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THE UNIVERSITY OF ALBERTA

A COMPARISON OF SURGICAL VERSUS MEDICAL TREATMENT OF THE SHORT BOWEL SYNDROME

by

DAVID L. SIGALET

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

IN

EXPERIMENTAL SURGERY

DEPARTMENT OF SURGERY

EDMONTON, ALBERTA

Spring 1989

ISBN 0-315-53022-7

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR: **DAVID LYLE SIGALET**

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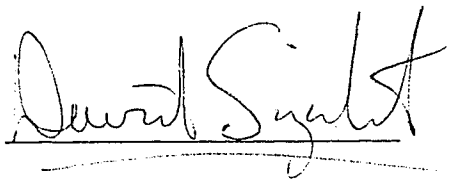
DEGREE: **MASTER OF SCIENCE**

YEAR THIS DEGREE GRANTED: **1989**



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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 **A COMPARISON OF MEDICAL VERSUS SURGICAL TREATMENT OF THE SHORT BOWEL SYNDROME**

submitted by **DAVID L. SIGALET**

in partial fulfillment of the requirements for the degree of **MASTER OF SCIENCE** in **EXPERIMENTAL SURGERY**

Supervisor

Date: October 20, 1988

This text is dedicated to my wife Elaine and

my son Geoffrey, who are my inspiration

ABSTRACT

This study examined the nutritional effects and adaptive response following massive small intestinal resection in the juvenile domestic pig. This model was then used to compare different treatments for the short bowel syndrome (SBS).

The initial experiments compared animals with a resection of the mid 75% of total small bowel length to a control group which underwent simple ileal transection. Animals were studied for 16 weeks. Feed intake was similar (per kilogram animal weight), but resected animals gained less weight than controls. Resected animals showed marked steatorrhea, and malabsorption of protein, carbohydrate and total energy. In vitro data showed increased passive uptake of fatty acids, cholesterol and L-glucose into the ileum, but no change in the active transport of glucose. The surface per villus increased 2-fold with resection, however, the density of villi decreased so that the net mucosal surface area per unit of serosal surface area was unchanged. Over the study period, the length of residual bowel increased by 75% in resected animals compared to 27% in the control transected group. Bowel diameter also increased in resected animals. These morphological changes resulted in a significant increase in the estimated bowel surface area of the resected animals. The nutritional and adaptive changes observed following massive small intestinal resection in the pig are similar to those noted in human studies, and support the use of this model in studying treatments for the SBS.

The second part of this thesis compared surgical treatment using isoperistaltic colon interposition (CI) or bowel lengthening (BL), and medical therapy with cimetidine and codeine (M) in juvenile pigs with a

75% mid small bowel resection. The control animals (C) in this experiment were resected, but not treated. Six weeks after resection, animals began medical therapy or underwent surgical treatment, and were sacrificed at week 16. BL and M improved the rate of weight gain and numerically increased the efficiency of feed to weight conversion when compared to C or CI. M and BL also significantly improved *in vivo* fat absorption, yet *in vitro* fatty acid and cholesterol uptake was lower in M than in the other groups. Active ileal uptake of D-glucose did not correlate with *in vivo* carbohydrate absorption. The mucosal surface area per unit area of serosa was similar in the four groups, and all groups had similar bowel surface area due to increased length and width.

The observed improvements in the rate of weight gain and fat absorption with bowel lengthening and medical treatment in this model suggest that these therapies are worthy of further study for treating the short bowel syndrome.

ACKNOWLEDGEMENT

I wish to thank the supervisors of this work for their help, guidance and inspiration. In particular, Dr. Lees provided the original idea for this study and the surgical expertise which made the lengthening possible. Dr. Thomson provided the experienced guidance in research which made the studies possible and allowed them to be much more complete. Dr. Aherne generously provided both his expertise and facilities for animal studies. Dr. Van Aerde added his famous enthusiasm and background in nutritional techniques. Finally, Dr. Thurston was invaluable for his advice.

I also wish to acknowledge the generous support of the Alberta Heritage Foundation for Medical Research and the Edmonton Civic Employees Union. Autosuture Canada, Smith, Kline and French, Canada Ltd., Bristol Laboratoties of Canada and Bristol-Myers Canada Inc. generously donated materials used in these studies.

Many people helped with this work, but special thanks are due to Ed Matcher, Ted Germaine, John Henriksen, Monica Keelan, Tracy Lam, Michele Tavernini, and Catherine Nicholls. Special thanks are also due for the expert secretarial assistance of Colleen Gardner and Rosemary Henley.

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CHAPTER I

INTRODUCTION

The survival of patients after massive small bowel resections (MSBR) has improved in recent years, due to refinements in surgical techniques, anaesthesia and general supportive care (1,2,3). This is particularly evident in the pediatric age group, where the routine survival of infants with as little as 20 cm of residual bowel has been reported (4). The development of the technique of total parenteral nutrition (TPN) has been particularly important in providing supportive care during the initial postoperative period, when the residual bowel is adapting to its increased functional requirements. However, in some cases there is insufficient residual bowel to achieve complete independence of TPN support, and so long term home TPN therapy is necessary. In infants, a unique form of progressive liver failure is commonly seen with prolonged TPN support (5,6). In newborns, this is universally seen on liver biopsy after 6 weeks or more of TPN (5). By 3 months of complete TPN dependence, the resulting hepatic failure can be lethal (6).

These problems in maintaining long term nutritional support in some patients after MSBR have stimulated interest in therapies to improve the function of the residual bowel. In reviewing the literature, it is apparent that there are few studies comparing different treatments, and none which use the same model of MSBR (7,8). Moreover, there is no animal model of MSBR which has been evaluated specifically for its suitability as a model of the condition in man.

The pig was chosen for these studies because of the similarity in anatomy and physiology of its digestive tract to man's. Many reviews have discussed these common features (9,10,11), which include anatomy and microscopic morphology (12), controls of gastric acid secretion

(13), GI hormonal profile (14) and digestive and absorptive processes (9,11,12). The pig's response to dietary manipulations of fiber, protein, and protein-calorie starvation has been shown to be similar to man's (15-17). Man and the pig have similar nutritional requirements (11). Given these similarities in form, function, and response to dietary manipulation, we felt that it would be useful to evaluate the pig as a model of SBS in humans.

The many therapies which have been used experimentally to treat SBS are reviewed in Chapter II. As outlined in more detail there, the surgical therapies which are most promising for pediatric patients, and have an acceptable cost-benefit ratio, are colon interposition (18), and bowel lengthening as described by Bianchi (19). Accordingly, these were the surgical treatments which we chose to evaluate using this model of SBS. Medical treatment consisting of cimetidine, and narcotic agonists such as codeine are widely used in the treatment of SBS, however these have never been compared directly with surgical therapy (8,20). These were chosen as medical treatment arm of the study. Many other treatments exist, however the surgical and medical therapies chosen are the most likely to be considered for clinical use at this time.

In this thesis, Chapter II reviews the pathophysiology of the short bowel syndrome, including the adaptive response of the remaining bowel, and the different therapies which have been previously evaluated. Chapter III evaluates a 75% resection of the small bowel of the domestic pig as a model for the short bowel syndrome (SBS) in man. It was our hypothesis that a 75% resection of the small bowel in a domestic pig would result in significant malabsorption, and that the ensuing adaptive process of the residual bowel would be similar to adaptation in man.

Chapter IV is a comparison of current surgical and medical therapy in the treatment of SBS. Our objective was to compare the effects on nutritional status of medical treatment with cimetidine, and surgical treatment with bowel lengthening or colon interposition. Our hypothesis was that bowel lengthening was optimal treatment for SBS.

The final chapter is a general discussion of the results, relating them to potential mechanisms, and possible therapeutic uses.

Data throughout this thesis is presented as mean ± standard error of the mean (SEM). Comparisons between the transected, and non-treated resected (NTR) control animals were done using Student's t-test, and between the NTR-controls and the different treatment groups using ANOVA. P values less than or equal to 0.05 were considered significant. Working with small groups of animals (5 to 8 in each treatment group) introduces a significant possibility of a type II statistical error. However, this study is the first to compare different treatments for the SBS using the same model. It is hoped that these preliminary studies will lead to further, more detailed investigations where indicated.

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CHAPTER II

THE SHORT BOWEL SYNDROME: CLINICAL FEATURES, SPONTANEOUS ADAPTATION AND THERAPY

INTRODUCTION

Conditions which necessitate the resection of major portions of the small bowel are relatively common. The metabolic consequences of such resections can be devastating, and in the past were the leading cause of death after the initial post operative period. In 1937, Haymond reviewed the world literature (1) and found that resections of less than one third of the small bowel length could fairly confidently be expected to survive, while resections of greater than one half the total bowel length did poorly. The introduction of total parenteral nutrition (TPN) has greatly improved the outlook for such patients, and recent reviews have reported the routine survival of patients with 20 cm of small bowel, with completely enteral nutrition (2,3), and survival of patients with even shorter lengths of bowel with home TPN support (4). These improved survival statistics have resulted in an increasing population of patients with the sequelae of massive resection, and this in turn has renewed interest in further improving therapy for these potentially complex cases.

I will first briefly cover the etiology and clinical presentation of major resections of the small bowel, and then focus on the adaptation process which is so critical in compensating for such losses. Finally, present medical and surgical treatments will be reviewed, along with possible areas for new therapies.

DEFINITION

The term "Short Bowel Syndrome" is used to describe the clinical consequences of extensive resections of the small bowel. However, this is by no means a well-defined entity. Rickham defined "Massive Small

Bowel Resection" in the neonate as resection leaving less than 75 cm of bowel (roughly 30%) (5). However, in this review we have defined the short bowel syndrome as resection which results in clinically important malabsorption.

ETIOLOGY

The conditions which necessitate surgical resection of the small bowel are listed in Table II-1. Overall, necrotizing enterocolitis and congenital atresias are the most common causes in newborns and infants, while inflammatory bowel disease and vascular accidents are more common in adults.(2,6)

TABLE II-1: Common Indications for Small Bowel Resection

AGE GROUP		
Pediatric	Adult	Geriatric
Volvulus of small bowel	Inflammatory bowel	Thrombosis
-due to malrotation	disease	or arterial
-due to intact	Trauma	embolism
vitelline duct	Volvulus	Venous
Congenital atresia	-due to adhesions	thrombosis
Omphalocele or gastro-	Radiation enteritis	Carcinoma
schisis	Bypass obesity surgery	
Necrotizing enterocolitis	Strangulated hernia	
Strangulated hernia		

CLINICAL SYMPTOMS AFTER EXTENSIVE RESECTION

The minimum length of small bowel required to support life is not known, but patients have survived with only duodenum and 15 cm of small bowel anastomosed to the colon (7). Small bowel length varies from 300 cm in life to 600 cm postmortem, after loss of muscle tone; these variables make accurate recording of the extent of resection difficult. The severity of symptoms following resection varies more with the length remaining than with the length resected. Other factors such as the presence or absence of the ileocecal valve, health of remaining bowel and other digestive organs and the length of time since resection are also important determinants in the patients symptomatology (Table II-2).

TABLE II-2: Factors Affecting Bowel Function Post-resection

- Length and type of remaining small bowel and colon
- Presence of ileocecal valve
- Adaptation or time since resection
- Ongoing disease in remaining bowel or other digestive organs

Bowel resection necessarily reduces the luminal length which is available for the digestion of food into an absorbable mix of basic nutrients. The surface area available for nutrient uptake is also reduced. Net bowel transit time is also shortened. Aside from the simple reduction in length, the resection of regions of bowel which normally coordinate motility (8) can lead to increases in transit rate

or intestinal hurry (9). This in turn further impairs digestion and nutrient absorption. The overall effects vary with the site of resection, and in reviewing this, it is helpful to keep in mind the physiology of normal nutrient digestion.

JEJUNAL RESECTION

In normal bowel, the bulk of fluid and electrolyte absorption occurs in the jejunum. The small bowel and colon routinely handle 2 L of ingested fluid and 5 to 6 L of endogenous secretions per day. Roughly half of this fluid is absorbed in the jejunum and the rest is taken up by ileum and colon. The uptake of water throughout the bowel is a passive process, following the uptake of nutrients and electrolytes. Jejunal content is kept isotonic, because intercellular junctions are "leaky" and allow back diffusion of water, while ileal and colonic junctions are tighter, allowing for hypertonic intraluminal content (10).

Water soluble vitamins, iron and the divalent cations Mg++, Ca++ and zinc are also primarily absorbed in the duodenum and jejunum, but this function is not exclusive to these regions (11).

Normally, nutrient absorption is completed in the jejunum (10). One would predict from this that ileal resection would cause less functional disturbance than jejunal resection, but this is not so. With jejunal resection, the increased fluid and nutrient load is usually well handled by the ileum and colon, and after a possible initial phase of diarrhea, all the functions of the jejunum can be handled by the ileum. The motility of the ileum, normally slower than jejunum, is preserved, so overall transit time is diminished due to the shorter length of bowel, but is slower than if an equivalent length of jejunum remained.

As well, the terminal ileum and ileocecal valve can affect proximal intestinal function. Unabsorbed nutrients, especially fat, in the distal ileum slows proximal jejunal transit (8). This mechanism may be mediated by enteroglucagon, or other gut hormones (see section on hormonal effects of SBS). The overall effects of such mechanisms to coordinate nutrient load, motility, and nutrient uptake are unclear, but they would likely help control the loss of unabsorbed nutrients from the ileum after a proximal resection. It has been observed clinically that after resection of only the jejunum, the major problems are transitory fluid and electrolyte disturbances.

With more extensive resection of jejunum and ileum, fluid and electrolyte depletion, with deficiencies of Ca++, Zn++, Mg++, and iron can occur. The volume of food and intrinsic secretions overwhelm the absorptive capacity of the residual bowel. Food may only be partially digested due to inadequate contact time with intraluminal and brush border membrane enzymes. As a result, fluid, electrolytes, partially digested polysaccharides, proteins and fats can enter the colon, setting the stage for bacterial overgrowth. If this occurs, bacterial fermentation will produce lactic acid and short chain fatty acids, worsening osmotic diarrhea, and producing gas (12,13).

ILEAL RESECTION

Ileal resections are not as well tolerated as jejunal resections. The ileum has the unique functions of vitamin B_{12} absorption and active uptake of conjugated bile salts (14,15). Normally, passive transport of bile salts occurs in the proximal bowel (16) and active ileal transport recovers the lower concentrations which remain (17). Resections of less than 100 cm of ileum can result in cholerrheic enteropathy (diarrhea

with little or no steatorrhea) (18). This occurs due to the loss of bile salt binding sites and the consequent wasting of bile salts in the fecal stream to the colon. There, they impair water and electrolyte uptake, and in high concentrations (>3 mM) can induce secretion of fluid by the colonic mucosa (15,18). Hepatic synthesis of bile salts increases to compensate for the ongoing losses and eventually a steady state is reached where lower than normal concentrations of bile salts exist in the small bowel, but they are still adequate for micelle formation and fat uptake. If greater than 100 cm of ileum is resected, bile salt losses exceed the liver's compensatory capacity and fat malabsorption results (steatorrhea) (19). Bile salt levels in the colon are low, so that they are no longer a factor in causing diarrhea.

Paradoxically, bile salts in the colon can stimulate the absorption of certain small molecules, such as oxalate. This is probably the main factor in the supernormal absorption of oxalate seen after ileal resection (20). Another factor is decreased levels of intraluminal free Ca^{++}, which normally binds oxalate. Ca^{++} is bound by unabsorbed free fatty acids, leaving increased levels of oxalate free for absorption. Ultimately, these chronically elevated oxalate levels can result in renal stones.

Gallstones are another common complication of alterations in the enterohepatic circulation of bile salts. Bile salt wastage leads to supersaturated or lithogenic bile (21). Roughly one third of patients with ileal resection will develop gallstones, however, 40% of these are radio-opaque, and so cannot simply be explained by a supersaturation of cholesterol (22). Alterations in biliary Ca^{++} metabolism induced by deconjugation of bile salts by colonic bacteria, or by the altered bile

salt concentrations themselves may explain the occurrence of these calcium rich stones (23).

B_{12} absorption also varies with the extent of ileal resection. Resection of less that 50 cm has little effect, however, resection of between 60 and 120 cm will significantly impair B_{12} uptake (14).

Moreover, with ileal resection motility is relatively increased, because the remaining proximal bowel has an intrinsically faster transit time than the resected ileum. The previously noted mechanism for coordinating proximal intestinal motility with nutrient load and absorption, the "ileal brake", is also lost, potentially increasing transit rate even further (8).

In summary, resections of less than 50 cm of ileum in adults are well tolerated, but longer resections lead directly to malabsorption of vitamin B_{12} and bile salts, with the resulting disturbances in bile salt metabolism, fat absorption, and colonic fluid and electrolyte secretion, as detailed above.

COLONIC RESECTION

From the foregoing, it is evident that resection of color, normally a site of electrolyte and water absorption, if combined with small bowel resection, will further impair water and electrolyte resorption. In health, the colon can absorb up to 5 L per 24 h, and can actively conserve Na^+ against a gradient (24). In those cases where bile salt and fatty acid losses induce secretion of fluids in the colon, the removal of the "end organ" might be expected to improve matters. Clinically, this is not so, and colonic resection worsens fluid and electrolyte losses in short bowel patients (12).

ILEOCECAL VALVE

If resected, the normal mechanism for maintenance of small bowel sterility is lost and so the risk of bacterial overgrowth increases (13). The ileocecal valve also helps coordinate bowel motility via the previously noted "ileal brake". Resection will also eliminate this (8).

GASTRIC HYPERSECRETION

When considering the effects of resection, it is easy to overlook the fact that the gut is an active endocrine organ. For many years gastric and duodenal ulceration have been known to occur following major resections (25). This led to the theory that resection led to an increase in gastric acid output. Much work has been done in this area, and it has been shown that while gastric hypersecretion does occur after a major resection in the dog (25), this is not necessarily so in the human (26). In man, gastric hypersecretion is transient, and with time reverts to normal (26,27). The observed early increase in gastric output is probably due to increased gastrin levels, discussed further below. When gastric hypersecretion is present, gastric fluid output and acid secretion are both increased, especially in response to meals (27). This increase in fluid output contributes to malabsorption by increasing the volume that the residual bowel must handle, and reducing the small intestinal pH below optimal levels for the activity of pancreatic enzymes. It has been observed that patients undergoing a major resection who had a previous vagotomy and pyloroplasty, did better than expected (28). Prior to the development of H_2 blockers, vagotomy and pyloroplasty were advocated to control these complications, and also to slow transit (29,30).

ADAPTATION

The ability of the gut to compensate, with time, for very major resections has been observed clinically for many years (1). This phenomenon, known as adaptation, is still not totally understood and several recent reviews cover the known experimental and clinical data well (11,31,32). There are a variety of models which simulate massive resection in the human, but interpretation of the data can be difficult because of variations in response in different species (31,33).

MORPHOLOGICAL AND FUNCTIONAL CHANGES

In vivo assessments in the rat, dog, and human have established that nutrient absorption per unit length of bowel increases following major resection (33-37). This in turn improves the overall nutritional status of the animal, and is the essence of the adaptive response. In Diamond and Karasov's excellent review of this topic (38), they classify adaptation of nutrient uptake into two categories: 1) increases in uptake of specific nutrients in response to changes in their level in the diet; and 2) generalized increases in the uptake of all nutrients. Examples of this are adaptation that occurs after resection in response to cold, hyperphagia or lactation. The theoretical mechanisms which could account for this more generalized type of adaptation are: 1) improved intraluminal digestion; 2) increased activity of brush border membrane (BBM) digestive enzymes; 3) increased affinity of a receptor for a given substrate; 4) increased numbers of receptors per enterocyte; 5) increased numbers of functional enterocytes per villus; 6) increased nutrient accessibility of uptake sites (decreased thickness of the unstirred water layer [USWL]) or increased permeability of the enterocyte BBM; 7) increased mucosal surface area per unit of serosal

surface area (e.g. increased individual villus height and width or an increase in the number of villi); and 8) increases in gross bowel length and diameter. For nutrients which are passively absorbed, the changes related to receptor activity would not apply, while changes in USWL thickness and the permeability properties of the enterocyte become more important.

The animal model of adaptation to resection which is best understood is the rat. In this animal, the pivotal event seems to be an increased "load" of nutrients which causes an increase in the rate of crypt cell production. This results in a more rapid progression of cells out of the crypt "nursery", and up the villus (31). If the rate of loss of cells from the villus tip remains constant, crypt and villus size must increase (hypertrophy), or the numbers of cells per unit length increase (hyperplasia). Dowling calls this a "Type I" response, as opposed to a "Type II" response to trauma, where increased cell production is negated by an increased loss of cells from the villi, as seen in sprue (32). In the rat, the mucosal surface area per unit serosal area increases two-fold due to the resulting increase in villus height and width (39). This may also increase the number of functional enterocytes per villus (40). Finally, adaptation in the rat also increases gross bowel length and diameter (41,42).

However, in the rat, there is no evidence to support increased numbers of nutrient carriers per unit weight of mucosa. In general, the rate of nutrient uptake (V^{max}) per unit weight of tissue for actively transported substances declines after resection (34,43,44). Data for receptor affinity for substrate (K_m) values of actively transported nutrients have not been reported for the rat, but in the rabbit the K_m

for glucose did not change after ileal resection (45). Changes in carrier affinity for substrate are difficult to determine, and are not a commonly used mechanism in adaptive regulation of nutrient transport (38).

In general, the activity of BBM digestive enzymes (per unit weight of mucosa) decreases after resection (46), however, some exceptions have been noted (47). This generalized decrease in enzymatic activity has led to the theory that the increased crypt cell production rate and more rapid migration of enterocytes (39), results in an immature population of functioning enterocytes (34,44). This may be generally true, however, as noted, this pattern is not universally seen, and the effects of resection may be controlled by discrete signals for morphological and functional changes (11).

In summary, the rat responds to intestinal resection by increasing mucosal surface area by increasing gross bowel length and diameter, and also increasing mucosal surface area per unit serosal surface area by increasing villus height and width. The number of functional enterocytes is increased, but carrier dependent nutrient uptake per enterocyte is either decreased or unchanged. However, the net effect of these changes is an increase in nutrient uptake per unit length of bowel, and an improvement in the overall nutritional status of the animal.

This sequence of adaptive changes cannot be assumed to occur in other species. Morphological changes with adaptation are much less marked in the rabbit or dog (33,45). There is no increase in mucosal surface area per unit serosal surface area as seen in the rat. Functionally, the dog has been shown to adapt with an increase in

segmental nutrient uptake (35), however, in both the dog and rabbit BBM enzyme activities and carrier mediated uptake specific activities (V^{max}) are either unchanged or increased by resection (33,45,48); this contrasts with the above noted decrease in specific activity of these functions in the rat.

In the human, nutrient uptake per unit length of bowel increases after resection (36,37). Although good data on morphological changes is sparse, the evidence is for modest villus hyperplasia, without marked hypertrophy (49). BBM activities and carrier mediated specific activities as well as activity per enterocyte seems normal (50).

The signals which control the mucosal hypertrophy observed in the rat post-resection are not known, however, the three factors which are most likely to modulate this response are: 1) luminal nutrition; 2) hormones; and 3) pancreatic and biliary secretions.

Luminal nutrition has been shown to be the most potent trophic stimulus for adaptation (31). Rats which have had transposition of ileum and jejunum undergo a marked adaptation response in the ileal mucosa; this is due to the increase in luminal nutrients. However, if there are no exogenous nutrients in the intestinal lumen, adaptation does not occur. In jejunectomized animals, oral alimentation causes marked ileal villus hyperplasia, while IV nutrition does not (35). Long chain triglycerides may be important in controlling this, since intragastric infusions of these fats specifically stimulates mucosal hypertrophy in jejunectomized rats (51).

Animals which have had ileal resections do undergo adaptive changes in the residual jejunum, and this cannot be explained using the theory of increases in luminal nutrition. Adaptive changes are observed in

Thiry-Vella loops, excluded from luminal nutrition, after massive resection in the remaining bowel (52). As well, in cross-circulation studies, intestinal resection in the donor animal stimulates small bowel mucosal hyperplasia in the recipient (53). These findings point to the involvement of hormonal factors; these are discussed below. It is likely that luminal nutrients act, at least in part, by triggering the release of trophic regulatory peptides, which can act locally or systemically.

Pancreaticobiliary secretions have been shown to cause ileal mucosal hypertrophy (54); this may be due to their protein content acting as a non-specific nutrient (32). Bile salts may also be trophic to the small bowel, however, mucosal adaptation will occur in the absence of pancreatic and biliary secretions (55) and so these factors must be considered as secondary in the overall control of adaptation.

Other factors such as intestinal blood flow or neural factors may have a role to play in adaptation, but few studies have examined their effects (32).

HORMONAL CHANGES

Intestinal resection causes profound changes in the levels of gut related hormones, and this topic has been the focus of ongoing research. There is presently no unifying theory to relate the observed hormonal changes and the alterations in gut physiology after resection, however, our understanding of this is improving constantly. The known alterations in hormonal profiles will be reviewed here.

Gastrin

At one time this hormone was thought to regulate mucosal growth throughout the intestinal tract (56), and thus would be a likely

candidate to control the response to resection, however, this has been shown not to be so (57). Gastrin has been shown to be trophic for the antrum and duodenal mucosa, but not bowel more distally. Gastrin may also play a permissive role in the early development of the gut (58). Levels of gastrin do rise after a major resection, and probably play a role in the gastric hypersecretion seen soon after resections (25), however, with time the gastric response to these elevated levels diminishes, and acid output returns to normal (26). Gastrin given directly to animals does not provoke an adaptive response (57), nor are adaptive changes seen with pathologically high levels of gastrin, such as the Zollinger-Ellison syndrome (32).

Secretin-CCK

Given its physical similarity to gastrin, it is only natural that this hormone was initially considered as a candidate for the control of adaptation. Bioextracted secretin-cck does prevent mucosal hypoplasia associated with long term TPN, and it is trophic for the pancreas, but it does not stimulate mucosal hyperplasia or hypertrophy (32) when given to animals eating normally. It may be that the changes seen with infusion in animals on TPN are due to the increased output of pancreatic secretions, which are trophic themselves (54).

Enteroglucagon

There is evidence that this gut hormone may play a major role in regulating adaptation. Glucagon-producing tumors cause hypertrophy of intestinal mucosa that is identical to that seen in SBS (59). After extensive resection, enteroglucagon levels in the ileal mucosa, and the plasma increase (60,61). It has been shown in rats that chronic elevation in enteroglucagon levels stimulates small bowel hypertrophy

(62), however, interpretation of these studies is difficult because the methods used to elevate enteroglucagon levels were indirect. Enteroglucagon has not yet been synthetically produced, and so it has not been possible to use a pure preparation to test for a direct trophic effect on bowel mucosa. Glucagon has been tested for this, and no morphological adaptive changes were noted, but functional changes were evident (63).

It is interesting to note that the main site of production of enteroglucagon is the ileum, and that the normal signal for its release is undigested luminal fat (8). This may mean that proximal resections stimulate ileal production of enteroglucagon, and this in turn stimulates the adaptive process. It may also imply that the reason ileal resections are poorly tolerated is because of the ileum's unique hormonal properties, and not it's absorptive functions as is commonly believed.

PYY and Somatostatin

These hormones seem to function as generalized "inhibitory" peptides of the gut. PYY levels definitely increase after major resections (64), and thus may play a role in controlling the gastric hypersecretion which occurs immediately following resection and in reducing the responsiveness of the stomach to gastrin (26). PYY itself, when given to animals directly, does not stimulate an adaptive response (65). Somatostatin levels have not been specifically reported following major resection. However, somatostatin has been shown to reduce the crypt cell production rate (CCPR), and enteroglucagon levels when given following resection, and was not trophic to the small bowel proper (66). Somatostatin has been shown to reduce ileostomy output by reducing the

volume of intrinsic intestinal secretions (67). This type of hormonal therapy has interesting possibilities for controlling bowel function using physiological mechanisms, especially in such cases such as the SBS, where aberrations in the normal controlling mechanisms may worsen the clinical problem.

VIP

Levels of this hormone have been shown to rise following massive resection (68). VIP is not known to affect cell division rates, but may alter enterocyte function (69). The well-described association of elevated VIP levels and watery diarrhea suggests that the elevated levels of VIP in SBS may be a contributing factor to the diarrhea of SBS, but this remains to be proven (68).

Pituitary and Hypothalamic Hormones

It has been noted that hypophysectomy in rats causes intestinal mucosal hypoplasia; this can be partly prevented by the administration of ACTH and TSH. These changes may be due to the associated reduction in food intake, but hypophysectomy also reduces adaptation in rats with resection when food intake is controlled (32). This suggests that one or more of the hypothalamic hormones plays a permissive role in the adaptation process, but it is unlikely that they are the dominant factors in it's control. Lactation in rats stimulates a morphological change in the intestine which is very similar to that seen in adaptation to resection, however, this has been shown to be due to the increased food intake of the animal and not due to prolactin (70).

Epidermal Growth Factor

This hormone has been examined closely over the past few years for a possible role in the adaptive response to resection and as a

generalized factor controlling gut development. Its ability to stimulate tissue growth and differentiation in different organs, and the discovery of its presence in amniotic fluid, saliva, and duodenal secretions led to speculation that it might act locally to control mucosal growth. There is some evidence that it may do so (71), however, it is not a powerful effect. It does not seem likely to be the major factor controlling mucosal growth after resection (72).

Polyamines

The polyamines are a general class of compounds derived from the amino acid ornithine. Their intracellular levels vary in response to many different stimuli (73), and are generally related to cellular reproduction rates. This has led to speculation that they may act as "second messengers", for a variety of cellular stimuli. After a major intestinal resection, levels of these compounds do rise, and if this rise is prevented by using a specific blocking agent, adaptation does not occur (74). Further work to try and stimulate adaptive changes by manipulating polyamine levels is ongoing (74).

SUMMARY

This evidence has led to a postulated controlling mechanism for the adaptive response following massive resection: after resection, increased concentrations of undigested nutrients reach the distal ileum, and colon. This triggers the release of enteroglucagon, as well as other hormones, and in turn these trigger a rise in polyamine levels within the enterocyte. This then initiates the morphological and functional changes seen with the adaptive response.

CLINICAL STAGES OF ADAPTATION AND ASSOCIATED DIETARY THERAPY

The effects of adaptation are commonly seen in the clinical situation following a major small bowel intestinal resection; initially a period of profuse watery diarrhea ensues, but over 2 to 4 months this gradually improves, and with it, the ability to absorb nutrients from the GI tract. This is most evident with patients who have a high ileostomy or jejunostomy. It is useful to consider this process as three stages as defined by Pullan (75); these correlate directly with therapy (6).

STAGE 1 (0 to 2 months)

In this initial period, residual gut function is poor and little nutrient absorption occurs: the previously discussed high volume of endogenous secretions overwhelms the colon and massive diarrhea of 2-4 L/day results. All nutrition must be parenteral. Fluid, electrolyte, Ca^{++}, Zn^{++}, Mg^{++} and phosphate levels must be monitored closely.

STAGE 2 (2 to 6 months)

Gradually, the absorptive capacity of the bowel increases and the initial state of gastric hypersecretion diminishes. Oral intake can be increased slowly, so long as it does not markedly exacerbate the diarrhea. Typically an elemental diet is used, gradually increasing the strength and volume until oral intake exceeds 2,000 calories/day, at which point the TPN can be tapered. Since these diets are unpalatable, a soft gastric feeding tube and a constant infusion may be required to achieve sufficient intake (6,9,76). Controversy exists as to whether this expensive elemental diet is necessary, and certainly once adequate initial intake is achieved, the patient can be switched to regular food

(77). Long chain fatty acids have been shown to increase fluid loss from the small bowel and so should be avoided until the diarrhea is well controlled (78). Medium chain triglycerides, which are absorbed directly into the enterocyte without micelle formation, may be used to provide calories. Supplementation with minerals, fat soluble vitamins, B_{12} and rarely water soluble vitamins may be required.

STAGE 3 (6 months+)

At this point, maximal adaptation will be reached. Again, controversy exists as to whether a low-fat diet is required forever and so a liberalized, high carbohydrate diet should be gradually introduced. If increasing the fat content of the diet causes diarrhea or steatorrhea, then the low-fat diet is indicated (77,79). With any such diet, typical SBS patients absorb 60% of ingested nutrients, and will require roughly 40 kcal/kg.day to maintain weight. If this results in excessive diarrhea or an unacceptably high enteral intake, then long-term supplementation either using night time tube feeds or home TPN is indicated (76).

MEDICAL TREATMENT

Current medical treatment for SBS is largely supportive. As outlined above in the preceeding section, initial therapy is largely fluid and electrolyte supplementation with the judicious introduction of enteral feeds. However, some specific medications have been shown to be useful.

Cimetidine was originally used to control gastric hypersecretion, and has been very useful for this (80,81). The typical patient with SBS should not have problems with peptic ulceration with this treatment. As

well, cimetidine reduces the volume of gastric secretions, and so reduces the fluid load the remaining bowel must absorb (81). It has also been shown to improve nutrient absorption in man, possibly by optimizing intraluminal pH for the activity of pancreatic enzymes (80). Cimetidine has been shown to affect crypt cell production in the rat (82), and may improve the adaptive response (83,84). These effects on adaptation have not yet been demonstrated for other H_2 blockers, and so cimetidine is specifically indicated in the initial therapy of all cases of massive resection. The long term effects of this therapy are not clear, and it is not known whether the improvement in adaptation with the cimetidine therapy observed immediately post-resection results in a sustained increase in nutrient absorption, or if the natural adaptation process has just been speeded up.

Diarrhea may be worsened by rapid intestinal transit. This can be treated with either codeine or loperamide; loperamide has been shown to be the more effective drug in reducing salt and water losses (85). These narcotic agonists have long been known to slow transit (86), however, the mechanisms may not be as simple as once thought. One study showed that loperamide in SBS patients increased bowel activity, however, this was increased to and fro activity rather than integrated propulsive waves (87). This presumably increased the contact time of intestinal content with the absorptive surface. These drugs may also have a direct effect on salt and fluid resorption (86).

Occasionally, dilation of the bowel secondary to adaptation can be so massive that peristalsis becomes ineffective (88,89). In one reported case, cisapride, a prokinetic agent, was helpful in restoring gut motility (88). In this particular case, the improved motility

seemed to reduce bacterial overgrowth, and allowed the reintroduction of enteral feeds. Further research into the mechanisms and benefits of such therapy is necessary before it can be more generally recommended.

Bile salt wasting may contribute to cholerrheic enteropathy as discussed under ileal resection; if this is suspected cholestyramine resin may be helpful (90). If oxalate stones develop or urinary excretion of oxalate is elevated, then a low-oxalate diet, increased fluid intake and oral cholestyramine resin are indicated (9,20). If steatorrhea occurs then fat restriction and supplementation with medium chain triglycerides should be helpful (6).

Bacterial overgrowth may develop for a number of reasons: proximal malabsorption of sugars and fats; ileocecal valve resection; or, massive dilation from adaptation resulting in ineffective peristalsis. Broad spectrum antibiotics such as metronidazole, or ampicillin may be helpful (9).

Future therapies will ideally stimulate the adaptive response directly. Continued research into the role of the factors which are known to stimulate adaptation, such as long chain fats, enteroglucagon and possibly other gut peptides, will hopefully produce therapies which can do this directly. The use of somatostatin analogues to effect a hormonal control of excessive ileostomy output has already been noted (67), the other recently discovered inhibitory peptides may also prove useful for this type of treatment.

SURGICAL TREATMENT

At present there is no clearly defined role for surgical therapy in short bowel syndrome. Many possible procedures have been suggested,

however, none have been shown to be consistently beneficial. Nevertheless, interest in this type of therapy persists because as TPN techniques have been refined, more and more patients are surviving major resections, only to live a very confined lifestyle dependent on intravenous feedings (91) or to die from complications of long term TPN therapy (92).

Operations for SBS aim to improve nutrient absorption by slowing intestinal transit, and thus increasing the time for digestion and absorption, or by increasing the useful surface area for absorption. Gastric hypersecretion has also been treated surgically.

OPERATIONS TO SLOW INTESTINAL TRANSIT

Interposition of Antiperistaltic Lengths of Intestine

Overall, this has been the most intensively studied and the most commonly used strategy for slowing intestinal transit. Interest dates back to Mall's report in 1896, in which he reversed loops of varying lengths of small bowel in dogs (93) and found that all reversed loops retained their original directional polarity. Singleton confirmed this finding, and noted that if the reversed segment was shorter than eighteen inches, prolonged survival was possible (94). This implied that the reversed peristalsis in these shorter segments produced only partial obstruction, while longer segments caused complete obstruction and death within 5 days. Hammer was the first to show that such reversed segments improved survival after major resection (95); this has since been confirmed by many authors (96-98). Although the effect is not quantified, Hammer observed that a 2 to 5 cm reversed segment greatly delayed the passage of intestinal content. He speculated that

this improved absorption, since animals which did not have an interposed reversed segment died of cachexia (95).

Stahlgren et al performed 3 day balance studies of fat and nitrogen in order to quantify the effects of intestinal reversal on nutrient uptake (96). In their study, dogs underwent an 80 to 85% small intestinal resection. He showed that reversal of 5 to 18 cm of small bowel improved fat, water and nitrogen absorption. This was especially evident when the residual bowel was jejunum. Reversal of lengths greater than 18 cm caused lethal obstruction. Keller et al showed that using two separate reversed segments improved survival in even longer (90%) small bowel resections (98), but they did not investigate changes in nutrient absorption. Delany et al showed that, in animals undergoing an 80% resection of the mid small bowel, reversed segments actually worsened fat absorption and reduced the average animal weight, when followed for 10 months (99). He also showed that fat absorption improved with antibiotic therapy, suggesting that bacterial overgrowth may have been important in causing this fat malabsorption. In one of the most detailed studies of the effects of reversed segments of intestine, Barros D'Sa showed that after 75% bowel resection, including the distal ileum, reversal of 10 cm of the remaining distal jejunum improved fat absorption, weight gain, survival and small bowel transit time (100).

In summary, reversing segments of small bowel to treat SBS appears to favorably influence survival, slow nutrient transit through the bowel and, in some models, improve fat absorption. Differences between the studies may be due to the different types of resection employed initially, as well as variations in postoperative care. It has often

been assumed that the increase in contact time improves nutrient absorption, but this has not been proven (96,100). Tannar et al (101) have shown that reversal of a segment of jejunum increases the incidence of retrograde complexes within and below the reversed segment. This likely indicates that the reversed segment slows transit in the distal intestine. The possible consequences of this change in myoelectrical activity extend beyond motility; Bjorck et al (102) have shown that the improved absorption induced by electrical pacing is induced in part through adrenergic stimulation of enterocyte function. It is evident that more detailed study of the physiological effects of this procedure is necessary, before a true assessment of its value can be made.

Antiperistaltic segments of intestine have been used clinically for the treatment of SBS in at least 33 cases (103); almost all reports have been favorable. Most interposed segments have been 7 to 15 cm in length (103), with 10 cm being the ideal length in adults. In children, as little as 3 cm of reversed ileum has been helpful (104,105).

These enthusiastic clinical reports should be viewed with caution, given the normal bias in favor of reporting successful cases and the fact that most of the adult cases reported had greater than 120 cm of small intestine remaining. In those cases where metabolic studies have been done, improvements in fluid and electrolyte absorption have been documented (104,106,107). There is no evidence in man that nutrient absorption has been improved by this procedure. Prior to the availability of TPN, these procedures were generally used to prevent prolonged fluid and electrolyte loss, however, given the ability to maintain fluid balance with home TPN, this indication is now uncommon. In any particular case the risks of re-operation and the potential for

the loss of further bowel length must be carefully weighed against the possible benefits.

Intestinal Valves

Numerous procedures have been devised to directly slow intestinal transit by creating a "valve effect", these include plicating the bowel (108), denervating a section of bowel (109) or the creation of a mucosal flap valve with or without a myomectomy (110). Intussuscepted segments have been used, both to slow flow and to duplicate the ileocecal valve's normal function of maintaining the sterility of small bowel content (111-114). Such valves have been shown to slow transit, improve nutrient uptake and improve survival following major resection (109,110,114), but they have also caused obstruction, necrosis of the intestine and intussusception (112). There have only been two clinical reports of the use of such valves in humans: 1) Waddell et al reported variable results in 3 patients (115); and 2) Ricotto reported good results at 4 years with an artificial ileocecal valve (112).

Colon Interposition

Interposed segments of colon are thought to improve nutrient absorption by slowing transit, but they do not risk the loss of further lengths of small intestine. Experimental studies have been reported using both distal and proximal iso- and anti-peristaltic loops. Because the colon retains its intrinsically slower motility pattern, the length used is not as critical as with reversed small intestinal segments. Moreover, uptake of nutrients (amino acids and glucose), water and electrolytes from the interposed colonic segment have been documented, although whether this contributes significantly to the nutritional status of the animal is unclear (116). In dogs, Hutcher and Salzberg

showed that isoperistaltic segments of colon, placed proximally or distally in the bowel remnant, slowed transit and improved survival and weight gain (117,118). Fluoroscopy showed minimal peristalsis of the interposed colon, which acted as an aperistaltic conduit. However, there was no proximal obstruction. Fat absorption was slightly improved when the segment was interposed distally. Other authors saw no clinical improvement with antiperistaltic colon interposition placed distal to the small bowel remnant (119).

Good results have been reported in monkeys, using an antiperistaltic portion of colon which was interposed in mid small bowel after a 75% resection (120). All animals which had the colon interposition survived, while the controls did not. This report also showed improved xylose and fat absorption over time, however, since there was no control group, it is not clear that this was specifically due to the colon interpostion. Again, while there is good evidence that colon interposition prolongs transit time, it has not been shown that this necessarily improves nutrient absorption. It is also not clear what long term effects this may have on the myoelectrical activity of the bowel. As noted in the discussion of reversed segments of small bowel, the relationship between the myoelectrical and motility changes observed after this type of intervention and effects on nutrient absorption, are not clear. The myoelectrical effects of colon interposition have not been reported, but likely will slow distal transit and increase retrograde electrical activity at least as much as transection (101). This needs further study.

The clinical use of interposed segments of colon has been limited, but several authors have reported encouraging results. Brolin reported

the use of an 18 cm segment of sigmoid colon after massive midgut infarction in an adult (121). In this case, the patient requires TPN support daily, but can eat normally, and has only 2 to 3 stools daily. Eight pediatric cases have been reported (122-124), with 4 survivors and 4 deaths. In those children which survived, all have been successfully weaned from TPN. Survival was associated with a greater length of small bowel remaining after the initial resection, colon interposition at a younger age and a shorter duration of medical management prior to colon interposition (124).

Recirculating Loops

The concept of using recirculating loops of small intestine to improve nutrient absorption was a logical progression of the finding that interposed segments of reversed small intestine improved absorption (96). Several different procedures have been tried (125-127), and although some recirculation of intestinal content was demonstrated, nutrient uptake and survival were not improved.

Three clinical reports of the use of recirculating loops have been published, two report favorable results (125,128), while in the third the patient improved initially but died after 7 months of a bowel obstruction (129).

Intestinal Pacing

As noted in the preceding discussions of the pathophysiology of SBS, a major problem, especially of distal resections, is increased rates of transit of nutrients through the remaining bowel. Preliminary work in controlling bowel motility using electrical pacing has led to several trials of this modality in models of SBS (130-132). These have demonstrated increased water, electrolyte and nutrient uptake, as well

as improved weight gain and reduced fecal fat losses in dogs. However, these studies were very short term (2 weeks) and included the use of a pyloroplasty in one model (130), which does not fit well with the typical clinical scenario accompanying SBS. As noted, further studies into the physiology of this improved absorption suggest that it might be mediated through alpha-adrenergic mediated increases in enterocyte activity, rather than an effect on motility (102).

No clinical reports or studies of electrical pacing for SBS have been performed to date, however, preliminary work on the feasibility of pacing in humans has shown that it is difficult to electrically alter human pacemaker potentials, even after transection of the bowel (133). This may prevent the use of this therapy in humans, even if it proves to be effective in animals.

METHODS TO INCREASE ABSORPTIVE SURFACE AREA

Tapering Enteroplasty

As noted during the discussion of the pathophysiology of the SBS, the adaptive process can lead to marked dilatation of the residual bowel. This can progress to the point where peristalsis becomes ineffective (134), leading to bacterial overgrowth and stasis. This is particularly common in pediatric cases of SBS secondary to congenital atresia. No good experimental model of this problem has been reported, however, there have been 2 publications detailing 17 clinical cases where antimesenteric tapering enteroplasties have been performed (89,135); all cases had a favorable outcome and were apparently helped by the procedure.

Bowel Lengthening

An elegant extension of the tapering enteroplasty is the bowel lengthening procedure described by Bianchi (136). First performed experimentally in pigs, it is done by dissecting between the 2 peritoneal layers of the mesentery of the bowel. The vasa recti of the small bowel in both the pig (136) and man (137) separate after leaving the marginal vessel. They then assign themselves to one side of the mesentery or the other, so that between them an avascular plane can be developed. After transecting the bowel, this space can be dissected free. The bowel can then be divided longitudinally along the antimesenteric and then the mesenteric borders, leaving 2 halves of the circumference, each with its own blood supply. These can then be approximated, leaving 2 lumens, each one-half the diameter of the original bowel. These 2 segments can then be anastomosed end to end directly or in a spiral as reported by Aigrain et al (138).

This has since been used in at least 7 cases clinically, with good results reported in each case (134-141). The most common indication has been ineffective peristalsis in the dilated bowel remnant of infants with short gut. The average segment lengthened was 29 cm, with an average final bowel length of 68 cm. All cases have been weaned from TPN, and have been able to maintain themselves enterally. The most common indication for the initial resection is intestinal atresia, which has not seemed to alter the vascular anatomy of the remaining bowel. In an eighth case, the procedure was attempted, but one hemiloop became ischemic, and required resection. The child did benefit from the resulting tapering (89).

To date, there have been no studies examining the effects of bowel lengthening on nutrient absorption, gastric hypersecretion, or bowel

transit time. Bianchi, in his original report, did mention that peristalsis of the lengthened segment appeared normal with fluoroscopy (136).

Growth of New Intestinal Mucosa

The use of serosal patches to repair gastric and duodenal perforations led to investigations which demonstrated the growth of "neomucosa" over the serosa of the patching viscus (142). This neomucosa has been shown to be functional (143). Various applications of this method have been used to produce neomucosa, including the use of Dacron patches (144), Dacron tubes (145), colonic serosa (146) and abdominal wall pedicles (147). However, synthetic patching material is often extruded, and other tissues undergo marked contraction, thus reducing the end surface area (147). The one experimental report of the use of this technique in the treatment of SBS showed an improved weight gain in pigs which had 16 to 46 cm longitudinal colonic serosal patches created after 75% small bowel resection (146). This report has been criticized because it did not include an appropriate control group undergoing a longitudinal enterotomy without patching. This would be required to control for the effects the enterotomy might have had on motility, and subsequent weight gain. There is no reported clinical experience with this technique.

Intestinal Transplantation

Transplantation of the small bowel would clearly be an ideal treatment for the SBS if it were feasible. Many of the technical problems limiting this technique have been solved (148); however, major problems with immunosuppression have limited its use in humans (149). Seven cases of transplantation in humans have been reported (150); all

ended in death with the longest survival being 79 days. Recent improvements in immune suppression have revived interest in the use of this technique in humans (150); this work must be regarded as highly experimental at present.

GASTRIC HYPERSECRETION

As discussed in the sections on the hormonal and gastric responses in the pathophysiology of the SBS, there is a definite and long lasting increase in gastrin levels following MSBR (26). This leads to an initial state of gastric hypersecretion, which can worsen diarrhea, and inactivate pancreatic enzymes (9). Interest in the use of vagotomy and pyloroplasty to treat SBS was prompted by the observation that patients undergoing MSBR who had previous vagotomy did much better than expected (28). Many reports of the experimental use of these procedure exist (25,29,151,152), however, only a few clinical reports have been published (29,153) and these have generally been favorable. The development of H_2 blockers has made surgery to control gastric hypersecretion unnecessary (see section on medical therapy). With the risk of gastric incontinence after vagotomy (154), such procedures are now contraindicated (155).

SUMMARY

As noted at the outset, no one surgical therapy has been shown to be consistently useful in the treatment of SBS. Presently, the main role of the surgeon in the therapy of SBS is to conserve as much intestinal length as possible at the initial resection (151). Attempts to specifically treat the SBS should only be made in stable patients,

after maximal adaptation has occurred. The role of some of the surgical therapies discussed above, such as the use of reversed intestinal segments, colonic interposition, intestinal pacing, lengthening, tapering and transplantation continues to evolve. It can only be hoped that the surgeon will eventually be able to play a part in the "cure" of a disease which surgery so often creates.

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CHAPTER III

THE PHYSIOLOGY OF ADAPTATION TO SMALL BOWEL RESECTION IN THE PIG: An Integrated Study of Morphological and Functional Changes[1]

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[1]A version of this chapter has been submitted for publication. Sigalet DL, Lees GM, Aherne FX, Van Aerde JEE, Fedorak RN, Keelan M and Thomson ABR. Gastroenterology (Submitted).

INTRODUCTION

The management of patients after massive bowel resection causing malabsorption (the "Short Bowel Syndrome", or SBS) can be a difficult clinical problem. Increased understanding of the physiology of the bowel's adaptation to resection could improve clinical treatments (1). Significant recent advances have been made in our understanding of the process of adaptation, but the majority of this work has been done in rodents. Resection in rats starts a cascade of linked events: luminal nutrients stimulate an increased crypt cell production rate, which in turn increases crypt and villus size, and the number of functioning enterocytes (2,3,4). With these morphological changes, brush border membrane (BBM) enzyme and nutrient uptake activity are altered (3,5). Although these changes are variable, they tend to follow a pattern of reduced enzymatic expression typical of the immature enterocyte (2,3,6). Morphologically, increases in mucosal surface area compensate for this reduction in enzyme specific activity, so that nutrient uptake per unit length of small intestine may be increased, while nutrient uptake and BBM enzymatic activity per unit weight of mucosa may be decreased (7).

This sequence of adaptive changes cannot be assumed to occur in other species. For example, morphological changes with adaptation are much less marked in the rabbit or dog (8,9). The intestine of the dog does adapt with an increase in segmental nutrient uptake (10), yet in both the dog and rabbit BBM enzyme and carrier-mediated uptake specific activities are either unchanged or increased by resection (8,9). This contrasts with the decrease in specific activity of these functions found in the rat (6,7,11).

We wished to develop a model of short bowel syndrome which more closely parallels the clinical situation in humans. Digestion in the pig is similar to the human (12), and the pig can reliably tolerate a massive resection of the small bowel (13), presumably due to the effectiveness of its adaptive processes. Furthermore, the young pig rapidly gains weight and an alteration in this usual weight gain would be readily demonstrable as the result of a surgical insult such as extensive bowel resection. Accordingly, we undertook to investigate the physiology of adaptation to massive resection after 75% small bowel resection in juvenile domestic pigs. The use of rapidly growing animals allows weight gain to be used as an objective parameter to follow the efficacy of adaptation of nutrient absorption. Other parameters followed included feed consumption, gross and microscopic bowel morphology and nutrient uptake (both *in vivo* and *in vitro*). These assessments were performed to test the hypotheses that 1) morphological and functional intestinal adaptation occurs following 75% intestinal resection in the juvenile pig; 2) there is an association between the morphological and functional adaptation; and 3) the adaptation of the morphology and absorption which occurs in the residual intestine demonstrates the malabsorption associated with short bowel syndrome.

MATERIALS AND METHODS

1. ANIMALS

Female domestic pigs (Sus scrofa: Pig Improvement Canada strain) aged 5 to 8 weeks, and weighing 15 to 25 kg were used. Animals were housed in individual pens with free access to food and water, except during the perioperative period. Room temperature was maintained at

20±2°C, and light-dark cycles of 12-12 h were used. Animal care was in accordance with the Canadian Council in Animal Care (14) and the experimental protocol was approved by the Animal Welfare Committee of the University of Alberta.

Animals were maintained on a standard grower diet (University of Alberta Research Farms: 18% protein, 69% carbohydrate, 4% fat and 4% fiber and 5% Ash), supplemented with medium-chain triglycerides (MCT Oil, Bristol-Myers Canada Inc., Ottawa, ON) as 50% of total fat calories. The diet was made of: wheat 24%, barley 53%, soy been meal 15.5%, MCT oil 4%, iodized salt 0.5%, calcium phosphate 1%, calcium carbonate 1% and vitamin-mineral mix 1%. No supplemental antibiotics were used. Animals were allowed to eat and drink ad lib. Feed intake and the animals' weight were determined weekly.

2. STUDY DESIGN

At time 0, animals had a laparotomy, with measurement of gross bowel morphology as described below. Animals were randomly assigned to the resection or transection groups. After 2 weeks, a feeding trial to monitor the efficiency of feed conversion to weight was begun, and continued for a further 6 weeks. At 10 weeks a second 6 week feeding trial was begun. Over the final week an in vivo nutrient absorption study was performed and in the sixteenth week the animals were re-operated upon. They again underwent an assessment of gross bowel morphology, samples were taken for in vitro nutrient uptake studies and microscopic morphology, and the animals were then sacrificed.

3. OPERATIVE TECHNIQUE

Animals were fasted overnight, anesthetized with halothane-oxygen administered by mask, and were explored through a midline abdominal incision. The small intestinal length was measured along the antimesenteric border from the ligament of Treitz to the ileocecal valve, using a pre-measured umbilical tape. Bowel circumference was measured in the jejunum 10 cm distal to the ligament of Treitz and in the ileum 10 cm distal to the anastomosis. Measurements were performed by placing the bowel flat on a warm saline-soaked gauze on top of the measuring tape, and then laying the tape over the exposed surface with minimal tension. Measurements were done in duplicate and averaged. Animals with adhesions were excluded from analysis of gross morphology. Reproducibility of both length and circumference measurements was ±10%. This was done as a routine immediately after anesthetic induction and laparotomy.

The control group had a simple transection and biopsy with end-to-end re-anastomosis at a point 12.5% of total small bowel length proximal to the ileocecal valve. The resected group had a resection of the central 75% of small bowel, leaving equal lengths of residual jejunum and ileum of 12.5% of original total bowel length each. There were 6 transected and 8 resected pigs. All anastomoses were completed with single layer interrupted 4-0 silk. The abdominal incision was closed with interrupted 0, and the skin was closed with a running subcuticular 3-0, polyglycolic acid suture. Hydration was maintained intraoperatively with intravenous lactated Ringer's solution given at 10 mL/kg.h via an ear vein. All animals received a single dose of penicillin-streptomycin antibiotic intramuscularly immediately

preoperatively (penicillin 10,000 u/kg, streptomycin 10 mg/kg). Morphine sulphate intramuscularly (0.2 mg/kg q6h) was given for 36 hours postoperatively for analgesia. Water was allowed immediately post-operatively and feeds were restarted after 24 h.

At 16 weeks the animals were anesthetized again, using the same protocol and drugs, and the gross bowel morphology was measured as described for the initial laparotomy. The ileum distal to the anastomosis was resected quickly and taken for in vitro uptake studies, as described below. The animals were then sacrificed with a lethal injection of thiopentone and intestinal sections were taken for histology. Microscopic morphological measurements were performed using previously described techniques (15).

4. NUTRITIONAL INDICES

At 6 weeks after initial operation and at sacrifice, blood was collected for determination of hemoglobin concentration, white blood cell count (M4-30 Coulter Electronics, Hialeah, FLA), total protein and albumin. Alkaline phosphatase, blood urea nitrogen (BUN), creatinine and serum glutamicoxalacetic transaminase (SGOT) (IL-Multistat III, Instrumentation Laboratories, Lexington, MA) were also determined at sacrifice.

5. NUTRIENT ABSORPTION

The standard method of monitoring the efficiency of feed to weight conversion is the feeding trial, where variations in nutrition are assessed by monitoring the weight gain and feed intake over a specified period (20). In this study the effect of small bowel resection was assessed by monitoring weight gain and feed intake over the initial 2-8 week period immediately postoperation. This was compared to the weight

gain and feed intake over the final 6 weeks of the study period (10-16 weeks postoperation).

For 10 days prior to sacrifice in vivo measurements of macronutrient (protein, carbohydrate and fat) uptake were determined using the method of Kennelly et al (17). Briefly, this involves the use of an inert marker, dysprosium, mixed in the feed; final concentrations in the feces reflect absorption of the diet by the animal.

Fat concentrations in feed and feces were determined using the methods of Jeejeebhoy et al (18), and protein by the micro Kjehldahl method (19). Carbohydrate energy was determined by subtracting known protein and fat energy from the total sample energy, as determined by bomb calorimetry (20); the difference was attributed to dietary carbohydrate (16). Dysprosium concentration was measured using instrumental neutron activation analysis (INAA) with the Canadian SLOW POKE Reactor (17).

In vitro measurements of ileal nutrient uptake were obtained using previously described methods (8). Unlabelled and 1-^{14}C-labelled fatty acids were greater than 99% pure as supplied by Applied Science Laboratories, Inc. (State College, PA) and by Sigma Chemical Corp. (St. Louis, MO). [μ^{14}C]glucose, and [G-^{3}H]inulin were obtained from New England Nuclear (Boston, MA). All other compounds were of reagent grade and were obtained from Fisher Scientific Co. Ltd. (Edmonton, AB).

The technique used for the preparation of the test solutions containing fatty acids has been published elsewhere (21). Briefly, an appropriate amount of both a ^{14}C-labelled and unlabelled probe molecule was dissolved in 150 mL Krebs-bicarbonate buffer to yield final concentrations of 0.1 mM for the fatty acids and 0.05 mM for

cholesterol. The fatty acids included palmitic (16:0), stearic (18:0), oleic (18:1), linoleic (18:2) and linolenic (18:3). To solubilize these lipid probes, micellar solutions were prepared with 20 mM taurodeoxycholic (TDC) acid (21). An appropriate amount of both a ^{14}C-labelled and unlabelled cholesterol or fatty acid was dissolved in an exact volume of chloroform:methanol (2:1, v:v) in an incubation beaker, and the chloroform:methanol phase was then evaporated to ensure complete removal of these organic solvents. Seventy-five milliliters of a 40 mM TDC solution in Krebs-bicarbonate buffer was added to the beaker and the solution was stirred with a magnetic bar for 2 h. The solution was then further diluted by the addition of 75 mL of Krebs-bicarbonate buffer to give a final volume of 150 mL and a final TDC concentration of 20 mM. The beaker was gassed with 5% CO_2 in O_2 for 2 h at 37°C and, if necessary, the pH was readjusted to 7.4. A trace amount of radiolabelled volume marker [G^{3}H]inulin was then added and the solution was ready to be used for the determination of tissue uptake rates. The counting activity of the solutions was approximately 100,000 c.p.m/mL of ^{14}C-labelled compounds, and 250,000 c.p.m./mL of [G^{3}H]inulin. The non-absorbable inulin marker was used in all experiments, and similar volumes were estimated for the adherent mucosal fluid in the control and the resected animals.

D-glucose was prepared in concentrations of 1.0, 5.0, 10.0, 20.0 or 40.0 mM: the concentration of L-glucose was 1.0 mM.

6. TISSUE PREPARATION

The ileum distal to the anastomosis was resected at terminal laparotomy and as outlined in detail elsewhere (22,23), a short segment was rapidly removed, rinsed with cold saline, opened along its

mesenteric border and the mucosal surface was carefully washed with a stream of cold saline from a syringe to remove visible mucus and debris. The intestine was mounted as flat sheets in the incubation chambers, and clamped between 2 plastic plates so that the mucosal and serosal surfaces were exposed to separate incubation solutions, with apertures in the plates exactly 0.5 cm in diameter. The chambers were transferred to beakers containing continuously oxygenated Krebs-bicarbonate buffer at 37°C for a pre-incubation period of 30 min. The chambers were then transferred to other beakers for specific experiments.

The pre-incubation and incubation solutions were mixed at identical stirring rates with circular magnetic bars, and the stirring rates were precisely adjusted by means of a strobe light. In all of these studies the bulk phase was stirred at 600 r.p.m. to reduce the effective thickness of the intestinal water layer, and to better reflect changes in transport function (23). After pre-incubation of Krebs-bicarbonate buffer for 30 min, the chambers were transferred to other beakers containing [^{3}H]inulin and the various concentrations of ^{14}C-labelled cholesterol, fatty acids and glucose in continuously oxygenated Krebs-bicarbonate buffer at 37°C. After incubation for 6 min, the experiment was terminated by removing the chamber and quickly rinsing the ileal tissue in cold saline for approximately 10 seconds. The exposed mucosal tissue was then cut out of the chamber with a circular steel punch, blotted on filter paper and placed in a tarred counting vial. The tissue was dried overnight in an oven at 75°C and the dry weight determined. The sample was then saponified with 0.75 N NaOH, scintillation fluid was added, and radioactivity was determined by means

of an external standardization technique to correct for variable quenching of the two isotopes.

7. STATISTICAL METHODS

All comparisons were made using Student's t-test. A p value ≤ 0.05 was considered to be statistically significant. All results were expressed as the mean ± standard error of the mean (SEM).

RESULTS

1. ANIMALS

A) Complications

The animals tolerated the procedures well, with no anesthetic deaths and no perioperative complications. All animals were drinking on the first and eating on the third postoperative day. The resected animals had 5-7 diarrhea stools daily during the first 3-7 postoperative days. After this time all had one formed stool per day and ate and played normally. One of the resected animals developed an incisional hernia, which did not appear to affect it's early clinical course, but this animal later died unexpectedly of a bowel obstruction. A second resected animal had an anastomotic stricture noted at terminal laparotomy, and was therefore excluded from analysis. This left data for analysis from 5 transected and 6 resected animals.

Three of the resected animals had gastric ulcerations noted at terminal laparotomy; none of the transected animals had this complication. The ulcerations were consistently at the junction of the body and antrum; there were no esophageal or duodenal ulcerations.

B) Feed intake and Weight Gain

Feed intake was greater [when expressed as total intake (kg/day)] in the transected group than in the resected pigs (Table III-1), both from 2-8 and from 10-16 weeks. However, there was no difference in feed intake when expressed as kg feed intake per kg animal body weight per day. Although the efficiency of feed conversion (g/kg.day) was numerically higher in transected than in resected pigs at 2 to 8 and 10 to 16 weeks, these differences failed to achieve statistical significance ($p>0.05$).

There was no difference in the initial weights of the animals in the two groups (22.9±2.2 kg for transected and 19.1±3.6 kg for the resected group, $p>0.05$). Over the 16 weeks the transected animals gained 78±4.3 kg and the resected pigs gained only 28±7.1 kg ($p<0.001$). The transected animals gained weight steadily at an expected rate of 700±40 g/day (Table III-1). The resected animals gained less weight over the first 6 weeks (260±65 g/day), but this rate of weight gain increased to 330±80 g/day over the final 6 weeks. These rates of weight gain were less than in the transected groups ($p<0.02$).

2. NUTRITIONAL INDICES

At 6 weeks there was a significant drop in the concentration of hemoglobin, total protein and albumin in the resected animals as compared with the transected controls. By 16 weeks these values had declined in the transected animals, resulting in a small and insignificant difference between the two groups (Table III-2). There were also no significant differences between the groups in their liver enzymes at 16 weeks.

3. NUTRIENT ABSORPTION

There was a significant decrease in the *in vivo* absorption of all nutrients in the resected as compared to the transected group at 16 weeks (Table III-3). Quantitatively, fat absorption was affected the most, with the net absorption of ingested fat in the resected group being 15.3±8.4%, compared to 64.0±3.1% in the control group ($p<0.02$). Protein absorption was 79.5±1.8% in the resected group, which was less than the 85±1% absorption of the transected group ($p<0.01$). Carbohydrate absorption in the resected animals was 80.8±1.9% as compared with 85±0.9% ($p<0.02$) in the resected group. Total energy absorbed was also reduced in resected animals as compared to transected animals (75.2±3.1% versus 84.2±1.1% $p<0.01$).

The contribution of passive permeation to glucose uptake was measured with 1 mM L-glucose. L-glucose uptake was higher in resected than in transected animals (1.4±0.1 versus 1.0±0.1 nmol 100 mg.min, respectively, $p<0.05$). When the uptake of D-glucose was corrected for passive permeation, a similar curvilinear relationship was noted between glucose concentration and uptake in resected and transected pigs (Figure III-1). The uptake of long-chain fatty acids and cholesterol was increased ($p<0.05$) in resected as compared with transected pigs (Table III-4), with a greater relative enhancement for the more lipophilic cholesterol (500%) as compared with the less lipophilic palmitic acid (138%).

4. BOWEL MORPHOLOGY

Over 16 weeks the diameter of the residual bowel increased 86% in the resected animals, compared to 42% in the transected controls. Bowel length increased 74±17% in the resected as compared with 27±10% in the

transected animals (Table III-5). Villus surface area of the residual ileum doubled in the resected animals, but there was an associated decrease in the number of villi/unit serosal area, so that overall there was no change in the mucosal surface area/unit serosal area in resected as compared with transected pigs (Table III-6).

Taking into consideration the changes in bowel length and width (Table III-5), and the mucosal surface area per unit serosal area (Table III-6), the estimated bowel surface area increased from 81,000±2500 to 166,000±7000 cm^2 in transected pigs from time 0 to 16 weeks, and increased from 14,800±3100 to 55,200±4300 cm^2 in resected animals over the same time interval (Table III-6). Bowel surface area increased in resected as compared with transected pigs by 270% versus 95%. Thus resected animals began the experiments with only 18% of the mucosal surface area of the transected animals. As adaptation occurred, principally through increases in gross length and diameter, this increased so that at the end of the experiment the mucosal surface area of the resected group was 33% of the area of the transected animals.

DISCUSSION

Transected animals grew at the rate typical of grain-fed pigs (16). There was a significant decrease in the absolute weight gain as well as the rate of weight gain in resected animals (Table III-1). From week 2 to 8 the efficiency of feed conversion was numerically lower in resected than in transected pigs (but not statistically significantly) although by weeks 10 to 16 the efficiency of feed conversion was similar (Table III-1). The digestible (or absorbed) energy cost of fat or protein retention has been estimated to be 12.5 Mcal of DE/kg for pigs in the

50-100 kg weight range (24). Given this estimate of the energy required for weight gain, the observed values for energy absorbed from the diet in the two groups (Table III-3), and the average daily feed intake over the final 6 weeks (Table III-1), the expected weight gains of the two groups would be 785 g/day for the transected and 330 g/day for the resected animals (assuming constant maintenance energy requirements, which would be as the results in favor of the resected animals, since these were smaller). These values are in close agreement with the final observed rates of weight gain of 710 g/day for the transected and 330 g/day for the resected groups (Table III-1). This implies that energy, once absorbed by the resected animals, can be converted to weight as efficiently as in normal animals. Thus, the lower rates of weight gain in resected animals were likely due to malabsorption and reduced food intake rather than to reduced feed utilization.

The simplest adaptive mechanism after intestinal resection would be to increase the surface area available for absorption by increasing the length and diameter of the bowel. This did occur in the resected animals (Table III-5), and at the end of the study this adaptation resulted in a significantly greater proportional increase in the surface area of the residual bowel, when compared to the increases in transected animals (Table III-6). The pitfalls of using such simple measurements to approximate bowel surface area are well described (4), but they do serve to illustrate the adaptive changes induced by resection. Increases in bowel diameter after resection have been noted in many species, including dogs, rats and man (4,25-27). Lengthening of residual bowel has been noted in puppies (25,26) and in humans (27) following massive resection, but the percentage increases reported were

lower than those seen in this study. The reason for this higher percentage increase in pigs is unclear.

The second adaptive mechanism to increase the surface area available for absorption would be the increase in the mucosal surface area per unit of serosal area, such as by increasing the height, width and density of the villi. We found that resection induced an increase in villus thickness and lesser increases in height and width, which resulted in a significant increase in surface area per villus (Table III-6). However, the density of the villi declined. Thus, resection was associated with fewer, larger villi, so that there was no change in the net mucosal surface area per unit area of serosa. Furthermore, there was no alteration in the distribution of phlorizin-binding sites along the villus in the two animal groups (Fedorak R: unpublished observations, 1988). Nonetheless, with the gross and microscopic adaptations in intestinal morphology, the estimated intestinal surface area of the intestine in resected animals rose from 18% of the value in transected pigs (due to the extensive surgical resection of an estimated 75% of the small intestine) at week 6, to 33% of the value at week 16. Thus, the morphological adaptation occurring in the residual intestine results in a marked increase in the mucosal surface area.

In the rat, decreased numbers of larger villi also occur with adaptation, yet each villus enlarges enough so that net mucosal surface area per unit serosal surface area increases (4). Our findings underscore the importance of using a true three-dimensional determination of surface area: if these results had been reported using two-dimensional measurement of only villus height and width, a false impression of increased mucosal surface area would have resulted. This

lack of reliability of two-dimensional assessments in estimating changes in mucosal surface area has been reviewed previously (28). Clearly however, the alterations in the *in vitro* uptake of nutrients was not explained by changes in mucosal surface area. Similar disassociations between the adaptation of intestinal form and function have been reported previously (29).

In vivo assessments of nutrient uptake demonstrated a significant reduction in fat, protein, carbohydrate and total energy absorption after extensive intestinal resection (Table III-3). Fat is the macronutrient most affected by massive resections (30) and this was confirmed in the present study. Although the normal pig obtains only 6% of its total calories from fat, the reduction in fat absorption after resection accounted for 46% of the reduced energy absorption in the resected animals.

The more normal *in vivo* absorption of amino acids and carbohydrates after resection may have been due to adaptive-compensation, such as the increased total surface area of the bowel or increased passive uptake, as was shown for L-glucose. There was no change in the active transport of this hexose. This contrasts with the increase in maximal transport rates for glucose observed in adaptation in the rat, but is similar to the pattern observed in dogs (9), rabbits (8) and humans (31,32). There was also increased *in vitro* uptake of long chain fatty acids and cholesterol (Table III-4), but clearly this adaptation was insufficient to correct the severe steatorrhea following 75% intestinal resection. Thus, the membrane events associated with intestinal adaptation were sufficient to prevent the malabsorption of carbohydrates and amino

acids, but were insufficient to fully compensate for the malabsorption of lipids.

The final mechanism which could increase nutrient absorption is improved intraluminal digestion. This possibility was not examined in this study. However, in normal pigs fed a grain diet, greater than 50% of starch digestion and absorption occurs in the stomach and duodenum (33). Sambrook showed that despite the rapid enzymatic hydrolysis of starch, the accumulation of glucose was minimal (34), which implies that the normal pig has a very high capacity to absorb glucose in the proximal small bowel. The gastric ulceration observed in our resected animals suggests that these animals developed gastric hypersecretion. This in turn could affect digestion by shifting the intraluminal pH of the small bowel away from the optimum for pancreatic enzymes and thus slowing the normally rapid hydrolysis of starch. In contrast to carbohydrate, lipids are absorbed along the entire length of the small bowel (35). These findings in normal animals would suggest that the malabsorption of fat in resected animals noted in the in vivo but not in the in vitro studies of fat absorption could be caused by both a decrease in the intraluminal digestion of nutrients and by a decreased mucosal surface area available for absorption.

The rat's ability to adapt using the process of increased mucosal surface area, with reduced enterocyte specific activity may be relatively unique: this pattern of morphological and functional changes has not been noted in the dog (9), rabbit (8), or in these studies using pigs. Evidence in humans is for adaptation with modest villus hypertrophy (36), and with normal function per villus (31,32). The adaptive changes in active transport kinetics are not well established

in man (31,32), but there is an increase in nutrient uptake per unit length of bowel (37). Thus, the young growing pig may be more appropriate than the rat for studying modalities of medical or surgical treatment of short bowel syndrome which are applicable to man.

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Table III-1: Animal Characteristics

Parameter	Transected	Resected
1. 2-8 WEEK STUDY PERIOD:		
Feed intake		
Total (kg/day)	2.3±0.06	1.12±0.10*
Per kg animal body weight (g/kg.day)	37.7±7.6	45.8±13.3
Weight gain (g/day)	700±90	260±65*
Efficiency of feed conversion [gain/feed] (kg/kg.day)	0.31±0.04	0.22±0.04
2. 10-16 WEEK STUDY PERIOD:		
Feed intake		
Total (kg/day)	2.7±1.2	1.3±0.3*
Per kg animal body weight (g/kg.day)	31.0±7.7	32.7±5.7
Weight gain (g/day)	710±40	330±80**
Efficiency of feed conversion [gain/feed] (kg/kg.day)	0.25±0.02	0.22±0.04
Final Weight (kg)	107.5±3.4	51.2±8.7***
Total Weight Gained (kg)	78.0±4.3	28.0±7.1***

† = mean±SEM

* = $p<0.05$

** = $p<0.02$

*** = $p<0.001$

Table III-2: Nutritional Indices

	Time (weeks post-resection or transection)			
	6 weeks		16 weeks	
Value	Transected	Resected	Transected	Resected
Hemoglobin (g/dL)	3.9±0.7	12.2±0.1**	13.1±0.6	11.2±1.8
Total protein (g/dL)	7.1±1.5	5.3±0.7*	5.2±0.6	3.9±1.8
Albumin (g/dL)	3.9±0.6	2.3±0.5**	3.0±0.4	2.1±1.1
SGOT (IU/L)	--	--	19.9±5.4	40±30
Alkaline Phosphatase (IU/L)	--	--	109±21	125±56

† = mean±SEM

* = $p<0.05$

** = $p<0.001$

Table III-3: In Vivo Macronutrient Absorption at Week 16
(% of ingested nutrient absorbed)†

NUTRIENT ABSORPTION	Transected	Resected
Fats	64.0±3.1	15.3±8.4*
Protein	85.0±1.0	79.5±1.8**
Carbohydrate	85.0±0.9	80.8±1.9*
Total Energy Absorbed (Digestible Energy)	84.2±1.1	75.2±3.1%**

† = mean±SEM

* = $p<0.02$

** = $p<0.01$

Table III-4: Lipid Uptake (<u>in vitro</u>)†

Substrate	Transected	Resected
FA 16:0	0.13±0.2†	0.18±0.02*
FA 18:0	0.07±0.01	0.24±0.03*
FA 18:1	0.11±0.01	0.24±0.02*
FA 18:2	0.11±0.01	0.20±0.02*
FA 18:3	0.16±0.02	0.28±0.03*
Cholesterol	0.07±0.07	0.36±0.07*

† = mean±SEM nmol/min.100 mg tissue

* = $p<0.05$, resected versus transected.

Table III-5: Gross Morphology of the Residual Small Intestine†

	Transected	Resected
Bowel Diameter (cm)		
initial diameter:		
(time 0)		
jejunum	1.43±0.1	1.20±0.1
ileum	1.73±0.1	1.36±0.1
final diameter:		
(16 weeks)		
jejunum	2.18±0.1	2.66±0.2*
ileum	2.29±0.1	2.99±0.15**
Bowel Length (cm)		
initial (time: 0 weeks)	1735±48	301±37***
final (time: 16 weeks)	2190±60	641±37***
total length increase (cm) over study	454±158	264±43.9
percentage length increase	27±10%	74±17%*

† = mean±SEM

* = $p<0.05$

** = $p<0.01$

*** = $p<0.001$

Table III-6: Microscopic Morphology†

Morphological Index	Transected	Resected
Crypt depth μm	221±16	207±13
Villus height μm	536±31	592±48
Villus width		
(at 1/2 height) μm	162±10	168±12
(at base) μm	175±14	190±17
Villus thickness	314±23	447±35*
Villus surface area μm^2/villus	390±90	802±78*
No. of villi/mm		
serosal length A	5.98±0.48	5.67±0.54
serosal length B	3.34±0.24	2.39±0.22*
No. of villi/mm^2 serosa	19.08±1.55	12.68±1.21*
Mucosal surface area mm^2/mm^2 serosa	10.83±1.39	9.68±0.74
Estimated Total Bowel Mucosal Surface Area (cm^2)		
0 weeks	81,000±2500	14,800±3100***
16 weeks	166,000±7000	55,200±4300***
% increase over 16 weeks	95±12%	270±70%**

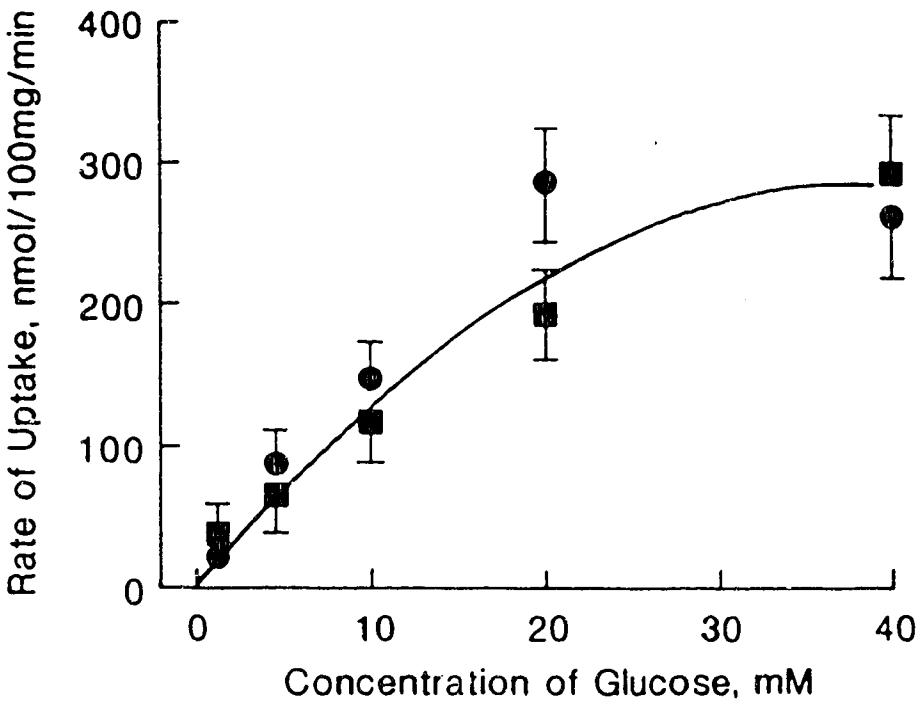
† = mean±SEM

* = $p<0.05$

** = $p<0.02$

*** = $p<0.001$

FIGURE III-1


Rate of Uptake, nmol/100mg/min
400
300
200
100
0
0
10
20
30
40
Concentration of Glucose, mM

CHAPTER IV

A COMPARISON OF SURGICAL VERSUS MEDICAL TREATMENT OF THE SHORT BOWEL SYNDROME[1]

[1] A version of this chapter has been submitted for publication. Sigalet DL, Lees GM, Aherne FX, Van Aerde JEE, Fedorak RN, Keelan M and Thomson ABR. Journal of Pediatric Surgery (Submitted 1989).

INTRODUCTION

The management of the patient with malabsorption due to massive small bowel resection remains a difficult clinical problem (1). With less extensive resections, the adaptive capability of the remaining bowel will eventually allow for the reestablishment of enteral nutrition. However, with shorter lengths of residual bowel, this may not be possible. In such cases, the patient is dependent on total parenteral nutrition (TPN). After 6 weeks of TPN, hepatic changes of cholestasis are universally seen in infants (2), and by 3 months the resulting liver failure can be lethal (3,4). Thus, the reestablishment of enteral nutrition may become critical for survival.

Unfortunately, there are no known medical therapies which reliably improve nutrient absorption or hasten the adaptive process in short bowel syndrome (SBS). Medical treatment with cimetidine has been shown to be helpful (5-7), but its long-term effectiveness in intestinal adaptation is unclear. Other therapies, such as hormonal stimulation of adaptation with epidermal growth factor or enteroglucagon, remain experimental and are not widely available for clinical use (8,9). A number of surgical therapies have been evaluated for their usefulness in increasing nutrient absorption. For example, in pediatric patients the interposition of an isoperistaltic segment of colon has been used (10). This procedure avoids the potential complications of a reversed small bowel segment. Colonic interposition is presumed to be effective as a result of slowing the transit of chyme through the small intestine, thereby prolonging contact time for nutrient absorption. Surgical approaches to increase surface area available for absorption are less well established. The procedure described by Bianchi (11,12) has been

used with good results in eight infants (12-15). This seems to be particularly useful when adaptation has resulted in massive dilation of the bowel with ineffective peristalsis.

Choosing between these surgical therapies is difficult. To date, no studies have compared different treatments using the same animal model. The pig has been shown to be a suitable model for human nutritional studies (16). We have recently reported the use of a 75% small bowel resection in the juvenile domestic pig as a model of SBS (16). We wished to test the hypothesis that bowel lengthening achieved by the Bianchi method represented optimal therapy for SBS in the pig. We compared the effects of medical treatment with cimetidine and codeine versus the surgical treatments of colon interposition or small bowel lengthening. The end-points of benefit included: weight gain; feed consumption; efficiency of feed conversion, hematological and biochemical nutritional indices; bowel morphology (gross and microscopic); and nutrient uptake *in vivo* and *in vitro*.

MATERIALS AND METHODS

1. ANIMALS

Female domestic pigs (Sus scrofa: Pig Improvement Canada strain), aged 5 to 8 weeks and weighing 15 to 25 kg, were used. Animals were housed in individual pens with free access to food and water, except during the perioperative periods. The room temperature was maintained at 20±2°C, and light-dark cycles of 12-12 h were used.

After the induction of the short bowel syndrome (SBS), all animals were maintained on a standard grower diet (University of Alberta Research Farms: 18% protein, 70% carbohydrate, 4% ether extract, 4%

fiber and 5% ash) supplemented with medium-chain triglycerides (MCT Oil, Bristol-Myers Canada Inc., Ottawa, ON) as 50% of total fat calories. The diet was made from: wheat 24%, barley 53%, soy bean meal 15.5%, MCT oil 4%, iodized salt 0.5%, calcium phosphate 1%, calcium carbonate 1% and vitamin-mineral mix 1%. No routine antibiotics were used Animals were allowed food and water ad lib, except during the perioperative period. Feed intake and animal weights were determined weekly.

2. OPERATIVE TECHNIQUES

The previously described model of SBS was used (16). Animals were fasted overnight, anesthetized with halothane-oxygen administered by mask, and explored through a midline abdominal incision. The small intestinal length was measured along the antimesenteric border from the ligament of Treitz to the ileocecal valve, using a pre-measured umbilical tape immediately after induction and laparotomy. Bowel circumference was measured in the jejunum 10 cm distal to the Ligament of Treitz and in the ileum 10 cm distal to the anastomosis. At the initial operation, all animals had a resection of the central 75% of small bowel, leaving equal lengths of approximately 20 cm of residual jejunum and ileum. All anastomoses were completed with single layer interrupted 4-0 silk. The abdominal incision was closed with interrupted 0, and skin with a running subcuticular 3-0, polyglycolic acid suture. Intraoperatively, animals received lactated Ringer's solution intravenously at 10 mL/kg.h via an ear vein. Except as noted, all animals received a single dose of penicillin-streptomycin antibiotic intramuscularly preoperatively (penicillin 10,000 U/kg, streptomycin 10 mg/kg). Morphine sulphate intramuscularly (0.2 mg/kg q6h) was given postoperatively for analgesia for 36 h. Except as noted, water was

allowed immediately post-operatively and feeds were restarted after 24 h.

The resected animals were left untreated for 6 weeks, and then were randomized to one of four groups, each of which contained 6 animals: 1) non-treated resected controls (C); 2) medically treated (cimetidine plus codeine) (M); 3) colon interposition (CI); or 4) small bowel lengthening (BL). The details of these treatments are given below. Ten weeks after the second surgery ("treatment" period) and 16 weeks after the initial small bowel resection, the animals were anesthetized using the same protocol and drugs, and gross bowel morphology was measured as described above for the initial laparotomy. The animals were then sacrificed with a lethal injection of sodium pentobarbital, and sections of intestine were taken for histology.

3. TREATMENT GROUPS

GROUP A: Controls (C). These animals received no specific treatment for their SBS. They were allowed ad libitum access to the standard grower diet.

GROUP B: Medical treatment (M). These animals with SBS received cimetidine 20 mg/kg.day and codeine 2 mg/kg.day during the treatment period. Drugs were mixed with the standard grower feed, which the animals ate ad libitum.

GROUP C: Colon interposition (CI). After the 6 week adaptation period for SBS, these animals underwent an interposition of 10 to 15 cm of distal colon. This was based on the middle colic artery, and interposed 10 cm distal to the ligament of Treitz, as described by Hutcher (17,18). Perioperative care and anesthetic technique was as described in the "Operative Techniques" section.

GROUP D: Bowel lengthening (BL). After the 6 week adaptation period for SBS, these animals underwent a lengthening of 25 to 30 cm of jejunum, as described by Bianchi (11). Intestinal continuity being reestablished using the spiral technique described by Aigrain, et al (15). The jejunum lengthened was that section beginning 10 cm distal to the ligament of Treitz. The procedure resulted in a gain of 25 to 30 cm of small bowel length, of half the initial diameter. In general, interrupted 4-0 silk sutures were used for all anastomosis, including the longitudinal reconstruction of the two hemiloops. Vascular clamps were not used (15). Each end of the bowel was divided using Metzenbaum scissors, with needle point cautery being used sparingly to control bleeding. The central section of the lengthening was done by hand in the first two animals (12), and in the subsequent animals was done using a GIA stapler, with a Penrose drain used to guide the anvil through the mesentery, as described by Boeckman and Traylor (13). We found this was quicker and gave less bleeding.

Because of the time required to complete this procedure (4 to 6 h) more extensive perioperative support was required for this group. After induction with halothane-oxygen by mask, endotracheal intubation was performed. The animals were allowed to breath spontaneously, and halothane-oxygen was used to maintain anesthesia. A servocontrolled heating pad was used, and warmed saline solutions were used throughout.

Upon completion of the lengthening, a 20 Fr. Foley catheter was used to perform a Stamm gastrostomy for gastric decompression; the catheter was brought out through a separate stab wound, sutured and taped into place. A 2 mm internal diameter Silastic (R) tube (Dow Corning Corp., Midland, Michigan) was used to form a feeding

jejunostomy, 25 cm distal to the lengthened segment. This was tunnelled subcutaneously to an exit site between the scapulae (19).

Cephalothin 500 mg intravenously was given preoperatively and then every 6 h for 3 days postoperatively.

Postoperatively, the animals were kept on nothing by mouth for the first 48 h, with the stomach decompressed every 6 h by unclamping the gastrostomy tube. They were maintained with intravenous fluids (5% dextrose in saline, 50 mL/kg.day). On the third postoperative day they were allowed water ad libitum and started on enteral fluids via jejunostomy. The enteral fluid was comprised of Flexical HN (R) (Mead Johnson Canada, Belleville, ON) one half strength, again at 50 mL/kg.day. On the fifth to seventh postoperative day, Flexical HN (R) by mouth was offered. When the animals were taking this well (6 to 10 days postoperatively), the jejunostomy and gastrostomy tubes were removed, Flexical was stopped, and a solid diet was restarted.

4. BOWEL MORPHOLOGY

The gross morphology of the intestine was measured at each laparotomy as described under operative techniques. Animals with multiple adhesions were excluded from the assessment of gross morphology. The reproducibility of these measurements was ±8%. Microscopic morphology was determined using previously described techniques (16,20).

5. NUTRITIONAL ASSESSMENT

The nutritional status of the pigs was determined prior to the initial resection, after the 6 week adaptation period, and again after the 10 week medical or surgical treatment period. Parameters measured were white blood cell count, hemoglobin concentration (M4-30 Coulter

Electronics, Hialeah, FLA), total protein, albumin, glucose, alkaline phosphatase, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), and serum glutamic-oxalacetic transaminase (SGOT) (IL-Multistat III, Instrumentation Laboratories, Lexington, MA).

The effect of treatments on the efficiency of feed to weight conversion by the animals was assessed using published methods (21). Weight gain and feed intake were monitored over the final 6 weeks of treatment, and the weight gain per kilogram of feed ingested was calculated.

6. NUTRIENT ABSORPTION

A) In Vivo

In vivo measurements of macronutrient (protein, carbohydrate, and fat) uptake were determined, using the method of Kennelly et al (22). Briefly, this method uses an inert marker, dysprosium, mixed in the feed. Final concentrations in the feces reflect absorption of the diet by the animal. Dysprosium concentrations were measured using instrumental neutron activation analysis (INAA) with the Canadian SLOW POKE Reactor (22). Fat concentration in feed and feces (ether extract plus medium chain triglycerides) were determined using the method of Jeejeebhoy et al (23) and protein was measured by the Kjeldahl method (24). Carbohydrate energy was determined by subtracting known protein and fat energy from the total sample energy, as determined by bomb calorimetry; the difference was attributed to dietary carbohydrate (25).

B) In Vitro

In vitro measurements of nutrient uptake were determined using previously described methods (26). Chemicals were greater than 99% pure as supplied by Applied Science Laboratories, Inc. (State College, PA)

and by Sigma Chemical Corp. (St. Louis, MO). [^{14}C] glucose [^{3}H]-phlorizin, phenyl-3,3', 5,5'-(^{3}H), propanone-3-(^{3}H) (60 μCi/mmol) and [G-^{3}H] inulin were obtained from New England Nuclear (Boston, MA). All other compounds were of reagent grade and were obtained from Fisher Scientific Co., Ltd. (Edmonton, AB).

The technique used for the preparation of the test solutions containing fatty acids has been published (26,27). Briefly, an appropriate amount of both a ^{14}C-labelled and unlabelled probe molecule was dissolved in 150 mL Krebs bicarbonate buffer to yield final concentrations of 0.1 mM for the fatty acids and 0.05 mM for cholesterol. The fatty acids included palmitic (16:0), stearic (18:0), oleic (18:1), linoleic (18:2) and linolenic (18:3) acid. To solubilize these solutions, micellar solutions were prepared with 20 mM taurodeoxycholic acid. A trace amount of radiolabelled volume marker [G-^{3}H] inulin was then added and the solution was ready to be used for the determination of tissue uptake rates. The counting activity of the solutions was approximately 100,000 c.p.m./mL of ^{14}C-labelled compounds, and 250,000 c.p.m./mL of [G^{3}H]inulin. The non-absorbable inulin marker was used in all experiments, and similar volumes were estimated for the adherent mucosal fluid in each treatment group.

D-glucose was prepared in concentrations of 1.0, 5.0, 10.0, 20.0 or 40.0 mM; the concentration of L-glucose was 1.0 mM.

The ileum distal to the anastomosis was resected at terminal laparotomy. The intestine was rapidly removed, rinsed with cold saline, opened along its mesenteric border, and the mucosal surface was carefully washed with a stream of cold saline from a syringe to remove visible mucus and debris. The intestine was mounted as flat sheets in

the incubation chambers, and was clamped between two plastic plates so that the mucosal and serosal surfaces were exposed to separate incubation solutions, with apertures in the plates exactly 0.5 cm in diameter. Each animal had three adjacent sections of ileum tested in triplicate, so that nine samples from each animal were tested. The chambers were transferred to beakers containing continuously oxygenated Krebs-bicarbonate buffer at 37°C for a pre-incubation period of 30 min. The chambers were then transferred to other beakers for specific experiments.

The pre-incubation and incubation solutions were mixed at identical stirring rates with circular magnetic bars, and the stirring rates were precisely adjusted by means of a strobe light. In all of these studies the bulk phase was stirred at 600 rpm to reduce the effective thickness of the intestinal water layer. When the bulk phase is stirred, uptake is greater than when the bulk phase is unstirred (28), and therefore this condition of stirring was chosen to better demonstrate possible changes in transport function resulting from intestinal adaptation.

After pre-incubation of Krebs-bicarbonate buffer for 30 min, the chambers were transferred to other beakers containing [^{3}H]inulin and the various concentrations of ^{14}C-labelled cholesterol, fatty acids, and glucose in continuously oxygenated Krebs-bicarbonate buffer at 37°C. Previous validation studies had demonstrated a linear rate of uptake between 2-10 min, with a constant volume of adherent mucosal fluid volume, and extrapolation of zero uptake at zero time. After incubation for 6 min, each experiment was terminated by removing the chamber and quickly rinsing the ileal tissue in cold saline for approximately 10 seconds. The exposed mucosal tissue was then cut out of the chamber

with a circular steel punch, blotted on filter paper and placed in a tared counting vial. The tissue was dried overnight in an oven at 55°C and the dry weight was determined. The tissue sample was then saponified with 0.75 N NaOH, scintillation fluid was added and radioactivity was determined by means of an external standardization technique to correct for variable quenching of the two isotopes.

7. ELECTRICAL MEASUREMENTS

Tissues were removed immediately after the animal was killed, cut open along the mesenteric border and incubated with a solution of the following ionic composition (mM): Na, 143; K, 5; Mg, 1.1; Ca, 1.25; Cl, 124; HCO_3, 25; HPO_4, 16.5; H_2PO_4, 0.3; and, fructose 40. This solution was gassed with 5% CO_2 in O_2. At 37°C it had a pH of 7.4. Intestinal segments of 2-3 cm were stripped of their serosa and underlying muscle layer and mounted in Ussing chambers as previously described (29). Mucosal strips were then mounted in Ussing chambers, and transmural electric potential difference, resistance and short-circuit current (Isc) were determined as previously described (29). A Cl- and HCO_3-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 dependency of glucose-induced changes in short-circuit current.

8. PHLORIZIN BINDING TO INTACT TISSUE

Binding of [^{3}H]-phlorizin to intact tissue was measured at 37°C in an oxygenated bath following a 20 min equilibration period. One centimeter tissue discs were stripped of their serosa and muscle layers by blunt dissection and bathed in Ringer containing either D-glucose (40 mM) or fructose (40 mM) for 2 min prior to addition of [^{3}H]-phlorizin,

(0.89 μM, 50 μCi/mL). At varying time intervals following [^{3}H]-phlorizin addition, the tissue disc was removed from the isotope containing solution and the tissue surface washed in ice cold 300 mM mannitol at 1000 rpm for 20 sec. A 20 sec rinse with iced-mannitol solution removes 30-40% of nonspecifically bound phlorizin, but essentially no specifically bound phlorizin (30). The tissues were then blotted on absorbant paper and placed in 1 mL of 10% trichloroacetic acid. After 24 h samples were vigorously vortexed, the supernatant dissolved in 4 mL scintillation fluid and assayed for radioactivity. Specific binding was determined from the difference between binding in the presence of fructose, i.e., total binding, and binding in the presence of D-glucose, i.e., nonspecific binding.

9. STATISTICAL METHODS

All comparisons between treatment groups were made using ANOVA. A p value of ≤ 0.05 was considered to be statistically significant. All results are expressed as the mean $\pm$ standard error of the mean (SEM).

RESULTS

1. ANIMALS

A) Weight Gain and Feed Intake

The animals tolerated the procedures well. After the initial resection, diarrhea (consisting of 3-8 loose bowel motions per day) lasted 3-7 days, and then all animals had a normal bowel habit of one to two stools per day.

Feed intake (g/day and g/kg body weight.day) and the means of the final weights were similar in the four groups (Table IV-1). The medically treated (M) and bowel lengthened (BL) groups had significantly

greater rates of weight gain (590±70 g/day and 550±40 g/day respectively) when compared to the non-treated resected controls (C) (330±80 g/day, $p \leq 0.05$, Table IV-1) and when compared to the colon interposition animals (CI) (360±90 g/day, $p < 0.05$). The efficiency of feed conversion was numerically higher in M and BL than in C or CI, but this difference failed to achieve statistical significance (Table IV-1).

B) Complications

The most common complication was the development of incisional hernias (Table IV-2). These did not appear to affect the nutritional status of the animals. Three pigs, each in a different treatment group, died from bowel obstruction. At necropsy, these were typical small bowel obstructions secondary to adhesions. Two animals in BL died of anaesthetic related complications: one animal died from an anesthetic overdose; and a second animal aspirated immediately post-operation, dying the next day of pneumonia.

Two other animals in BL developed anastomotic leaks: one was recognized and re-explored. After lavaging the abdomen, two leaking sites from the edge of the hand sewn longitudinal anastomosis were identified, and a serosal patch with adjacent jejunum performed over each. This animal subsequently did well, and did not develop a fistula. The second animal's leak was not recognized, and unfortunately it died. At necropsy it was noted to have a large walled-off leak from the proximal end of the longitudinal anastomosis. The remainder of the lengthened segment was intact, with no signs of infarction at histological examination.

Three of the control group animals and one in CI had gastric ulcerations noted at terminal laparotomy. The ulcerations were

consistently at the junction of the gastric body and antrum. There were no esophageal or duodenal ulcerations.

Two of the BL animals were noted at terminal laparotomy to have small fistulas between the lengthened segments; data from these animals were included in all analyses. This does bias the results against BL, yet despite this the group as a whole did significantly better than the controls.

2. NUTRITIONAL INDICES

All groups had decreased concentrations of hemoglobin, albumin, and total protein at 6 weeks post-resection (Table IV-3), as compared to transected animals of a similar age (16). Over the treatment period these values normalized, so that at week 16 there were no significant differences between the treatment groups. Liver and kidney function tests were normal throughout the study period.

3. MORPHOLOGY

The bowel length and diameter increased to a similar extent from 6 to 16 weeks in C, M, CI and BL (Table IV-4). This was similar to the increases in bowel length and diameter which were previously reported in untreated juvenile pigs with SBS (16). In the bowel lengthened groups, the lengthened segments increased in diameter from 1.0±0.1 cm at initial operation to 2.2±0.1 cm at sacrifice ($p<0.001$, using Student's t-test for paired observation). The length of the intestine in these lengthened segments did not change, nor did the interposed segments of colon change in size in the CI group. Overall, the increases in surface area which occurred after lengthening (due to the increase in diameter of the lengthened segments) were negligible when compared to the spontaneous increases in surface area seen in all groups.

Treatments (M, CI and BL) were associated with increased crypt depth and villus width, but mucosal surface area was similar in the four groups (Table IV-5). Interestingly, BL had an increase in villus thickness, which resulted in an increase in surface area per villus [surface area μm^2/villus - 1208±42 (BL) compared to 802±78 (C), and 830±32 (M), $p<0.05$]. However, as the villus size increased, the density of villi decreased, and so there was no net change in mucosal surface area per unit serosal surface area.

Since there were no significant differences between the mucosal surface area per unit serosal surface area (Table IV-5) in the different groups, the final bowel surface area can be approximated by the serosal surface area. This was calculated by averaging the jejunal and ileal circumferences and multiplying this by the measured length (Table IV-4). There were no significant differences between the different treatment groups.

4. NUTRIENT ABSORPTION

A) In Vivo

All groups of resected animals showed a significant decrease in absorption of all nutrients 6 weeks post-resection. After 10 weeks of treatment, nutrient absorption was altered with M and BL absorbing significantly more fat than C or CI (Table IV-6). Combining this data with the feed intake per animal (Table IV-1), the total value of the fat absorbed can be determined. Total fat calories absorbed per day were: C: 90±60; M: 90±55; CI: 85±50; and BL: 110±60, ($p>0.05$).

Protein absorption improved in all groups over the treatment period from an average of 67.4±1.5% at 6 weeks post-resection to 79.5±0.8% at 16 weeks. At 6 weeks post-resection, carbohydrate absorption was

78.2±1.3%, and this also increased to 81±0.8% at 16 weeks. There were no significant differences in protein or carbohydrate absorption between the treatment groups. Overall energy absorption from the diet was similar in all groups at 75±3%.

B) In Vitro

Uptake of 1 mM D-glucose was similar in C and BL (1.4±0.1 and 1.4±0.1, nmol/100 mg/min, respectively), but was less ($p<0.05$) in M (0.7±0.07 nmol/100 mg/min) and CI (0.9±0.1 nmol/100 mg/min). The uptake of D-glucose was greater ($p<0.05$) in CI than in C or M at concentrations of 1, 10 and 20 mM, whereas the uptake of 40 mM glucose was lower in BL than in C. After correction for the differences in passive permeation estimated with 1 mM L-glucose, the active uptake of glucose was consistently higher in CI than in the other groups (Figure IV-1).

Eadie-Hefstee plots were made of the changes in the in vitro short-circuit current (Isc) measured in response to varying concentrations of D-glucose (Figure IV-2). The lowest maximal transport rate (V^{max}) for D-glucose-induced change in Isc was observed in CI, whereas the values of the apparent Michaelis constant (Km*) was similar in C, M, CI and BL (Table IV-7).

C) [^{3}H]-Phlorizin Binding in Intact Tissue

The uptake of FA 18:0, 18:2, 18:3 and cholesterol was significantly less in M than in C (Table IV-8). The uptake of cholesterol was lower in BL and the uptake of FA 18:0 were lower in BL and CI than in C.

Figure IV-3 demonstrates the time-courses of total, nonspecific and specific [^{3}H]-phlorizin binding to intact (jejunum) from non-treated and treated small bowel resected pigs. In all groups, specific binding

reached equilibrium by 2 min and remained constant thereafter. [^{3}H]-phlorizin binding was similar in all groups, suggesting a similar quantity of Na-dependant glucose carriers per mg mucosa.

DISCUSSION

Although weight gain may seem to be a relatively crude index of nutritional well-being, in this population of genetically similar animals, which have been bred for rapid growth, it does accurately reflect nutrient availability. Moreover, it is the standard parameter by which nutritional manipulations in normal pigs are commonly judged (25). In this model of short bowel syndrome (SBS), medical treatment (M) and bowel lengthening (BL) improved the rate of weight gain when compared to non-treated resected control pigs (C) or when compared with animals with colonic interposition (CI) (Table IV-1). This was achieved without a significant alteration in food intake; the efficiency of food conversion was numerically but not significantly higher in M and BL. Thus, the explanation for the superior rate of weight gain in M and BL may relate to adaptation of the intestine leading to differences in intestinal absorption.

The superior rate of weight gain in M and BL was associated with greater <u>in vivo</u> absorption of fat (Table IV-6). Fat is typically the nutrient most profoundly affected by massive small bowel resection (31). The net effect on total energy absorption of these treatment-induced changes in fat absorption was negligible because these pigs were fed a diet low in fat. However, those groups that had improved rates of weight gain were more efficient at converting feed to weight, and these were also the groups with the improved fat absorption. Since all groups

absorbed a similar percentage of the total energy available from the diet, this implies that treatments may have had their effect by improving the efficiency of energy to weight conversion. Fat absorption in normal pigs occurs along the entire length of the small bowel, and this includes a large amount of endogenously secreted lipid from gastric and biliary-pancreatic fluid (32). If this lipid were lost in the feces, it would need to be re-synthesized at considerable metabolic cost to the animal. Thus, the improved fat absorption in BL and M may have improved the rate of weight gain by reducing the metabolic demands of the SBS, rather than by directly improving energy input.

The mechanism for the improved fat absorption in M and BL was not due to enhanced intestinal permeability of fatty acids (Table IV-8). While fatty acids are normally absorbed throughout the entire small bowel, the majority of carbohydrate absorption occurs in the duodenum and jejunum (33). The mucosal surface area per unit area of serosa was similar in the four groups, and the estimated total bowel surface area was also unchanged, so that the lower <u>in vitro</u> uptake of fatty acids in M but higher <u>in vivo</u> absorption must have been due to additional factors not elucidated in this study. For example, the effects of treatment in the intraluminal digestion of fat and other nutrients was not examined but could be an explanation for the improved fat absorption noted.

SBS in humans has been shown to cause gastric hypersecretion (34), and the resulting decrease in intraluminal pH has been suggested to be a cause of reduced pancreatic enzyme function (5). The cimetidine used in M would have reduced such hypersecretion, and would be expected to improve fat digestion. This study does support the use of cimetidine in patients with SBS. The mechanisms of the benefit of cimetidine plus

codeine in the medical treatment group needs to be established in pigs. We were unable to confirm the effect of cimetidine on intestinal adapcation reported in rats (35). Other H_2 blockers have been used with good results in controlling gastric hypersecretion, but it is unclear whether they also improve nutrient absorption (36). The codeine used for this group presumably slows transit time, increasing the contact of chyme with pancreatic enzymes and with the surface area available for absorption. However, codeine has not previously been shown to improve nutrient absorption (37).

The passive permeability of the intestine to glucose decreased in M and CI, and the active uptake of glucose increased in CI (Figure IV-1), yet the lowest maximal transport rate for D-glucose-induced change in short-circuit current (Isc) was observed in CI (Figure IV-2 and Table IV-7). Specific [^{3}H]-phlorizin binding was similar in the four groups, and <u>in vivo</u> carbohydrate absorption was similar in the four groups (Table IV-6). Thus, it is unlikely that changes in the glucose uptake induced by treatment significantly affected the nutritional outcome of these animals.

If we examine the implications for clinical treatments, this study does not support the use of CI. The initial favorable reports of Hutcher and Salzberg on CI were based on dog studies, and the improvements noted by these authors may have been species-specific, or may have been related to the more extensive intestinal resection used in their study (17,18). The benefits noted with CI in human infants (10) may result from improved fluid and electrolyte absorption, one of the reliable consequences of this type of procedure (38). The mechanism of the enhanced <u>in vitro</u> uptake of glucose in CI (Figure IV-1) despite

reduced Isc (Figure IV-2), was not established in this study. However, our data does not support a benefit of this procedure for nutrient absorption and body weight gain in the pig. We suggest that it would be prudent to reassess the nutritional impact of this surgical procedure in clinical practice.

This study shows for the first time the efficacy of BL in improving weight gain, efficiency of feed conversion and nutrient absorption in the SBS. It remains to be shown whether it is best used in those cases where adaptation has caused dilation of the bowel with resulting ineffective peristalsis. Such situations are usually seen in infants (13,14) and are generally difficult to treat. Our experience with the lengthening procedure demonstrates a definite learning curve: four out of the first five animals had leaks or fistulas, while the last three animals had good results. However, the procedure is straightforward, and after appropriate animal experience, could be undertaken by any competent surgeon. The technical complications of fistula formation and anastomotic leaks can be minimized by injecting the lengthened segments with methylene blue-stained saline using a 50 mL syringe. This was done in the last three cases, and was found to be helpful. Careful attention to the location of vessels in the neo-mesentery is mandatory to prevent inadvertent occlusion with the suture. We found the use of the GIA stapler in the central sections of the lengthened segment speeded the process, while the ends were done by hand to allow tailoring of the anastomosis.

With these technical points in mind, the bowel lengthening procedure described by Bianchi has been shown to be a viable alternative to 'medical treatment' in the management of pigs with SBS, and may be

useful in treating human patients with this condition. More precisely defined indications for its use, and determination of the mechanisms by which it and medical treatment with cimetidine and codeine have their effects, await further study.

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Table IV-1: Animal Characteristics†

	Group C‡ (n=6)	Group M (n=5)	Group CI (n=5)	Group BL (n=6)
Final Body Weight, kg	51.2±8.7	56.8±6.5	46.3±9.6	54.1±6.4
Feed Intake, g/kg body weight.day	39.6±7.5	45.7±4.3	57.0±7.25	44.63±9.5
Efficiency of feed conversion [gain/feed] (kg/kg.day)	0.22±0.04	0.38±0.04	0.26±0.06	0.34±0.01
Rate of Gain over final 6 Week Treatment, g/day	330±80	590±70*	360±90	550±40*

† = mean±SEM

‡ = The groups were as follows: C, control untreated SBS; M, medically treated; CI, colon interposition; and BL, bowel lengthening

* = $p<0.05$ compared with controls

Table IV-2: Complications

	C‡	M	CI	BL
Adhesions	2†		3	
Incisional Hernia	1	3		1
Stricture	1*			1
Fistulae				2
Gastric Ulcer	3	1		
Anesthetic Deaths				(1)*
Bowel Obstruction	(1)*	(1)*	(1)*	
Anastomotic Leak				2 (1)*
Post-op Pneumonia				(1)*
Animals used in data analysis	6‡	5	5	6

† = See text: Animals with adhesions were not used in assessment of gross bowel morphology.

‡ = The groups were as follows: C, control untreated SBS; M, medically treated; CI, colon interposition; and BL, bowel lengthening

* = animal(s) excluded from data analysis

( ) = lethal

‡ see text

Table IV-3: Nutritional Indices†

Treatment Groups	Pretreatment Averages	C†	M	CI	BL
(weeks post-resection)	6	16	16	16	16
Hemoglobin (g/dL)	11.4±1.0	11.1±1.8	12.3±0.3	11.1±0.74	12.8±0.5
Total Protein (g/dL)	4.6±0.3	3.9±0.8	4.6±0.7	4.0±0.8	5.0±0.4
Albumin (g/dL)	2.1±0.1	2.0±0.5	2.5±0.4	2.0±0.3	2.8±0.3
Alkaline Phosphatase (IU/L)	155±12	139±55	169±24	142±37	192±35
SGOT (IU/L)	21±2	18±3	27±6	27±3	33±4
BUN mmol/L	2.5±0.1	2.3±0.2	2.1±0.4	2.2±0.3	2.0±0.1
Glucose mmol/L	5.1±0.2	7.8±1.5	5.1±0.4	5.9±1.0	5.1±0.3

† = mean±SEM

‡ = The groups were as follows: C, control untreated SBS; M, medically treated; CI, colon interposition; and BL, bowel lengthening

None of these differences was statistically significant.

Table IV-4: Gross Bowel Morphology†

	C‡	M	CI	BL
Jejunal Diameter				
initial, cm	1.25±0.1	1.4±0.3	1.5±0.2	1.3±0.03
final, cm	2.51±0.2	2.7±0.2	2.6±0.2	3.0±0.1
Ileal Diameter				
initial, cm	1.44±0.1	1.7±0.3	1.7±0.3	1.4±0.1
final, cm	2.85±0.1	3.2±0.3	3.0±0.1	3.0±0.1
Bowel length				
initial, cm	391±33	399±77	376±71	373±31
final, cm	627±33	645±24	606±32	621±63
Length increases				
actual cm	264±44	247±23	230±33	248±51
% increase	74%	63%	62%	67%
Estimated total serosal surface area (cm^2)				
0 weeks	1740±320	1930±90	1870±50	1590±160
16 weeks	6120±170	5330±650	4880±610	5100±920
% increase over 16 weeks	290±80	180±40	160±30	230±50

† = mean±SEM

‡ = The groups were as follows: C, control untreated SBS; M, medically treated; CI, colon interposition; and BL, bowel lengthening

Table IV-5: Microscopic Morphology†

Morphological Parameter	C‡	M	CI	BL
Crypt depth, μm	207±13	270±17*	260±12*	260±16*
Villus height, μm	592±48	583±24	670±33	572±17
Villus width at 1/2 height, μm	168±12	126±2*	138±6*	180±8
Villus bottom width, μm	190±17	135±8*	174±12	166±10
Villus thickness, μm	447±35	532±35	539±41	746±44*
Villus surface area μm^2/villus	802±78	830±32	963±47	1208±42*
No. of villi/mm serosal length A	5.67±0.54	7.71±0.59*	5.97±0.37	6.24±0.37
No. of villi/mm serosal length B	2.39±0.22	1.96±0.13	1.94±0.12	1.38±0.08*
No. of villi/mm^2 serosa	12.68±1.21	14.50±1.11	11.09±0.68	8.36±0.49*
Mucosal surface area mm^2/mm^2 serosa	9.68±0.74	12.14±1.22	10.66±0.79	10.00±0.50

† = mean±SEM

‡ = The groups were as follows: C, control untreated SBS; M, medically treated; CI, colon interposition; and BL, bowel lengthening

* = $p<0.05$ compared with controls

Table IV-6: In Vivo Macronutrient Absorption

(% of nutrient absorbed from diet)†

Treatment Group	Pretreatment Averages	C‡	M	CI	BL
(weeks post-resection)	6	16	16	16	16
Fat	16.9±3.6	15.3±8.4	42.5±7.6*	25.0±8.3	39.8±4.6*
Protein	67.4±1.5	79.7±1.8	78.4±2.0	80.1±2.0	79.5±1.2
Carbohydrate	78.2±1.3	80.8±1.9	79.4±1.7	81.2±1.7	82.6±1.3

† = mean±SEM

‡ = The groups were as follows: C, control untreated SBS; M, medically treated; CI, colon interposition; and BL, bowel lengthening

* = $p<0.05$ compared to controls

Table IV-7: Kinetic Constants of D-Glucose on Short Circuit Current (Isc) in Ileum from Pigs with Short Bowel†

Kinetic Constant	C‡	M	CI	BL
Maximal Transport Rate ($\mu A/cm^2$)	73	79	39	68
Apparent Michaelis Constant (mM)	1.3	0.9	1.3	1.7

† = Values are means for four experiments, each done in duplicate. Kinetic constants are derived from the Eadie-Hofstee plots shown in Figure IV-2.

‡ = The groups were as follows: C, control untreated SBS; M, medically treated; CI, colon interposition; and BL, bowel lengthening

Table IV-8: In vitro Lipid Uptake (nmol/min 100 mg)†

LIPID UPTAKE

Substrate	C‡	M	CI	BL
FA 16:0	0.18±0.02	0.26±0.04	0.21±0.01	0.24±0.02
FA 18:0	0.24±0.03	0.12±0.01*	0.17±0.02*	0.19±0.02
FA 18:1	0.20±0.02	0.18±0.01	0.17±0.01	0.21±0.02
FA 18:2	0.16±0.01	0.12±0.01*	0.16±0.01	0.18±0.02
FA 18:3	0.28±0.03	0.16±0.01*	0.23±0.01	0.24±0.02
Cholesterol	0.36±0.07	0.08±0.01*	0.25±0.09	0.14±0.02*

† = mean±SEM

‡ = The groups were as follows: C, control untreated SBS; M, medically treated; CI, colon interposition; and BL, bowel lengthening

* = $p<0.05$ compared to controls

FIGURE IV-1

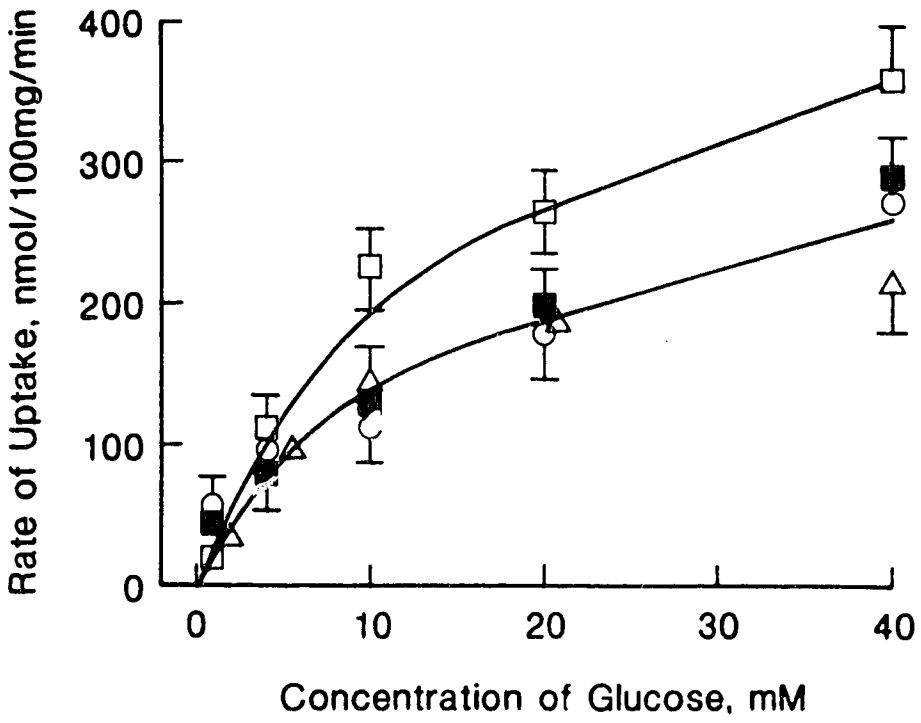

Rate of Uptake, nmol/100mg/min
400
300
200
100
0
0
10
20
30
40
Concentration of Glucose, mM

FIGURE IV-2

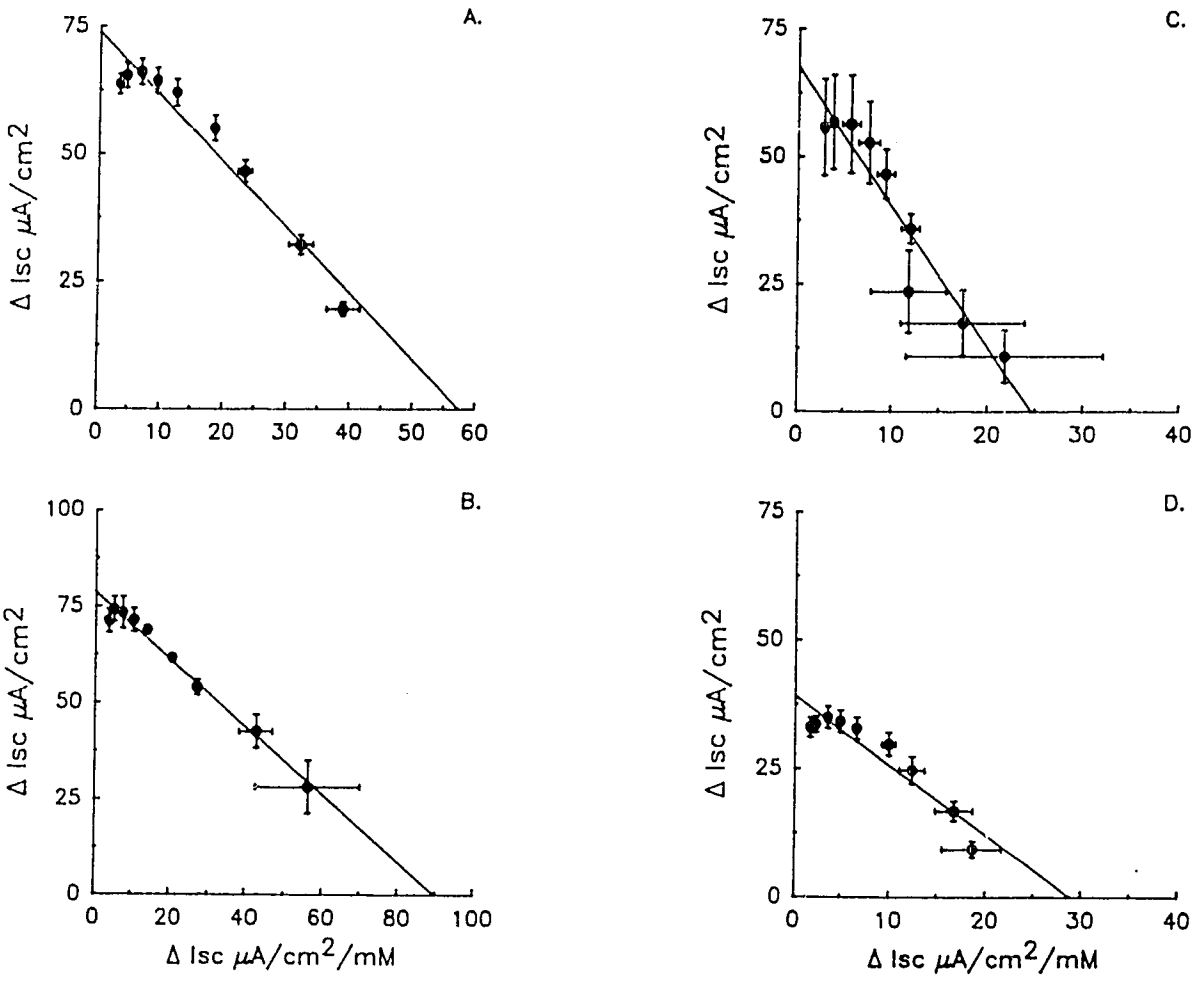


FIGURE IV-3

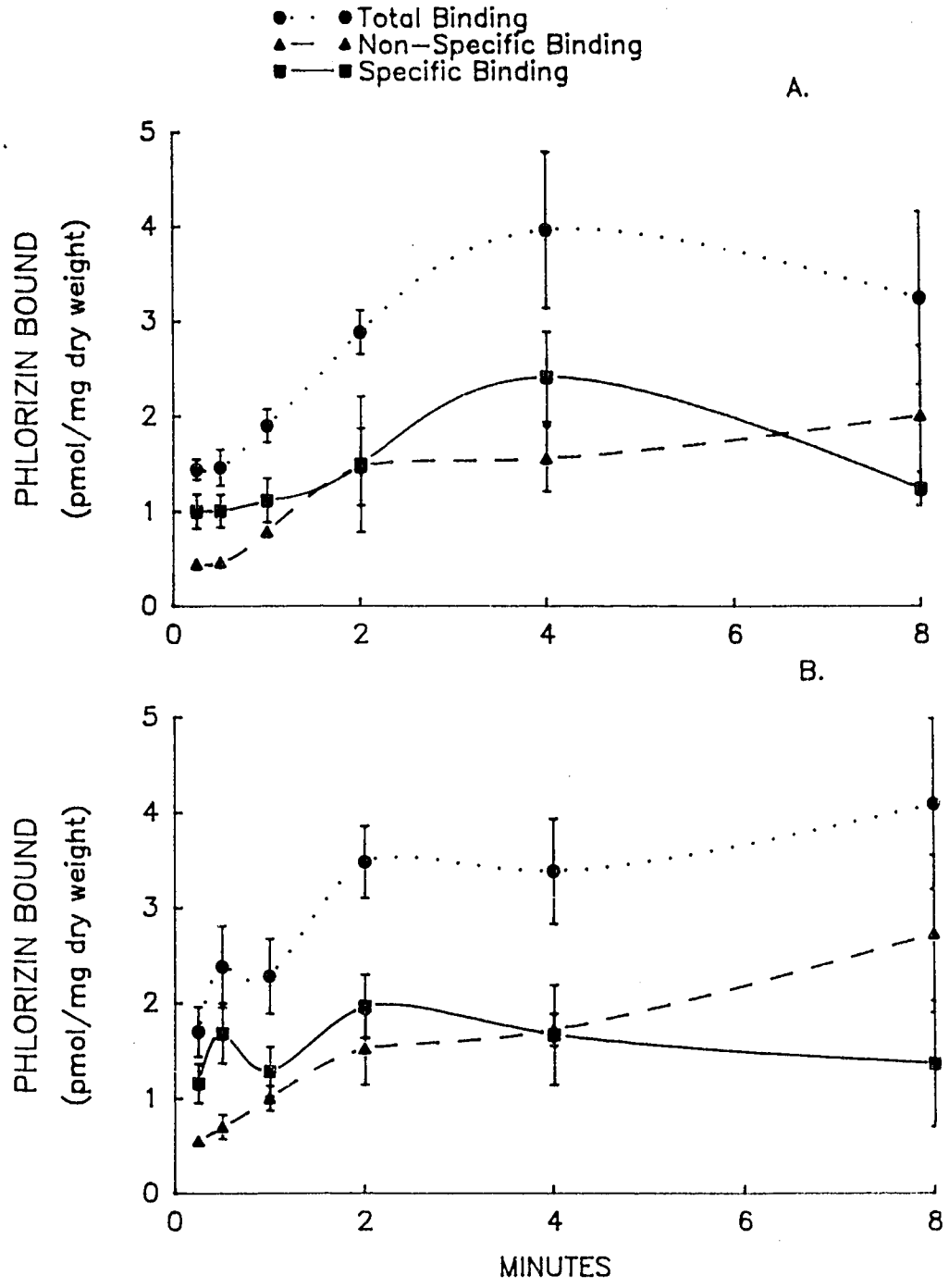
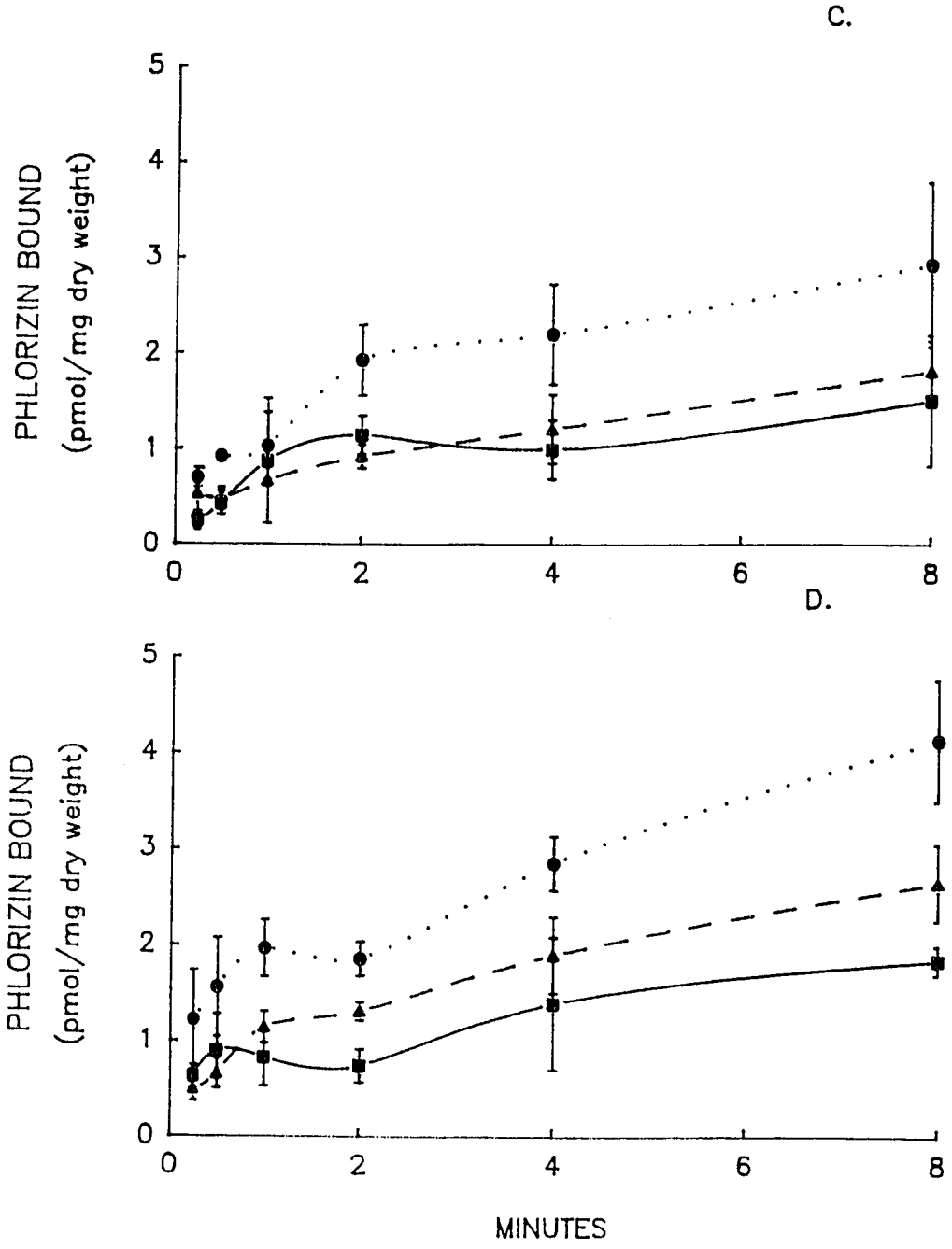

Total Binding
Non-Specific Binding
Specific Binding
A.
B.
PHLORIZIN BOUND
(pmol/mg dry weight)
0
1
2
3
4
5
0
2
4
6
8
MINUTES

FIGURE IV-3


C.
PHLORIZIN BOUND
(pmol/mg dry weight)
0
1
2
3
4
5
0
2
4
6
8
D.
PHLORIZIN BOUND
(pmol/mg dry weight)
MINUTES

CHAPTER V

CONCLUSIONS

In this study we examined the effects of treatment for the short bowel syndrome (SBS) using a juvenile domestic pig model. We first documented the nutritional effects and ensuing adaptive process following massive small bowel resection (MSBR) in untreated animals (Chapter III). Controls consisted of a group of animals which underwent simple transection without resection. Total weight gain, rate of weight gain and macronutrient absorption were all significantly reduced by resection. Fat malabsorption was particularly prominent, but carbohydrate, protein and net energy absorption were also significantly reduced in resected animals. Final nutrient absorption in the animals with massive resection was 15% of fat, 81% of carbohydrate, 79% of protein and 75% of total energy ingested (Table III-3). These are similar to the values reported for humans with SBS by Woolf et al (54% fat absorption, 61% carbohydrate absorption, 81% protein absorption and 62% total energy absorption) (1). The diet used for their studies was much higher in fat than the grain diets used for these studies. Thus, the nutritional effects of our experimental resection mimic those of the SBS in typical human patients.

Feed intake was similar in the two groups. The efficiency of energy to weight conversion after energy absorption was also similar in the two groups. This implies that within the sensitivity of our measurements there was no metabolic cost to the SBS (aside from the impairment of nutrient absorption).

It is interesting that the feed intakes of the two groups, per unit animal weight, were similar. It is generally believed that the normal pig eats to meet its energy requirements (2). In this study, despite the reduced energy absorption of resected animals, there was no

compensatory increase in feed intake. Therefore, this concept of eating to a constant endpoint determined by energy intake may not be valid after a massive resection. Alternatively, the reduction in net energy absorption may not have been great enough to signal an increase in feed intake. As an example, the fasting serum glucose levels in both groups were within normal limits (Sigalet DL, unpublished observations) so that if this forms part of feedback loop to stimulate more intake, resection did not make a significant impact and would not be expected to stimulate more food intake. Further studies examining the controlling factors for feed intake in this type of model are necessary, nevertheless, it is clear that the hyperphagia observed in rats after MSBR (3) does not occur in the pig.

The efficiency of feed:weight conversion was less in the resected group than in the transected animals (Table III-1). As the animals grew in size, the conversion efficiency of the resected animals remained constant, while the conversion values for the transected animals fell. This decrease in conversion efficiency with increasing size is the pattern typical of a normal growing pig (2). In this study, the changes in conversion efficiency did not reach statistical significance, but they do imply that the resected animals improved their nutrient extraction over the course of the study. This was confirmed in the experiment examining the effects of treatment, which included an assessment of nutrient absorption 6 weeks following the original resection and a second assessment after 10 weeks of therapy (16 weeks post-transection). The non-treated resected (NTR) controls showed a significant improvement in protein absorption over time, with no change in fat or carbohydrate absorption (Table IV-6). Similar patterns of

improvement in nutrient absorption have been documented in many animal species after massive resection, including the rat (4), dog (5) and human (6,7). Previous reviewers have discussed the possible heterogeneity of these adaptive processes in different species (8).

In reviewing the possible mechanisms for this improvement in nutrient absorption after resection, we noted a significant increase in bowel length, bowel diameter and an increase in serosal surface area in the resected animals (Table III-5). These changes in gross morphology increased the available absorptive surface area and would thus be expected to improve nutrient absorption. Increases in bowel length following resection have been noted in previous studies using juvenile dogs (9), rats (10) and human infants (11). Such increases were not noted in studies of human adults (12). None of these previously reported increases in bowel length observed in adaptation in other species approach the magnitude of the increases observed in this experiment. This may in part be explained by the remarkably long bowel of the domestic pig, which is roughly 1.4 times the length of a wild pig of similar weight (13). It is thought that centuries of selective breeding for efficient conversion of feed into body weight have resulted in a longer bowel with increased surface area. This phenotypic variation ultimately must be effected by changes in the growth pattern of the gut. Our understanding of the control of gut growth is just beginning, and this model may prove useful in investigating it further (14,15).

When gut morphology was examined microscopically after resection, the number of villi per unit of serosal surface area declined, while net surface area per villus increased significantly (Table III-6). Overall,

there was no net change in mucosal surface area per unit of serosal surface area. These findings parallel those noted in dogs (8), rabbits (16) and humans (17-18), however, they differ from the pronounced increase in mucosal surface area per unit serosal area found in the rat after major resection (10,20).

Overall, the adaptive process significantly increased the surface area available for absorption following resection, however, despite this increase, the final gut surface area of the resected animal was one-third of the transected groups (Table III-6).

Intraluminal digestion of nutrients was not examined in this study, and this may have played an important role in the adaptive process. Sambrook showed that normal pigs rapidly hydrolyze and absorb starch in the duodenum and proximal jejunum, but are slower to digest and absorb lipid (21,22). In animals with massive resection, gastric hypersecretion could affect the intraluminal pH of the bowel and this in turn would reduce the activity of all the pancreatic digestive enzymes. Furthermore, as noted in the preceding section, the resected animals had a smaller absorptive surface area for absorption and a shorter length. These factors would reduce the contact time of chyme with digestive enzymes and with the absorptive surface. Further study is necessary to quantify the importance of these changes, but it is likely, given the situation in the normal pig, that the absorption of carbohydrates would be minimally affected by a reduction in bowel length, since most carbohydrate absorption occurs in the proximal jejunum. Conversely, fats normally require the entire bowel length for digestion and absorption and so a massive resection would be expected to cause a major

reduction in fat absorption. This was confirmed by our findings (Table III-3).

The most fundamental unit of intestinal function is the enterocyte. Adaptation at this cellular level was examined using in vitro uptake of nutrients. We found an increase in the permeability of the mucosa, with enhanced uptake of L-glucose, long chain fatty acids and cholesterol (Table III-7). However, this enhanced uptake of passively absorbed nutrients noted in vitro did not correct the malabsorption in the intact animal. Presumably, if this adaptive increase in permeability had not occurred nutrient absorption and the overall outcome of the animal would have been worse.

The relationship of changes in permeability to the microscopic morphological changes observed is not clear. The changes in villus size and density may have affected changes in the enterocyte membranes and intracellular functions, which in turn would affect the permeability of the bowel. This requires further study, as do factors which may control such functional and morphological changes.

In summary, the adaptive response to massive resection in the juvenile domestic pig is characterized by a pronounced increase in the length and diameter of the remaining small bowel and an increase in villus size with a corresponding decrease in villus density. Functionally, the passive permeability of the ileal mucosa increases, but active uptake of nutrients does not. The morphological and functional changes may be linked and controlled via common mechanisms, but the nature of these controlling mechanisms are not clear from these studies.

With these features of the porcine model of SBS established, we then used it to compare different treatments of SBS. There are few therapies which reliably improve nutrient absorption in SBS. We chose to compare medical therapy using cimetidine and codeine, with surgical therapy, using either colon interposition or bowel lengthening.

Over the 10 week treatment period (between weeks 6 to 16), medical treatment and bowel lengthening significantly improved the rate of weight gain when compared with the colon interposition or NTR resected group (NTR-controls, Table VI-1). There were no differences in feed intake between the groups (Table IV-1). Medically treated and bowel lengthened animals also tended to have better feed:weight conversion efficiency, although this did not reach significance (Table IV-1). In considering this data from the intact animals, it is evident that medical treatment and bowel lengthening significantly improved the nutritional status of these animals with SBS. The reasons for this improvement are more difficult to discern.

Reviewing the efficiency of the animals in extracting the nutrients from their diet, we see that bowel lengthening and medical treatment improved the absorption of fat significantly. However, the absorption of protein, carbohydrate or total energy was not affected (Table IV-6). The previously noted differences in feed:weight conversion may indicate that the bowel lengthened and medically treated animals may have been more efficient at converting energy to weight after its absorption. This would be a difficult problem to examine in the intact animal, but we do have some clues from this study as to how this could occur. As noted previously in the discussion of adaptation after small bowel resection, fat absorption in normal pigs requires the entire small bowel

length (22). This includes a significant quantity of endogenously secreted lipid. If this lipid is lost, it would entail a significant metabolic load to the animal, even if the overall caloric value were low. The improvements in fat absorption caused by bowel lengthening and medical treatments may have reduced this metabolic load, and allowed more energy to be used for growth. This is at odds with our previous finding that massive small bowel resection did not appear to significantly alter the conversion of energy to weight in these animals (Chapter III). However, small changes in efficiency may not have been detected. More precise measurements of energy balance would clarify this issue.

Alternatively, the improvement in weight gain noted with the treatments may have been due to other nutritional effects not assessed in this study, such as the absorption of a specific limiting nutrient (eg. cysteine or methionine). Finally, treatments may have had their effects via non-nutritional mechanisms, such as changes in hormonal profiles. These factors were not examined in these studies, and would be useful in improving our understanding of the physiology of the bowel.

Whether or not fat absorption is the key to the improvement observed in the bowel lengthened and medically treated groups cannot be determined from this study. However, this specific effect is an important finding. Fat malabsorption is a major problem in human patients with SBS (1) and methods to treat this would be useful clinically. The typical human diet is much higher in fats than the largely grain diet of these pigs, so that in humans, improved fat absorption would have a greater impact on net energy absorption from the diet.

In reviewing the mechanisms which led to this improvement in fat absorption, no definite cause was demonstrated. Treatments did not effect the surface area available for absorption either grossly or microscopically (Table IV-5). Treatments did affect the permeability of the enterocyte membrane to lipid (Table IV-8), but paradoxically those animals with the best *in vivo* fat absorption had the lowest *in vitro* lipid uptake. It is therefore not clear whether the observed changes in permeability properties were a direct effect of the treatments, or an indirect effect mediated by the nutritional status of the animal. It is apparent that the improved fat absorption *in vivo* was not caused by an increase in passive permeability of the enterocyte.

The only major steps in nutrient absorption which were not examined are the intraluminal digestion of ingested food and the contact time of the resulting feed constituents with the intestinal mucosa. The treatments of bowel lengthening and medical therapy both would be expected to affect these factors and so these may have improved fat absorption.

Specifically, cimetidine has been shown to significantly improve fat absorption in other models of SBS, including man (23,24). It has also been observed to raise the intraluminal pH of the proximal small bowel and the implication is that this increases the activity of the pancreatic enzymes. This has not been confirmed directly and would be an interesting area for further research. The cimetidine group did not have any alteration in their microscopic morphology, so it is unlikely that the increase in crypt cell production rate noted in rats (25) could explain the nutritional effects in these animals.

The relationship between bowel motility and nutrient absorption is less clear. Many early investigators assumed that delayed transit meant increased contact time with the absorptive mucosa of the bowel and, thus, would improve nutrient uptake (26). It has been shown that fluid and electrolyte absorption can be increased by such delays in transit, but it has not been shown that the uptake of nutrients such as fat can be increased (27). Given our increasing knowledge of the relationships between the myoelectric activity of the bowel, transit and nutrient uptake, we may soon be able to say whether slowing transit is a rational approach for improving absorption (27-29).

In these studies, our initial attempts to monitor small intestinal transit time, using barium under fluoroscopy, were not successful. There were large variations in transit time which appeared to be induced by the stress of confining the animals (Sigalet DL, unpublished observations). Anesthetizing them altered transit time as well. Mouth to anus markers of transit are affected mostly by colonic transit time, which is not the site of nutrient absorption (30), and so this was not pursued. More sophisticated methodology, such as measuring transit time using breath hydrogen analysis (31), may be useful in future studies of this problem.

Given this background of methodological difficulties, we cannot comment on how the treatments used in this study affected gut motility. However, the extensive surgical manipulation of the lengthening procedure would have had at least as much effect as transecting the gut, which in itself has been shown to alter the propagation of migrating myoelectrical complexes (MMC), and to lower the intrinsic pacemaker rate of the bowel distally (28). Colon interposition would have a similar

effect, and so this basic change in motility cannot explain the observed improvement in weight gain and fat absorption in the bowel lengthening group.

Cimetidine has not been shown to affect gut motility (32), however, the codeine used in the medical treatment certainly does affect bowel motility. This can increase salt and water uptake, but has not been shown to affect macronutrient uptake (27). It is unlikely that the improvement in nutrient uptake in the medically treated group was due to the codeine, since such an effect has not been observed before with this commonly used and extensively investigated drug. Again, the effect of treatment on intraluminal digestion and motility, and their relationship to nutrient absorption is certainly an area for further study.

The observation that the lengthened group and the medically treated animals did not develop gastric ulceration is noteworthy (Table IV-2). The known reduction of gastric acid output with cimetidine likely explains why the medically treated group did not develop ulcers (23), however, it is not clear what effect of bowel lengthening should protect against ulceration. The wide ranging effects of resection on gut hormones could be a factor (Chapter II); this is also an area for further study.

In summary, this comparison of treatments for SBS has shown that medical treatment with cimetidine and codeine, and surgical treatment with bowel lengthening, significantly improved weight gain, and fat absorption in this model of SBS in pigs. Our original hypothesis that bowel lengthening would be optimal treatment for SBS was partially confirmed. Medical treatment and bowel lengthening were roughly

equivalent in improving these parameters. Colon interposition did not significantly effect either weight gain or nutrient absorption.

This data confirms the findings of others that cimetidine and codeine are useful treatments for the SBS (23). Given the minimal risk of such treatment, they are indicated in the initial therapy of SBS. The place of bowel lengthening in clinical practice is not as clear. Clinically, it has been used in cases where extensive dilatation of the residual bowel, with ineffective peristalisis, has occurred (33-35). In these reports, lengthening improved the motility of the residual bowel. With this, there was a general improvement in the clinical status of the patients, and they were able to support themselves with completely enteral nutrition. This study did not duplicate the massive dilatation of residual bowel of these clinical reports, but given the improvement in nutrient absorption noted herein in normal sized bowel it certainly supports the use of bowel lengthening with such cases of massive dilatation. Our findings also support the use of lengthening in those cases where improved function of more normal sized bowel is critical to the survival of the patient and medical treatment has not been effective.

The possibility of clinical application for these treatments raises many further questions. This study did not specifically examine the effects of lengthening on animals already receiving medical therapy. Although lengthening could be justified in those situations where a patient is critically ill and medical treatment was not effective, it would be useful to investigate their combined effects in a more controlled experimental setting. As well, the optimal timing of a lengthening procedure is not clear. Clinically, it has not been used

until a patient is thought to be deteriorating despite maximal non-surgical therapy. It may be that this is too late, and earlier surgery would be more useful.

The jejunum was chosen as the site for lengthening in these studies because this is the area of bowel most commonly left after massive resections. However, the optimal length segments to use for lengthening is not clear. If lengthening has its effect via an alteration in intraluminal digestion, motility or hormonal profile, rather than a simple increase in surface area, it may be that only a short segment would require lengthening to give a benefit. Similarly, lengthening ileum may have a different effect than was seen in this study. These features could have important implications in the clinical application of this procedure, and should be examined experimentally.

The effects of cimetidine also deserve further study. The dosage used in this study was a typical therapeutic dose for ulcer therapy. This may not be optimal, and should be substantiated in a more controlled fashion. Other types of H_2-blockers exist and their effects on nutrient absorption in SBS should be investigated. As well, many other classes of ulcer therapy such as simple antacid therapy, antisecretory drugs (somatostatin, omeprazole) and the prostaglandins could potentially be useful. The possibility of manipulating the adaptive process to improve nutrient absorption is very exciting, and could be useful in other diseases where malabsorption occurs.

An interesting possibility would be the combination of medical and surgical therapy. If the specific factor(s) which produce the marked dilation of bowel in some uses of SBS could be identified, these could

be exogenously administered in a controlled fashion. When this bowel reaches a suitable diameter, it could then be lengthened.

The lack of a beneficial effect of colon interposition in this study contradicts the experience of previous workers (36,37). However, these previous studies did not examine the nutritional effects of colon interposition directly, and instead compared survival. This is not a valid technique, since animals with SBS will often die from fluid and electrolyte losses, rather than malnutrition per se. In the clinical setting, fluid and electrolyte losses can be managed quite easily, so that surgical therapy is not indicated. Accordingly, our findings do not support the use of colon interposition in clinical practice.

Although there are many unanswered questions surrounding the mechanisms underlying the improvements in weight gain and fat absorption noted with bowel lengthening, and medical treatment, it is heartening to note that bowel function was improved. Hopefully, as we investigate the mechanisms underlying these effects we will find other methods of manipulating bowel function which will be useful in treating both SBS and patients with other types of malabsorption.

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