to detect. If fat had made up a larger portion of the diet, as it does in the human situation, the digestibility of energy may have also shown a significant change.

Intolerance to fat is very common in the early adaptation to Short Bowel Syndrome and many authors have stated that fat intake should be restricted in the short bowel population. Recent studies in humans have shown that malabsorption of fat is very similar to malabsorption of other nutrient groups and in a stable short bowel patient, total adaptation to a diet which is 46% caloric fat has been demonstated (70). Fat may be extremely important in adaptation. Specifically in the form of long chain fatty acids, it has been shown in rats to prevent intestinal atrophy experienced by animals fed entirely on parenteral nutrition (71). Fat is also felt to be primarily responsible for the ileal brake mechanism to proximal jejunal motility and many feel that this is one of the

reasons why there is better functional adaptation to proximal resection (72).

Adaptation to massive intestinal resection implies that residual bowel increases its ability to absorb nutrients per unit of mucosal surface area. This has been demonstrated for fluid and electrolytes, glucose, protein, and fat in both animal models (66,67,73) and in humans (74,75). Although glucose absorption is enhanced when expressed as a function of intestinal length, there are some contradictions in that rat models show reduced enzyme levels and tissue accumulation of sugars when expressed per unit of dry tissue weight (67). This has been postulated to be due to the increase in mucosal surface area which is known to occur and to the high rate of glucose metabolism in the rat intestine. In the dog, on the other hand, both individual cells and intestinal segments have normal transport capacity and normal enzyme levels (56). Although the overall trend is towards increasing transport capacity, clearly there are differences in species specific details.

The ability of pig mucosa to actively transport D-glucose <u>in vitro</u> per unit area of mucosa decreases with the age of the pig (Table VII). Massive intestinal resection caused transport to decrease in both the ileum and the jejunum when

compared to sham-operated controls. A Bianchi procedure caused a further reduction in maximum transport capacity (V_{max}) specific to residual ileal mucosa which was half the non-treated short bowel ileal mucosal value. Carrier affinity remained the same ($K_{0.5}$), however, the change in V_{max} means either a change in specific transport function (unlikely), a change in the number of carriers per unit area of mucosa, or a change in the lipid composition of the membrane. These results are completely opposite to other short bowel animal models in which it is felt that the short bowel remnant is made up of more cells per unit area which are functionally immature (when compared to normal mucosal cells) with the net effect of segmental hyperfunction (55). This may represent species differences.

These results suggest that 1) surgical resection has a profound negative effect on residual bowel function, 2) a Bianchi procedure is detrimental to glucose transport in residual ileum, especially if the procedure is performed in the ileum, and 3) the Bianchi segment itself has no special intrinsic adaptive ability with respect to glucose transport and performs at a level below the neighbouring "parent" bowel. The implications are that the Bianchi procedure is actually a hypo-functioning segment and surgical

manipulation to create the segment not only inhibits the adaptive response in the Bianchi segment but also inhibits the adaptive response in the remaining bowel.

The possible mechanism(s) behind the Bianchi procedure fall into four categories:

1. Bowel lengthening. When the increase in bowel length is plotted against weight gain, there is no relationship. This may be due to the fact that the Bianchi segment made up only 8% of the total length of the bowel and, thus, any effect it may have had was overshadowed by the functional adaptation of the remaining bowel. However, it raises the possibility that bowel lengthening may be a misnomer and have no role in the function of the Bianchi segment.

2. Segmental hyperfunction. Active transport of glucose was significantly decreased in both ileal and jejunal Bianchi segments. This and the fact that active transport in neighbouring bowel is hindered by a Bianchi procedure suggests that segmental hyperfunction does not exist.

3. Altered motility. The procedure may be an elaborate form of small bowel obstruction. This is unlikely as very few individual segments showed proximal dilatation. In addition, there was no significant difference between the pre- and post-segmental jejunal and ileal diameters. The

time course of the study, however, may not have allowed this to occur. Furthermore, proximal obstruction should be associated with early satiety and decreasing appetite but, in fact, the opposite result was observed.

The other possibility is that the segment either has an altered motility pattern within its length or causes a disruption of the distal propagation of peristaltic waves. This possibility was not examined in this study, however, it is supported clinically as these infants have an extremely prolonged post-operative ileus (38-41). Experimentally, transection of the bowel causes a loss of distal propagation of peristalsis (76).

4. Indirect systemic effects. No direct measurements were taken to support or refute this concept. However, indirect evidence is provided by the different effects of jejunal and ileal Bianchi procedures on residual ieum. The procedure appears to disrupt glucose transport in the ileum. This effect could be through either a neural or hormonal mechanism or a combination of both.

In conclusion, within our model of Short Bowel Syndrome, we found the use of jejunum preferential for the construction of a Bianchi segment. Short bowel animals treated with a jejunal Bianchi procedure demonstrated a

significantly greater rate of weight gain, allowed for greater, although not significant, feed intake and feed-to-weight-gain efficiency over untreated short bowel animals. The jejunal Bianchi segment demonstrated greater segmental function with respect to active transport of glucose than ileal segments and was less inhibitory to transport in neighbouring ileum. Mechanistically, the Bianchi segment functions not through bowel lengthening or segmental hyperfunction, but through altered bowel motility and possibly through systemic neurohumoral effects.

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CHAPTER V

CONCLUSIONS

The treatment of Short Bowel Syndrome, at present, remains largely symptomatic and supportive. Not all forms of treatment, whether medical or surgical, are effective in all individuals and until small bowel transplantation is a viable alternative, no "cure" is available. The Bianchi procedure as a form of surgical treatment has been relegated to a small subgroup of the short bowel population with small bowel dilatation in whom all other treatment modalities have failed (1). The procedure is not without its own inherent complications. The most serious of these is ischemia which can lead to problems ranging from strictures as observed in our swine model to complete loss of one segment resulting in dead bowel and eventual resection (2).

Our experimental data supports the observation that a jejunal bianchi procedure offers an advantage to a short bowel pig with respect to the rate of weight gain. It also appears to have a positive effect on appetite. Whether or not the change in weight can be explained entirely on the

basis of appetite and feed intake is unclear. The basic premise that a swine acts to maintain a certain energy intake does not seem to apply to the short bowel animal (3).

Massive intestinal resection of small bowel in pigs appears to have a negative effect on appetite. This has also been observed in the clinical situation and may be due to the persistent feeling of ill health due to diarrhoea and cramping with the ingestion of food. Massive resection of small bowel also appears to have a detrimental effect on glucose transport in residual pig bowel. The mechanism for this is not known, however, it suggests that the short bowel syndrome is not only due to the loss of bowel but also to loss of function in the residual bowel. Finally, the small bowel has a limited functional reserve with respect to glucose transport which cannot be enhanced through surgical manipulation. The Bianchi procedure appears to alter the adaptive response in residual bowel. The segment cannot become hyper-functional, and may be hypo-functional.

In clinical cases of Short Bowel Syndrome, it is extremely rare to have residual ileum and as such it would be rare to find patients who could undergo an ileal Bianchi procedure. This is fortunate for an ileal Bianchi procedure appears to give no advantage experimentally to the short

bowel animal. This is surprising in light of the greater adaptability exhibited by residual ileum; one would expect an ileal Bianchi segment to perform better.

In the paediatric population, most of the short bowel patients have small lengths of jejunum which could be used for lengthening (4). In the adult population, however, many short bowel cases arise from Crohn's disease with resultant loss of ileum (5). Aside from the fact that technically the procedure poses higher risks from the inherent problems with strictures and fistulas in these patients, our study shows that ileal lengthening does not increase the intrinsic function of the manipulated bowel. The ability of the bowel to transport glucose fell dramatically after manipulation. Extrapolating further, it would be very surprising if the other functions specific to the ileum, such as bile salt resorption were not affected in a similar manner.

From a technical standpoint, the procedure can be performed by any well-trained general surgeon. A few general points should be made:

1. The procedure is best performed with dilated bowel. Not all short bowel patients have post-resectional dilatation, however, the procedure is technically easier and may have a beneficial effect on peristalsis (2).

2. Meticulous attention to the anastomotic sites must be maintained. During the procedure, the mucosa becomes extremely edematous due to the interruption of lymphatics and venous congestion. It is important that the mucosa is inverted so that when the edema resolves, there are no defects in the suture closure. Furthermore, meticulous attention to the blood supply is necessary. When there is doubt as to the primary side of the bowel a vasa recti supplies, it should be apportioned to the side opposite to its neighbouring vessel.
3. The most important anastomosis is the central anastomosis. The bowel is smallest at this point and also has the most tenuous blood supply. The bowel should be rotated a quarter turn at this point so that it is not anastomosed mesentery to mesentery in the usual fashion. This creates two "T"-shaped suture lines instead of one "+"-shaped line.
4. We found the use of the GIA stapler to be advantageous in terms of both speed and blood loss. The terminal portion of each segment should be sewn by hand to allow tapering of each anastomosis.

5. Re-approximating the bowel using the Spiral of Agrain allows continuity without tension on the mesentery and does not appear to increase the rate of fistulization due to close proximity of the long suture lines (6).

Several lines of further investigation have arisen from this study. First, the optimal time for intervention is not known. At present, the procedure is used in patients in whom all other treatment modalities have failed, however, earlier use may prove to be of greater benefit. The combination of bowel lengthening and optimal medical therapy has not been evaluated critically in animal models to ensure that bowel lengthening does offer added benefit to other non-invasive therapy. Finally, the question as to whether the procedure works through the reduction of intestinal diameter without an obstructive component or through a partial small bowel obstruction has not been conclusively answered. Mechanistically, our data does not support the theories of bowel lengthening or segmental hyperfunction. Altered motility and systemic factors have yet to be investigated.

It is well described that the swine is a good model for human GI function, however, there is still the question as to whether a 75% mid small bowel resection in the pig is a

good model of Short Bowel Syndrome. During the study, all animals experienced some degree of malabsorption with diarrhoea and poor appetite for up to ten days post-resection. Furthermore, all resected animals had slow growth curves implying malabsorption, maldigestion or increased maintenance energy requirements. Unfortunately, significant malabsorption could not be demonstrated for dry matter, protein, fat or energy. Possibly the change in malabsorption was too small to be detected with the methods used or the intrinsic reserve of the swine gut easily compensated for the loss of 75% of its length. The latter is the most likely explanation as even the non-treated short bowel group adapted clinically over time. One animal in that group had a final weight of over 80 kg. The fact that there was no significant alteration in hematologic parameters supports this as well. Thus, to improve the model a more severe resection is necessary so that the control-resected animals have a flat growth curve.

There is extreme variability in an organism's ability to compensate for a percentage resection of bowel. This is explained partly by the tremendous variability in bowel length for any given range of weight and age. For this reason, a percentage resection may favour certain

individuals. Furthermore, it is well known that two patients with identical lengths of residual bowel may have completely different clinical courses. A resection to a specific residual length may help to solve this problem. A mid small bowel resection can also be criticized for not reflecting the human situation: in most short bowel patients, the ileo-caecal valve along with the terminal ileum are removed (7). Loss of one or both of these regions is known to be detrimental to adaptation, however, resection of these areas would complicate the nutritional picture through alterations in bile salt metabolism and retrograde bacterial colonization. The use of the present model to discuss the simple loss of intestinal length is justified for the sake of simplicity, however, another short bowel model should be created to include the loss of the terminal ileum and ileo-caecal valve regions.

Finally, weight gain, although a standard measure of animal growth and well-being is not the best indicator for adaptation (3). One could argue that morbidity and a predictable mortality would be more finite endpoints, as they are directly related to the severity of resection. Unfortunately, significant malnutrition from malabsorption is known to inhibit the adaptive response. Unless the

animal is supported with fluids, electrolytes and, nutritionally with TPN, as in the human situation, any results would be difficult to interpret (8,9).

Given the limitations of the short bowel model as outlined above, our results support the use of a jejunal Bianchi procedure in the treatment of Short Bowel Syndrome. There appears to be no advantage to an ileal Bianchi procedure. Many questions regarding the mechanism of action still need to be answered. With the delineation of mechanism, hopefully, the short bowel patients who stand to gain the most from the Bianchi procedure can be identified.

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TABLE I - MORBIDITY AND MORTALITY

Group	Total Animals	Deaths	Cause	Total Survived	Non-Fatal Complications	Internal Complications At Autopsy
Sham-operated Controls	6	1	Intussuception	5	---	
Short bowel Controls	8	1	Acute gastric Dilatation	6	(1) pneumonia	(1) partial obstruction
		1	Small Bowel Obstruction		(1) gastric dilatation	Internal hernia
Jejunal Bianchi-Treated Short Bowel	8	1	Small Bowel Obstruction	6	(1) ventral hernia	(1)* fistula (1)* stricture
		1	Sudden death			(1) adhesions
Ileal Bianchi-Treated Short Bowel	8	1*	Small Bowel Obstruction	6	(1) pneumonia	(1)*ischemic stricture
		1	Anastomotic leak		(1) ventral hernia	(1)*internal Partial bowel obstruction
TOTAL	30	7		23	5	6

* Directly attributable to the Bianchi procedure

TABLE II - GROSS MORPHOMETRIC DATA AT TIME O

	WEIGHT (kg)	POST RESECTION BOWEL LENGTH (cm)
Sham operated Control	16.8 ± 0.5	---
Short bowel Control	15.8 ± 0.4	414 ± 8
Jejunal Bianchi-Treated Short Bowel	16.4 ± 0.5	434 ± 13
Ileal Bianchi-Treated Short Bowel	16.3 ± 0.2	450 ± 20

TABLE III - WEIGHT GAIN, FEED INTAKE AND EFFICIENCY FROM WEEKS 8 - 18

	Weight Gain (kg/wk)	Feed[1] Intake (kg/d)	Efficiency Feed/Wt Gain (kg/kg)	Final Weight (kg)
Sham-operated Controls	4.5±0.24	1.6±0.2	2.6±0.1	84.4±3.1
Short bowel Controls	3.4±0.4	1.6±0.2	3.3±0.2(b)	63.0±6.6(b)
Jejunal Bianchi-Treated Short Bowel	5.0±0.32(a)	2.1±0.1	3.0±0.2	78.8±4.9
Ileal Bianchi-Treated Short Bowel	4.4±0.6	1.8±0.2	3.0±0.2	69.3±6.9
National Research Council Standards (for swine 50 kg in wt)[2]	4.9	1.9	2.7	—

1 Feed-Grower Diet (University of Alberta Farm) - 18% protein, 4.5% fat; 3300-3500 kcal DE/kg

1 Nutrient Requirements of Swine, 9th ed. Subcommittee on Swine Nutrition, Committee on Animal Nutrition, Board of Agriculture, National Research Council, National Academy Press, Washington, DC, 1988;50.

(a) $p < 0.05$ compared to short bowel control
(b) $p < 0.05$ compared to short bowel control

TABLE IVa - BOWEL MORPHOLOGY: CHANGES IN LENGTH

	Length (cm) Time 0	Length (cm) 6 wk	Final Length (cm) 18 wk	0-18 wk Percentage Increase (%)	Bianchi Segment Percent of Final Length (%)
Sham-operated Controls	1595±47	1669±99	1764±64	10.6%±0.4 (169 cm)	
Short Bowel Controls	414± 8	—	620±39	49.8%±8.2 (206 cm)	
Jejunal Bianchi-Treated Short Bowel	434±13	612±37	655±43	51.7%±11.4 (222 cm)	8.5%
Ileal Bianchi-Treated Short Bowel	450±20	603±39	684±57	52.3%±12.3 (234 cm)	7.7%

TABLE IVb - BOWEL MORPHOLOGY: CHANGES IN DIAMETER

	Initial Diameter (cm)	Final Jejunal Diameter (cm)	Final Ileal Diameter (cm)	Final Bianchi Diameter (cm)
Sham-operated Controls	1.9±0.1	3.9±0.2	3.2±0.3	---
Short Bowel Controls	1.8±0.1	5.1±0.5*	3.8±0.1	---
Jejunal Bianchi-Treated Short Bowel	1.6±0.1	6.5±0.5*[1] 6.3±0.5*[2]	4.2±0.2*	3.7±0.4
Ileal Bianchi-Treated Short Bowel	1.9±0.1	4.6±0.3	4.3±0.2*[1] 4.8±0.3*[2]	2.6±0.2

* $p < 0.05$ compared to the Sham-operated Controls
1 Measurement taken immediately proximal to Bianchi segment
2 Measurement taken immediately distal to Bianchi segment

TABLE IVc - BOWEL MORPHOLOGY: RELATIVE CHANGES IN JEJUNAL AND ILEAL LENGTH FROM 0 TO 18 WEEKS

	Residual Bowel Length At Time 0 (cm)	Jejunal Length At 6 wk (cm)	Ileal Length At 6 wk (cm)	Jejunal Length At 18 wk (cm)	Ileal Length At 18 wk (cm)
Short Bowel Controls	207± 4	---	---	317±54	313±41
Jejunal Bianchi-Treated Short Bowel	217± 6	313±26	299±13	---	---
Ileal Bianchi-Treated Short Bowel	225±10	308±23	296±15	---	---

TABLE V - NUTRITIONAL BLOOD WORK FROM PIGS AT 0, 6 AND 18 WEEKS

		Sham-operated Controls	Short Bowel Controls	Jejunal Bianchi-treated Short Bowel	Ileal Bianchi-treated Short Bowel
T = 0	Hct	36.62±1.3	28.8 ±2.2	32.6 ±2.3	32.2 ±2.3
	WBC	11.6 ±2.1	12.4 ±1.4	15.0 ±2.0	13.1 ±0.6
	Hb	11.2 ±0.5	-8.7 ±0.5	10.0 ±0.7	10.1 ±0.8
	Ca	9.36±0.1	10.17±0.1	-9.92±0.1	9.53±0.2
	PO_4	11.23±1.0	9.61±0.2	9.93±0.3	9.19±0.5
	Alb	2.94±0.1	2.78±0.1	3.00±0.1	2.96±0.1
T = 6 wk	Hct	38.4 ±1.2		34.6 ±1.6	35.1 ±1.0
	WBC	15.6 ±2.4		13.2 ±1.3	15.5 ±1.5
	Hb	11.8 ±0.7		10.74±0.4	10.9 ±0.4
	Ca	8.79±0.1		-9.24±0.4	8.82±0.5
	PO_4	10.63±0.7		7.86±0.3	7.87±0.4
	Alb	2.63±0.1		2.53±0.1	2.32±0.2
T = 18 wk	Hct	41.2 ±2.2	36.2±1.9	38.6±1.1	39.1 ±1.0
	WBC	16.1 ±2.4	12.4 ±3.0	16.4 ±1.5	14.2 ±1.4
	Hb	13.1 ±0.8	11.5 ±0.7	12.6 ±0.3	12.5 ±0.3
	Ca	10.64±0.2	9.43±0.5	-9.52±0.4	9.31±0.4
	PO_4	14.31±0.2	9.94±1.3	10.53±1.3	10.01±1.8
	Alb	3.27±0.1	2.65±0.1	2.85±0.1	2.71±0.2

Hct - Hematocrit (%)
WBC - White Blood Cell count x 10^3 per mm^3
Hb - Haemoglobin gm/100 mL
Ca - Calcium mEg/L
PO_4 - Phosphorus mg/100 mL
Alb - Albumin gm/100 mL

TABLE VI - DIGESTIBILITY CO-EFFICIENTS OF DRY MATTER, NITROGEN, LIPID, AND ENERGY

	6 WEEKS				18 WEEKS			
	Dry Matter	Nitrogen	Lipid	Energy	Dry Matter	Nitrogen	Lipid	Energy
Sham-operated Controls	75.5 ±3.9	74.4 ±4.4	34.4 ±8.2	76.4 ±4.0	76.3 ±1.9	77.0 ±2.5	39.7 ±2.8	77.5 ±2.4
Short Bowel Controls	77.8 ±1.9	72.2 ±4.5	25.9 ±7.8	76.3 ±2.3	77.3 ±1.4	79.6 ±3.02	28.2 ±5.0	76.1 ±2.1
Jejunal Bianchi-treated Short Bowel	80.1 ±1.2	76.8 ±1.8	33.0 ±8.0	79.3 ±1.4	76.9 ±1.6	77.2 ±2.7	39.1 ±4.7	76.4 ±1.9
Ileal Bianchi-treated Short Bowel	79.3 ±1.6	74.2 ±4.3	37.7 ±6.7	78.0 ±1.8	77.4 ±1.2	78.0 ±2.5	34.9 ±5.5	75.6 ±2.1

TABLE VII - KINETIC CONSTANTS FOR EFFECTS OF D-GLUCOSE ON SHORT CIRCUIT CURRENT (Isc) FROM CONTROL SWINE INTESTINE OVER 18 WEEKS.

GROUP (n)	JEJUNUM		ILEUM	
	Vmax ($\mu A/cm^2$)	$K_{0.5}$ (mM)	Vmax ($\mu A/cm^2$)	$K_{0.5}$ (mM)
t=0 wk (6)	298.8±9.1*	0±0.2	201.6±2.3*	1.2±0.6
t=6 wk (6)	90.2±3.1	2.9±0.4	98.7±1.4	0.8±0.1
t=18 wk (5)	94.4±2.1	1.9±0.2	111.7±2.5	0.9±0.1

At initiation of the study (t=0 wk), swine were 8 to 10 wks of age with a mean wt of 16.8 ± 0.5 kg. Subsequently, six weeks (t=6 wk) and 18 wks (t=18 wk) later, paired intestine was removed for Isc measurements as described in METHODS. Young swine demonstrated an enhanced glucose Vmax which falls and plateaus with age.

* = $p < 0.01$ compared to all other time groups.

TABLE VIII - KINETIC CONSTANTS FOR EFFECTS OF D-GLUCOSE ON SHORT CIRCUIT CURRENT FROM SWINE INTESTINE WITH 18 WK OF 75% MID-SMALL INTESTINAL RESECTION AND SHAM-OPERATED CONTROLS.

GROUP	(n)	JEJUNUM		ILEUM		ANASTOMOTIC SEGMENT	
		V_{max} ($\mu A/cm^2$)	$K_{0.5}$ (mM)	V_{max} ($\mu A/cm^2$)	$K_{0.5}$ (mM)	V_{max} ($\mu A/cm^2$)	$K_{0.5}$ (mM)
Sham-operated Control	(5)	94.9±2.1[a]	1.9±0.2	111.7±2.4[a]	0.9±0.1	—	—
Short Bowel Control	(6)	71.2±4.1	2.7±0.4	72.9±2.5	1.1±0.1	—	—
Jejunal Bianchi-Treated Short Bowel	(6)	70.5±3.1	1.7±0.3	54.0±2.5[b]	0.9±0.2	52.4±3.7[c]	2.3±0.5
Ileal Bianchi-treated Short Bowel	(6)	74.6±5.4	2.6±0.6	39.2±2.0[b]	0.7±0.2	35.8±0.7	0.9±0.1

a = $p < 0.001$ compared to all short bowel groups
b = $p < 0.001$ compared to ileum from short bowel control group
c = $p < 0.001$ compared to adjacent jejunum from short bowel jejunal bianchi group

FIGURE 1. PIG WEIGHTS VS TIME
0 -7 WEEKS

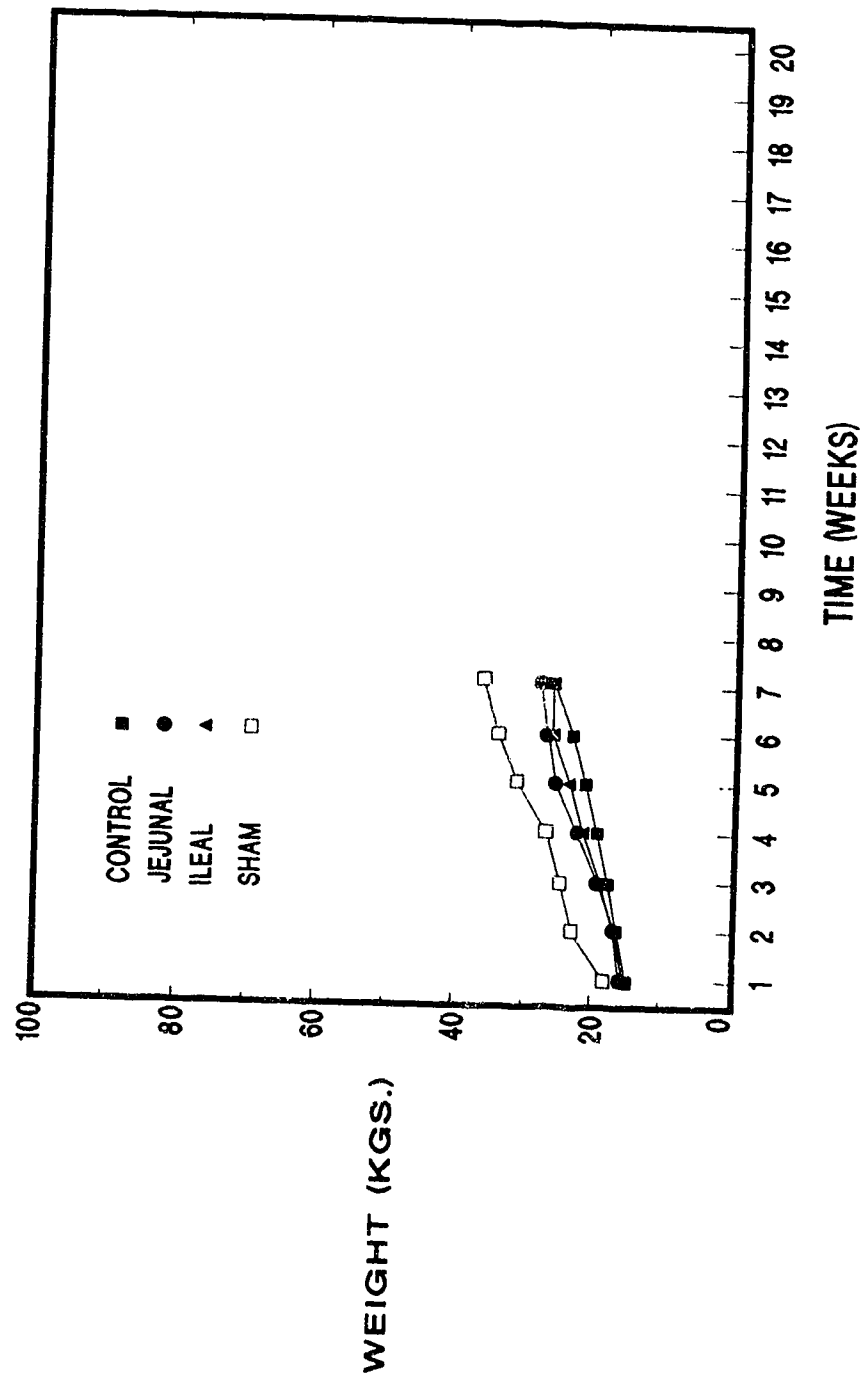

FIGURE 2. PIG WEIGHTS VS TIME
8 -18 WEEKS