MEDICAL GRAND ROUNDS

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JEJUNOILEAL BYPASS FOR THE TREATMENT OF OBESITY

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I. Introduction

The surgically-created intestinal bypass for the treatment of obesity is the most drastic and probably the most dangerous approach to the treatment of obesity yet devised by man. The justification for its application to selected patients whose weight vastly exceeds our present day norms is based on the following premises (1-4):

Massive obesity is a "morbid" condition
Other means of weight reduction are in large part unsuccessful
The benefits of the currently utilized jejunoileal bypass procedures outweigh the complications of both the procedure itself and of the untreated "morbid" condition.

The purpose of today's discussion is to review briefly the first two premises and discuss in more detail the complications and so-called benefits associated with the jejunoileal bypass.

II. Obesity and Associated Disorders

Obesity is a condition in which there is an abnormal enlargement of adipose tissue, and is primarily a result of excessive food intake associated in part with decreased physical activity (5). Certainly the vast majority of obese patients do not have a basic identifiable endocrine abnormality such as hypothroidism, hyperadrenalcorticism, hypogonadism, insulinoma, or hypothalamic disease as a cause of their obesity (6-8). However, obesity is a complex disorder which involves more than simple overeating, and a multitude of causative factors are potentially operative in any given patient, including familial, metabolic, psychological, social, and environmental ones. The finding of an irreversible adipose hypercellularity in patients whose obesity began prior to puberty raises questions concerning the regulation of eating behavior and perpetuation of body weight (9-11). Yet, no consistent metabolic lesion has been found in obese people that will explain their obesity (12).

There is a conspicuous association of obesity with a number of chronic diseases (5,13). However, to prove causation is in most cases difficult. Buchwald in proselyting the surgical "cure" of obesity states that corpulency is not only a disease but a harbinger

of other associated conditions and the morbidity of obesity rises geometrically as a function of the percent of increase in weight over "ideal weight" (4). This sort of deduction is based on data obtained from the questional practices of the insurance industry (5,13,14). Life expectancy tables are derived from highly selective and atypical populations, simple height and weight measurements, and the vagaries of death certificates (15).

A long list of disorders are clinically associated with obesity. Hyperphagia and obesity are thought to cause or exacerbate these disorders as a result of a mechanical, metabolic, or psychological burden (5,16).

1. Hypertension
2. Atherosclerosis
3. Hyperlipemia
4. Diabetes mellitus
5. Coronary artery disease, congestive heart failure
6. Cerebral vascular disease
7. Alveolar hypoventilation (Pickwickian Syndrome)
8. Venous insufficiency, thrombophlebitis
9. Cholelithiasis
10. Liver abnormalities
11. Reflux esophagitis
12. Orthopedic abnormalities
13. Intertriginous and statis dermatitis
14. Psychological and social

It must be emphasized that the true relationship between obesity and these chronic disorders is not known, since the methods to measure and classify degrees of obesity are limited in precision and feasibility; the causes of obesity are unknown; and the inter-relation between these disorders are complex irrespective of obesity (13). Furthermore, since obesity is in large part incurable, the long-term effect of weight reduction in arresting or reversing the effects of these chronic disorders is unknown.

III. Medical Approach to the Treatment of Obesity

A variety of diets, drugs, and psychosocial approaches have been utilized for the treatment of obesity (4,12,17). These include:

1. Caloric restriction or manipulation
2. Anorexigenic agents (sympathomimetic amines and their chemical congeners
3. Diuretics
4. Digitalis
5. Hormones
   - Human chorionic gonadotropin
   - Thyroid hormones
   - Human growth hormones
   - Progesterone

6. Group therapy and/or Behavior Modification

Caloric restriction is obviously the most desirable method of achieving weight reduction, but is in large part unsuccessful. The sympathomimetic amines, although aggressively promoted, have limited effectiveness for short term use, and the Federal Drug Administration currently discourages their use in the treatment of obesity in view of the potential for dependency and abuse. Diuretics and digitalis are obviously illogical and potentially dangerous. There is no doubt that high doses of thyroid hormone will reduce body weight, but there may be more loss of lean body mass than body fat, and the hazards are considerable. The effect of human growth hormone is largely theoretical, only limited supplies are available, and its long term efficacy is not known. Progesterone, although apparently effective in the treatment of alveolar hypoventilation has not been proven effective in inducing weight loss. Therefore, it can best be summarized that current pharmological approaches to the treatment of obesity are largely unsatisfactory, ineffective, irrational, or harmful (12).

The effectiveness of cooperative group therapy such as TOPS (Take Off Pounds Sensibly) and Weight Watchers is not known. Behavior modification may be effective but is untested in large numbers of patients over long periods of time (12).

IV. Proposed Indications for Surgical Treatment of Morbid Obesity

Because of the conspicuous association of obesity with numerous disorders, and the failure of medical manipulations to produce sustained weight loss in obese patients, a number of surgical procedures have been performed with the primary goal of allowing patients "to indulge in their gluttonous pleasures yet still lose weight" (2). Additional impetus to the development of controlled intestinal bypass was derived from the observations that massive resection of the small intestine performed for underlying pathological conditions or traumatic events caused a reduction in patient's weight if the patient survived the surgery (18).

In most of the reported series relatively strict criteria are utilized for the selection of patients for intestinal bypass procedures. The most commonly accepted indications are those of Scott or Payne (19,20).

Scott's Criteria

1. Obesity of massive degree (weights of 2 to 3 times ideal levels of at least 5 years duration).
2. Evidence from the attending physician indicating failure of dietary efforts to correct obesity over a period of years.
3. Evidence from the patient's history and evaluation indicating

incapability to adhere to prescribed dietary regimen and/or exercise programs
4. Absence of any correctable endocrinopathy (such as hypothyroidism or Cushing's syndrome) which might be the cause of obesity.
5. Absence of any other unrelated significant disease which might increase operative risk.
6. Presence of certain complications such as Pickwickian syndrome, hyperlipidemia, adult onset of diabetes, and hypertension which might be alleviated by significant weight reduction.
7. Assurance of patient's cooperation in conduct of pre and post-operative metabolic and body compositional studies and prolonged followup evaluation.

Payne's Criteria

The patient must:
1. Be 100 pounds overweight;
2. Have tried almost all other forms of treatment and failed to maintain satisfactory weight loss;
3. Be emotionally well motivated, neither hostile nor depressed, and willing to cooperate in an investigational study;
4. Accept the problem and inconvenience of drastic metabolic change;
5. Agree to undergo revision or restoration of intestinal continuity if necessary.
6. Have complications or diseases commonly associated with hyper-obesity, e.g., hypertension, Pickwickian syndrome, degenerative arthritis, menstrual disturbances, infertility, inability to care for body hygiene, diabetes, gout, venous stasis with edema, and ulceration.

Morbid obesity is obviously not precisely defined but is described by Scott in a somewhat vivid and functional manner (19). "When an obese individual attains the Gargantuan level of the fat man or fat woman in the circus and maintains this degree of massive obesity for many years, we believe the adjective morbid should be added to emphasize the serious health implications and severe, life-shortening hazards of such grotesque accumulations of fat". As with obesity in general, its morbidity and mortality, as well as the disorders associated with morbid obesity, are not well studied and are poorly defined. However, it is reasonable to assume that the risks to health are greater than those in the nonobese individual.

It is obvious that if the stated criteria are utilized for the selection of patients, many patients with only moderate obesity will be included. The indications themselves seem to be self-contradictory. Will a patient who is incapable of adhering to dietary and exercise programs cooperate in long term followup evaluation? Furthermore, it is clear that many patients who have submitted to bypass operations do not have significant problems associated with their obesity. Therefore, it should be emphasized that the large number of reports of the results of these operations include a very heterogenous group of patients, making evaluation of the results of surgery difficult.

V. Intestinal Digestion and Absorption

In order to understand the mechanism by which intestinal bypass results in weight loss, it is important to review briefly normal mechanisms and sites of absorption of foodstuffs. (Figure 1)

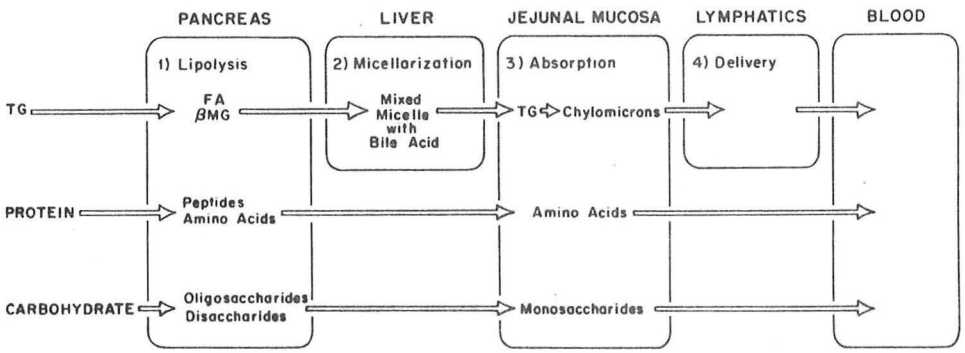

Figure 1. Absorption of triglyceride, protein, and carbohydrate.
From Wilson and Dietschy (21)

As outlined by Wilson and Dietschy, there are four major steps in the digestion and absorption of triglyceride, protein, and carbohydrate (21). Pancreatic enzymes secreted into the duodenum hydrolyze triglycerides to fatty acids and monoglycerides, proteins to peptides and amino acids, and carbohydrates to oligosaccharides and disaccharides. After further hydrolysis at the brush border, amino acids and monosaccharides are actively absorbed and transported into the portal circulation. Fatty acids, monoglycerides, cholesterol, and other fat soluble compounds require in large part bile salts for micellar solubilization prior to passive absorption. Triglycerides are reformed by reesterification, incorporated into chylomicrons, and pass into the lymphatics.

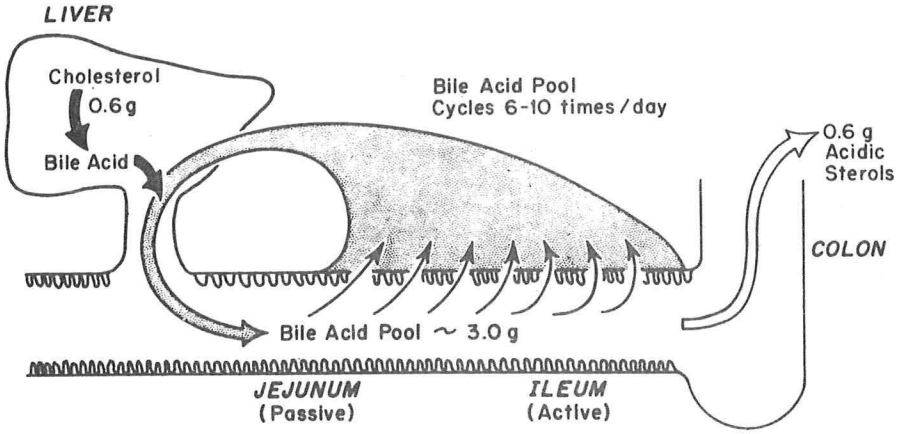

Figure 2

Adequate concentrations of bile salts for effective micellar solubilization of fatty acids, monoglycerides, cholesterol, and fat soluble vitamins are maintained by the reutilization of a relatively small pool of bile salts (22). Bile salts are synthesized from cholesterol in the liver, excreted into bile and reabsorbed primarily by the terminal ileum where they are recycled to the liver and resecreted in bile. (Figure 2). The pool is recycled six to ten times per day and about 4.0% is lost in the stool each day. This is replaced by synthesis from cholesterol in the liver, a process apparently controlled by a negative feedback mechanism (23). If the terminal ileum is resected or diseased and increased bile salt loss occurs in the stool, increase in synthesis of up to four to eight times normal can occur in the liver. With severe malabsorption of bile salts, synthesis may not be adequate to provide sufficient intraluminal concentrations for micellar solubilization of digested fats.

VI. Reserve and Regenerative Capacity of the Intestine

The majority of digested foodstuffs, vitamins, and minerals are normally absorbed in the proximal one-third of the small intestine but can also be absorbed in the distal two-thirds of the small intestine (21). Only vitamin B_{12} and bile salts require the presence of an intact ileum for adequate absorption (Figure 3) (24, 25). The generous length

of the small intestine ensures a large functional reserve (26). It is approximately 350 cm if measured in vivo by intubation, 600 cm if measured when relaxed after death, and 600 cm in women and 700 cm in men if measured during abdominal surgery (27). In massively obese patients, it

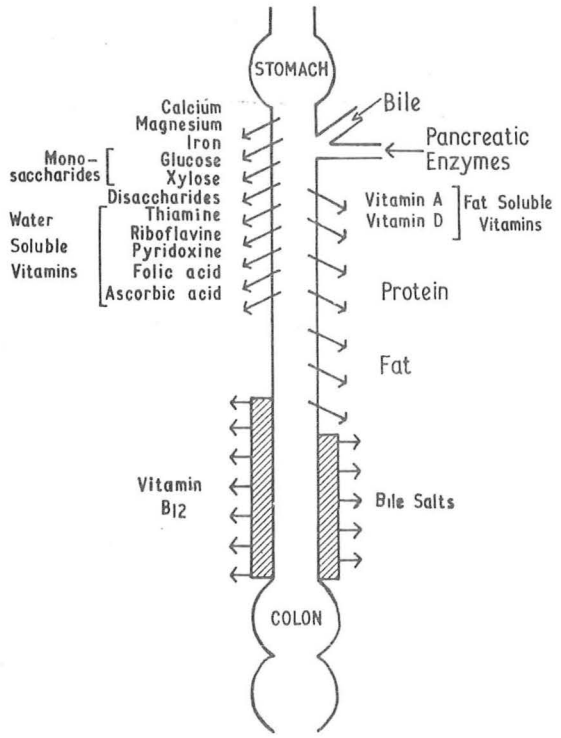

Figure 3

has been found to be somewhat longer than normal when measured at surgery - about 700 cm in women and 800 cm in men. After extensive small-bowel resection or bypass, the extent of malabsorption and malnutrition which develops depends on both the reserve capacity and regenerative capacity of the residual intestine to compensate for loss of absorptive surface.

After partial small intestinal resection in man and animals, most investigators have found an increase in absorption per unit length of bowel in the remaining small intestine (28-30). Villous enlargement occurs because of hyperplasia of mucosal cells. There is an increased number of cells and increased rate of migration up the villous. The enhanced absorption per unit length of bowel is probably a result of increased mucosal surface rather than adaptation of each individual cell (26, 31-34). The ileum appears to have a greater capacity to adapt in terms of both structure and function than the jejunum. The mechanisms for these adaptive changes are unknown, but increased nutritional loads, hormonal factors, changes in blood flow, and factors present in bile and pancreatic secretion may all contribute (26, 35).

In any case, if the proximal small intestine is excluded or resected, the distal half of the intestine can largely compensate and assume the mucosal function of the proximal intestine unless extensive mucosal surface is lost (35, 36). If the distal bowel is resected, severe B_{12} and bile salt malabsorption will occur with resultant fat malabsorption secondary to depletion of the bile salt pool, decreased hepatic secretion of bile salts into bile, and inadequate intraluminal bile salts for micellar solubilization. More severe malabsorption of other substances will also occur because the ability of the jejunum to adapt is not as great as that of the ileum (26, 31).

VII. Surgically Induced Malabsorption

Most surgical procedures are designed to bypass a certain percentage of the small intestine, and sometimes part of the colon, or to leave intact a specified length of jejunum and ileum.

A. Jejunocolic bypass (Figure 4)

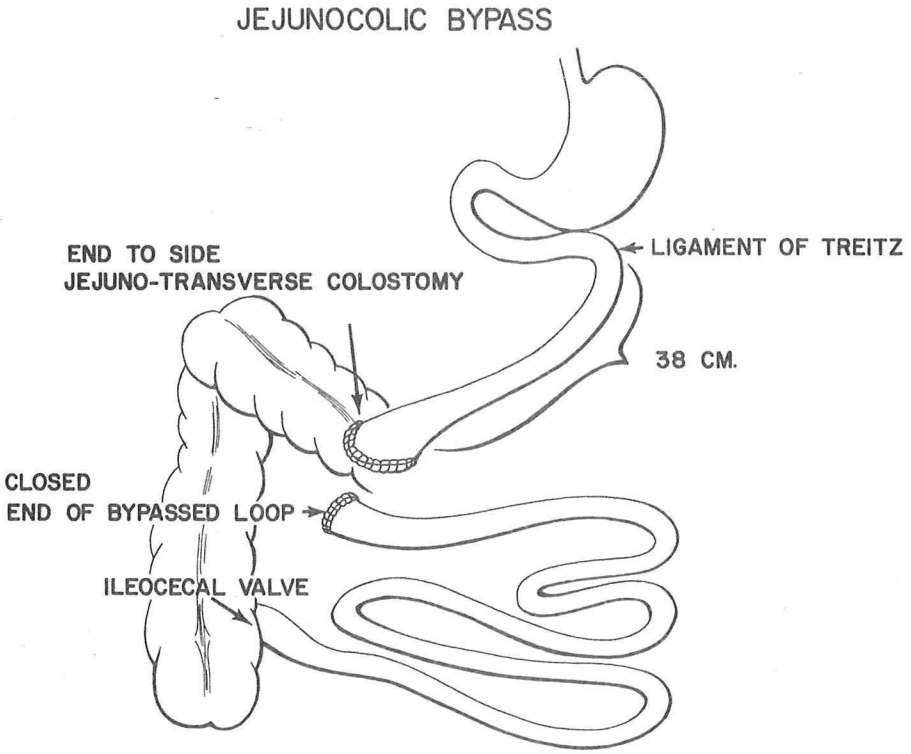

Figure 4

Payne, in 1956, initiated his clinical program for management of morbidly obese patients by bypassing nearly the entire small intestine, the right colon, and half of the transverse colon with an end-to-side anastomosis of the proximal 38 cm (15 inches) of jejunum to the mid-transverse colon (37). The results in 11 patients were not published until 1963 (7 years later). The weight loss was dramatic, but the morbidity (intractable diarrhea, electrolyte imbalance, liver failure) was prohibitive and 1 death was reported. This procedure or variants of it have been studied by others with disastrous results and has been condemned and largely abandoned (or should be) (38-42). The jejuno-colic bypass produces a state in which absorbable calories cannot equal energy expenditure, and water and electrolyte reabsorption is inadequate:

1. 38 cm of jejunum does not provide adequate length or surface for digestion and absorption of foodstuffs.
2. Bypass of the entire ileum and ileocecal valve causes massive bile salt malabsorption, rapid emptying of foodstuffs into the colon without time for digestion and absorption, and permits reflux of colonic contents into the jejunum.
3. Bypass of one-half of the colon causes a further decrease in absorptive surface for water and electrolytes.

B. Partial Ileal Bypass for Hyperlipidemia (16, 43) (Figure 5)

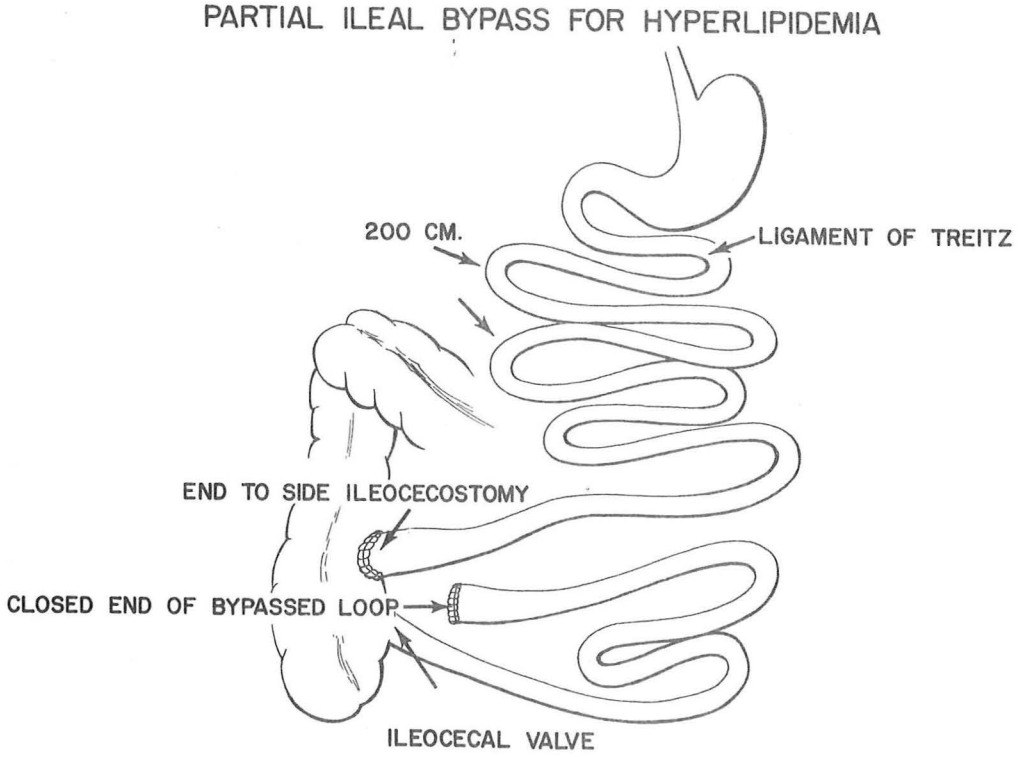

Figure 5

The bypass procedures for weight loss should be distinguished from the ileal bypass for patients with hyperlipidemia. In this procedure, 200 cm or about one-third of the small intestine is left intact and the entire ileum and part of the jejunum is bypassed. Buchwald, et al, has followed 126 patients for 3 months to 10 years, but has performed careful metabolic studies only on a few patients over short periods of time. The results are presented without regard to lipoprotein typing or statistical analysis but suggest that there is increased loss of bile salts and cholesterol in the stool, increased cholesterol turnover, decreased cholesterol pool size (both freely miscible and slowly miscible), and decreased serum cholesterol. Cholesterol synthesis is increased fivefold.

In patients with this procedure, one would expect that severe bile salt malabsorption would cause steatorrhea (including cholesterol malabsorption) and increased conversion of cholesterol to bile salts. Protein and carbohydrate digestion and absorption might be unaffected in large part since 200 cm of proximal intestine are present. It is surprising that Buchwald states (without presenting data) that no appreciable weight loss occurs. Diarrhea is an annoying side effect of the procedure and intramuscular vitamin B_{12} replacement is necessary.

Of the 126 patients subjected to the procedure, there has been one immediate post-operative death and 13 late deaths (11 acute myocardial infarctions, one cerebral vascular accident, and one viral hepatitis). Four cases of bowel obstruction occurred requiring surgery. It is apparent that inadequate data is available to assess the value of this procedure in treating various forms of hyperlipidemia and or preventing its presumed complications (44).

C. Jejunoileal Bypass for Obesity (Figure 6)

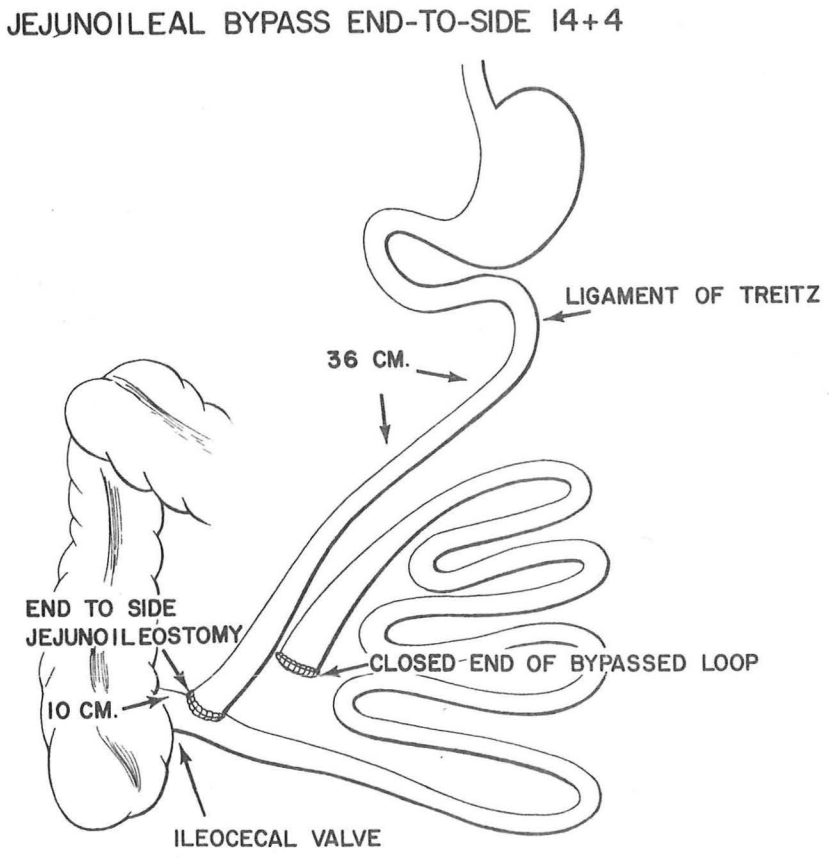

Figure 6

In order to avoid the complications of the jejunocolic bypass, Payne, et al, in 1963, and Sherman, et al, in 1965, devised a procedure whereby 10 cm of the terminal ileum and the ileocecal valve were preserved by an end-to-side jejunoileostomy performed with 36 cm of the jejunum distal to the ligament of Treitz and 10 cm of terminal ileum (37, 45) (Figure 6). This is the so-called "14 + 4" inch end-to-side jejunoileostomy. As can be seen in Table I, which is a partial list of published series, a large number of surgeons have performed an enormous number of these bypass procedures.

Table I SURGICAL SERIES OF JEJUNOILEAL BYPASS

End to Side	number	-cm- jejunum	ileum	Follow-up
Starloff (46)	273	36	10	4 mos-4 yrs
Baddeley (47)	60	36	10	1 mos-3 yrs
Drew (48)	550	36	10	not stated
Payne (20)	154	36	10	up to 14 yrs
Scott (49)	11	36	10	up to 8 yrs
Wills (50)	50	36	10	1 mo-3 yrs
Weismann (51)	123	36	10	7 mos-7 yrs
Baber (52)	68	variable		4 mos-10 yrs
Schwartz (53)	12	36	12	5 mos-1½ yrs
Brown (76)	36	36	12	not stated
	1337			
End to End				
Starloff (46)	202	30	20	4 mos-1 yr
Corso (54)	20	30	30	6 mos-3 yrs
	14	30	25	6 mos-3 yrs
Fikri (55)	52	36	10	up to 5 yrs
Dano (56)	11	36	12	3 mos-3 yrs
	13	24	24	3 mos-3 yrs
	12	12	36	3 mos-3 yrs
Scott (57)	12	30	30	up to 4 yrs
	21	30	15	up to 4 yrs
	106	30	20	up to 4 yrs
Salmon (18)	120	25	25	6 mos-3 yrs
Pace (58)	40	variable		not stated
Holtzbach (59)	25	25	25	up to 2 yrs
	588			

Scott, et al, at Vanderbilt performed this procedure in eleven patients and found it unsatisfactory because five of the eleven patients failed to lose weight adequately. Since radiological studies revealed impressive reflux of barium into the bypassed ileum, he suggested that nutrient rich chyme was refluxing into the bypassed intestine. Scott and later Salmon proposed the end-to-end anastomosis of the proximal jejunum to the terminal ileum (2, 18) (Figure 7). The bypassed jejunoileum is drained into the sigmoid or even transverse colon. Scott thought that "in theory, this modification provides more precise control of the dimensions of the surgically induced short bowel syndrome". A number of variations of the procedure have been performed anastomosing 12 - 36 cm of jejunum to 10 - 36 cm of ileum leaving intact from 46 - 60 cm of jejunum and ileum (Table I).

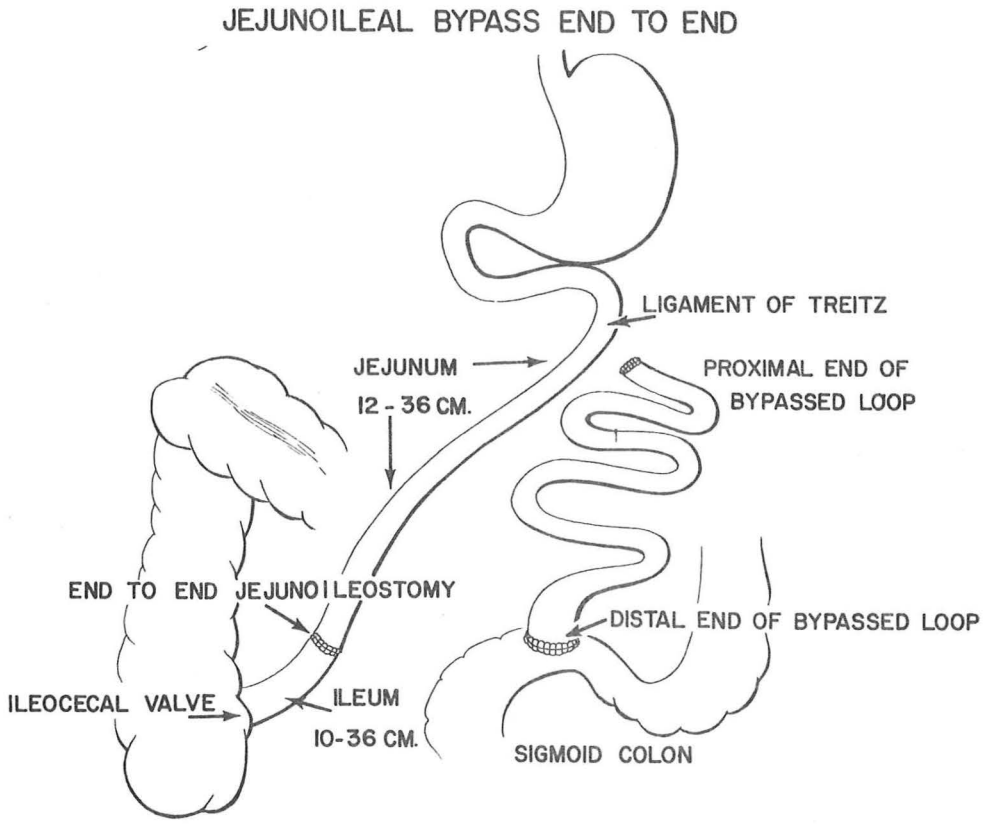

Figure 7

Weismann and others have advocated in some patients concomitant panniculectomy (removal of loose skin and subcutaneous fat) to provide better surgical exposure, decrease post-operative respiratory effort, and to remove adipose cells (48, 51, 60). The complications of this additional surgery is not known.

D. Gastric Bypass for Obesity

Mason, et al, have performed gastric bypasses on 442 patients for obesity (61). This procedure is basically a high gastrojejunostomy like a Bilroth II operation except the bypassed body and antrum remain attached to the duodenum. Patients lose weight because the remaining small fundic pouch causes early satiety or vomiting or because of malabsorption secondary to the afferent loop. Stomal ulceration is a complication of this procedure. Otherwise the results are difficult to evaluate because of short followup, and the advocated procedure has been revised several times (62).

VIII. Surgical Complications of Jejunoileal Bypass

A. Morbidity

Although there are over 1900 patients reported in the literature, it is difficult to assess accurately the surgical complications associated with the jejunoileal bypass. Follow-up is not well defined and varies from 1 month to 10 years, and detailed appraisal of immediate postoperative mortality and morbidity is lacking in most series. As summarized in Table II from selected series, postoperative non-fatal complications have been numerous. Major wound problems including infection or

Table II SURGICAL COMPLICATIONS

	No.	Major Wound Problems	Intussception or Obstruction	Thrombo-phlebitis	Pul-monary Emboli	Others
Scott (4)	150	15	1	2	1	1
Buchwald (4)	400	8	0	15	7	24
Payne (20)	153	3	2			6
Weismann (51)	123	7	1	1	2	6
Baber (52)	68	3	3			23
Corso (54)	34		1			20
Frikra (55)	52	6	2			43
Dano (56)	36	3	1	2	1	5
Willis (50)	50	6	3			12

dehiscence occurred in up to 12% of the patients, intussception or intestinal obstruction in up to 6%, and detectable thrombophlebitis in as many as 5%. Other complications included pulmonary embolism, pneumonia, electrolyte abnormalities, anastomotic leaks and fistulae, necrotizing enterocolitis, megacolon, pancreatitis, cholecystitis, bleeding gastric ulcers, and incisional hernias. Significant but non-fatal complications appeared to occur in 22% of the patients, ranging from 7% to as high as 99%.

B. Mortality

Table III MORTALITY OF JEJUNOILEAL BYPASS

	Number	Post-operative deaths number (%)	Total Deaths number (%)	Follow-up
Weismann (51)	123	2 (1.6)	3 (2.4)	7 mos-7 yrs
Starloff (46)	475	8 (1.7)	20 (4.2)	4 mos-4 yrs
Payne (20)	153	5 (3.3)	15 (10.0)	up to 14 yrs
Baddeley (47)	60	0 (0)	1 (1.7)	1 mo-3 yrs
Dano (56)	36	0 (0)	1 (2.8)	3 mos-3 yrs
Baber (52)	68	0 (0)	2 (2.9)	4 mos-10 yrs
Scott (49)	150	5 (3.3)	10 (6.7)	up to 8 yrs
Fikri (55)	52	1 (1.9)	3 (5.8)	up to 5 yrs
Corso (54)	34	0 (0)	0 (0)	6 mos-2 yrs
Salmon (18)	120	5 (4.2)	5 (4.0)	6 mos-2 yrs
Wills (50)	50	2 (4.0)	2 (4.0)	1 mo-3 yrs
Brown (76)	36	2 (0.6)	4 (11.0)	not stated
Drew (48)	550	4 (0.1)	10 (1.8)	not stated
	1907	34 (1.8)	86 (4.5)	

In selected series the average immediate post-operative mortality rate was 1.8% (ranging from 0-4.2%), and total mortality (including follow-up period) was 4.5% (ranging 0-11%). In the two series, Payne (20) and Scott (57), in which the patients were most closely followed, the overall mortality was 10% and 6.7% respectively. In most of these series very few patients have been followed for longer than 4 years, and 4.7% may be a significant underestimation of mortality considering the vast number of procedures performed throughout the country in which the results are not reported, or in which the patients are not followed for more than a few months. Causes of death include liver failure, pulmonary emboli, cardiac failure, pancreatitis, electrolyte abnormalities, renal failure, wound infections, intraabdominal abscesses, and cerebral vascular accidents. Late mortality was primarily due to liver failure and electrolyte abnormalities.

C. Reversals and Revisions

From the series in which it could be calculated, reversal or re-establishment of continuity of the intestine was necessary in 2% of 774 patients who survived the surgery (20, 46, 51, 55, 57). This was necessary because of psychological problems, diarrhea and electrolyte abnormalities, or liver disease. Revision of the shunt or shortening

of the bypassed segment was usually performed because of inadequate weight loss in 7/123 in Weissman's series (51), 16/140 in Payne's series (20) and 2/145 in Scott's series (57). Most of these patients had initially Payne's 14" and 4" end to side jejunoileostomy.

IX. Benefits from Jejunoileostomy

A. Weight Loss

The most easily measured benefit of the shunt procedure would appear to be the degree of weight loss. Paradoxically, the results as reported in most series are difficult to analyze. Buchwald calculated from several reports that the average weight loss was 35% of the initial weight (1, 18, 55, 63, 64). The meaning of this is not clear since the initial weights and ideal weights are not given. However, it is apparent from these studies that many patients have weight loss which is judged unsatisfactory. Several groups of investigators have found that in general the loss of weight in kilograms was the same for all patients independent of initial body weight (18, 56, 65). However, Hallberg and Backman in a careful analysis of body weight after intestinal bypass found that the rate and degree of weight loss was significantly dependent on the initial body weight (66).

Data from studies of Weismann and Juhl, et al, indicate that weight loss is related to the length of intestine left in continuity after small-bowel bypass (51, 67). The relative lengths of jejunum and ileum left in continuity and the type of anastomosis (end to side or end to end) as well as the total length of intestine left in continuity would also appear to be important determinants of weight loss (68). However, Dano, et al, compared three types of end to side shunts with 46 cm of intestine in continuity (36-12 cm, 24-24 cm, and 12-36 cm). He found no difference in weight loss after these three procedures (56). This suggests that with an end to side anastomosis where reflux into the bypassed intestine could occur, the ratio of functioning jejunum to ileum is not important if the total length of preserved bowel is the same (48 cm).

Scott, et al, compared the results of 4 different procedures during follow-up periods up to 4 years (49). Weight loss including body fat and lean body mass was determined utilizing isotopic total body potassium and tritiated water. As seen in figure 8, those patients with Payne's procedure, Group 1 (30 cm to 10 cm end to side jejunoileostomy) and one-half of those with a 30 cm to 30 cm end to end jejunoileostomy (Group 2) had an early precipitant weight loss but subsequently plateaued after 12 to 18 months. A few patients in Groups 1 and 2 began to gain weight.

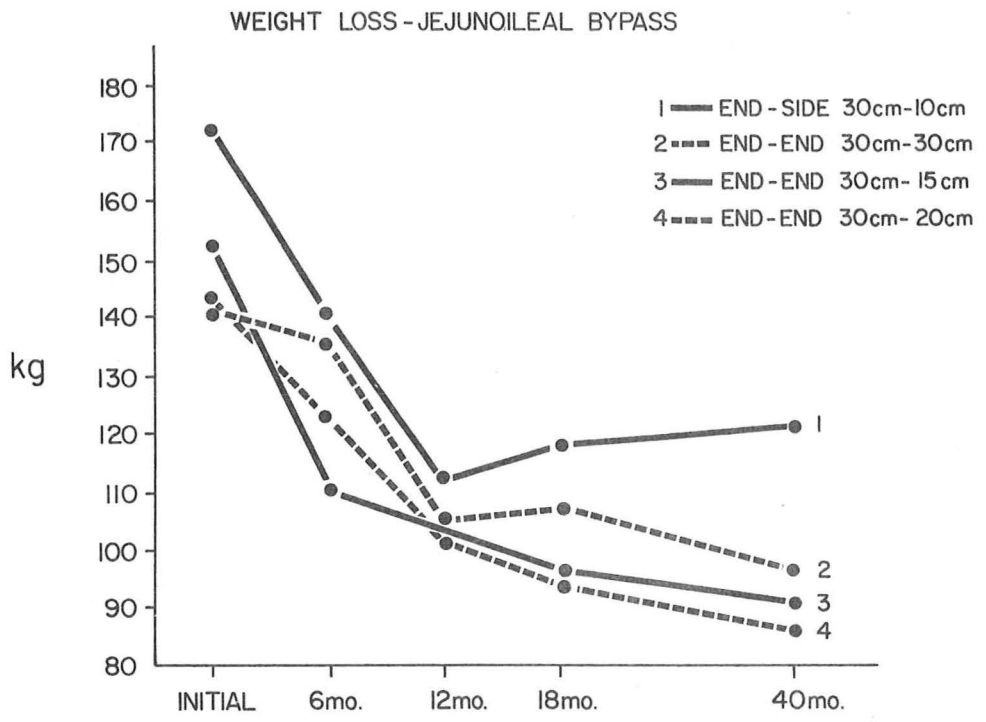

Figure 8. Weight loss with four different procedures. Adapted from Scott, et al (49)

Those patients with a 30 cm to 15 cm (Group 3) and 30 cm to 20 cm (Group 4) end to end jejunoileostomy had a more rapid rate of weight loss during the first year, and more than 70% achieved reductions to the range of ideal weight. Weight loss in these patients was primarily body fat but included up to 20% of lean body mass. In this select group of patients none of the 11 patients in Group 1 patients had satisfactory results while 6/12 (50%) of Group 2, and 61/80 (76%) of Groups 3 and 4 were thought to have satisfactory weight loss without significant complications.

The reason for inadequate weight loss in Group 1 according to Scott is reflux of nutrients into the bypassed segment, whereas in Group 2, it would appear that the 30 cms jejunum in continuity with 30 cm of terminal ileum does not permit adequate malabsorption. Quaade, et al, however, has been unable to relate the degree of weight loss to reflux of barium into the bypassed loop (65).

The cause of weight loss would therefore appear to be severe malabsorption due to decreased surface area for absorption and loss of absorptive sites for bile salts in the terminal ileum with resultant ineffective micelle formation. Scott, et al, measured fecal fat in patients less than one year after surgery and found the patients excreted in the stool from 39.5 to 106 gms of fat per day. The type of surgery performed is not indicated, and the fat intake is not recorded so coefficients of fat absorption cannot be calculated (69).

The role of bile salt malabsorption has been studied by utilizing the bile salt breath test (70-72). Glycine-1-^{14}C-cholate is given orally and $^{14}CO_2$ is measured in breath samples. $^{14}CO_2$ is increased in the breath when bacterial deconjugation of glycocholate occurs in the colon with absorption and oxidation of glycine to CO_2. Dano, et al, performed the breath test in a group of patients with three variants of the end to end jejunoileal bypass (73), Table 4.

BILE ACID BREATH TEST
(Dano, et al, Scand J Gastro 1974)

Type	Normal before surgery	Abnormal at 13 months
36-12 cm (EE)	4/4	9/9
24-24 cm (EE)	3/3	10/13
12-36 cm (EE)	6/3	7/12

Table 4

Although the degree of bile acid malabsorption is not given, it is evident that 12 cm of terminal ileum is not adequate for normal bile salt absorption, whereas when 36 cm of terminal ileum is left intact, almost 50% of the patients appear to have normal absorption of bile salts as assessed by the breath test. This may explain in part why patients with longer ileal segments do not have satisfactory weight loss (57). Wise, et al, studied bile salt deconjugation and excretion in 26 subjects before and 8-10 days and 5-12 months after a 35 and 10 cm end to end jejunoileal bypass (72) (Figure 9). A significant increase in breath $^{14}CO_2$ was found 8-10 days post-operatively indicating malabsorption and deconjugation of bile salts. By 5-12 months, the breath $^{14}CO_2$ had decreased significantly. Measurements of ^{14}C in the stool were increased early post-operative also indicating bile salt malabsorption (72).

After 5-12 months, fecal ^{14}C activity had decreased in the stool. Therefore conjugated bile salts pass into the colon after the shunt procedure and are in part deconjugated and in part lost in the stool intact. After varying periods of time it appears that the adaptation of the residual terminal ileum results in decreased malabsorption of the bile salts (73).

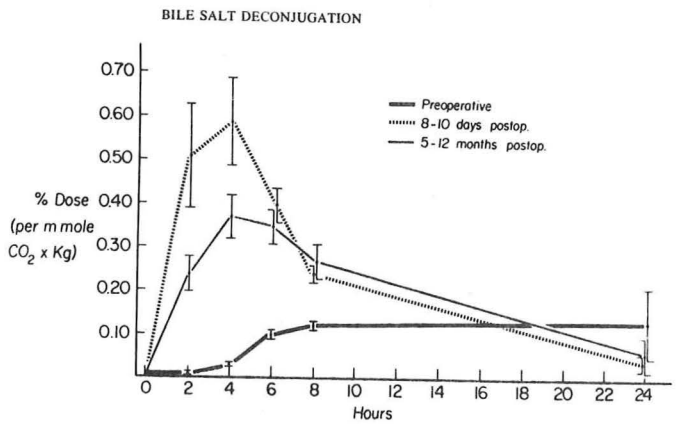

Figure 9 $^{14}CO_2$ excreted in breath after administration of glycine-1-^{14}C-cholic acid.

Another reason the patients lose weight may be by decreased caloric intake. Mulcare, et al, studied three patients after bypass and found the patients significantly reduced their dietary intakes to avoid diarrhea (74). As suggested by Hirsch, the shunt may work as a "form of gastrointestinal Antabuse" - the patients become conditioned to eat less (75).

B. Hyperlipidemia

A number of investigators have noted a decrease in serum cholesterol and/or triglyceride after jejunoileal bypass (20,49,51,56,76). Scott, et al, examined serum lipids 2 to 36 months after jejunoileal bypass and in 34 patients with hyperlipoproteinemia (27 with type IV, six with type II, and one with type V) (69). During the period of follow-up study, the serum lipids reverted to normal in all patients. Apparently none of the patients had been treated specifically for hyperlipidemia prior to the bypass procedure.

C. Psychosocial Effects

Several investigators have commented on the favorable psychosocial effect of weight loss produced as a result of the jejunoileal bypass in patients with morbid obesity (46,49,51,56). An improvement in life pattern and quality of life has been reported. Many patients demonstrated greater maturity and increased emotional stability in response to personal and external stress as judged by psychological testing (51). Solow, et al, studied the psychosocial consequences of intestinal bypass surgery and weight loss in 29 massively obese patients (77). By means of "semistructured" psychiatric interviews and a series of questionnaires administered before and up to 46 months after surgery, the authors found improvement in mood, self-esteem, interpersonal and vocational effectiveness, body image and activity levels, and a decrease in the use of denial. Most of these improvements were said to be directly proportional to the magnitude of weight loss. Solow, et al, concluded that the reversibility of many of these psychosocial disturbances associated with severe obesity without the development of substitution symptoms, supports the view that these psychosocial symptoms are as much the consequences as the cause of obesity. It is of interest that of the 29 patients, the diagnosis of schizophrenia (three cases), neurosis (five cases) and personality disorder (four cases) were made prior to surgery. Six patients experienced psychiatric illness during follow-up and two requiring hospitalization.

D. Other Medical Benefits

Improvement in glucose tolerance test with decreased insulin requirements in diabetics, and decrease in blood pressure in patients with hypertension have been noted by several investigators (20,51,53,55). There has also been reported improvement in patients with alveolar hypoventilation, thrombophlebitis, varicose veins, pedal edema, and symptoms of degenerative joint disease. However, no objective measurements of these improvements are documented.

X. Medical Complications of Jejunoileal Bypass

A. Diarrhea

Diarrhea is a universal problem after the jejunoileal bypass. If a patient is to lose weight and still ingest 4000-10,000 calories per day, severe malabsorption must occur. Patients who do not have increased bowel frequency either do not lose weight or have markedly decreased their dietary intake.

Diarrhea occurs because of the effect of the dihyroxy-bile salts on the colon, inducing net water and electrolyte secretion (78). In addition, the bulk and osmotic effects of malabsorbed foodstuffs produce diarrhea. Unabsorbed fatty acids can be hydroxylated by bacteria, and when the hydroxy-fatty acids reach the colon, they produce a net secre-

tion of water and electrolytes (79). Due to intestinal adaptation, one would anticipate that over a period of time, a decrease in diarrhea will occur.

Severe, intractable diarrhea occurs in up to 6% of the patients and often is a reason for reestablishment of continuity of the bowel (18, 46, 55, 57). After one year as many as 87% of the patients have at least 4 semi-formed stools per day (4, 18, 46). This seems to decrease with time and is thought to be due to intestinal adaptation. If the patients reduce dietary fat intake, the diarrhea will also decrease. The diarrhea often worsens when the patient has an infection and/or is administered antibiotics. Buchwald reported that diarrhea accentuated a pre-existing anal abnormality in 26 or 200 patients and resulted in the need for fissurectomy or hemorrhoidectomy (4). Most investigators administer prophylactic antidiarrheal agents and calcium carbonate.

B. Hypokalemia

In Buchwald's series, 28% developed hypokalemia associated with diarrhea, vomiting, or failure to take prophylactic KCl supplements, and 4% required hospitalization for hypokalemia (4). Dane, et al, reported that 50% of their series developed serum potassium levels below normal values (56). Several deaths have been attributed to hypokalemia (55, 46), and it is generally recommended that potassium supplements be given prophylactically for the first few months after surgery (46, 51, 55).

C. Hypocalcemia, hypomagnesemia

Symptomatic hypocalcemia has been reported frequently (4, 18, 46), and has been attributed to impaired parathyroid response to hypocalcemia due to associated hypomagnesemia. From 9 - 40% of patients in whom serum calciums were measured developed serum calcium concentrations below normal values (18, 46, 47, 55, 56). The significance of this is uncertain since a large percentage of the patients also develop hypoalbuminemia.

Measurements of calcium absorption by ^{47} Calcium arm counting test after administration of oral ^{47}Ca indicate that calcium absorption is impaired in 20 - 25% of the patients after jejunoileal bypass, and the severity is inversely related to the length of ileum left intact (80). Bone material content is decreased by 5 - 15% after 1 year as measured by direct photon absorptiometry. This suggests that vitamin D malabsorption due to intraluminal bile salt deficiency is an important cause of impaired calcium absorption. Other possible causes of calcium malabsorption are precipitation of calcium with unabsorbed fatty acids and loss of mucosal surface for adequate absorption of calcium. The development of osteo-

malacia may ultimately be a major problem in these patients. Buchwald and Starkoff, et al, recommend that oral calcium supplements be given not only for diarrhea but to prevent hypocalcemia (4, 46). Vitamin D supplements probably should also be administered after surgery.

Magnesium deficiency has been reported in several cases (55, 56, 81). Oral replacements are not well tolerated since the usual form of therapy, magnesium hydroxide, causes diarrhea.

D. Hyperoxaluria

Recent studies indicate that as many as 33% of patients develop hyperoxaluria after jejunoileal bypass (16, 55, 56, 82-84). In patients followed for 5 years, as many as 23% developed calcium oxalate renal stones. It is well known that a large percentage of patients with inflammatory disease or resection of the terminal ileum develop recurrent calcium oxalate renal stones as a result of excessive urinary excretion of oxalate (85, 86). Furthermore, patients with the largest resections and the most severe steatorrhea have the greatest degree of hyperoxaluria (87).

Hofmann, et al, initially suggested that the glycine moiety of increased quantities of glycine-conjugated bile salts in the colon is metabolized by bacteria to glyoxylate which is absorbed and converted to oxalate by the liver (Figure 10) (85).

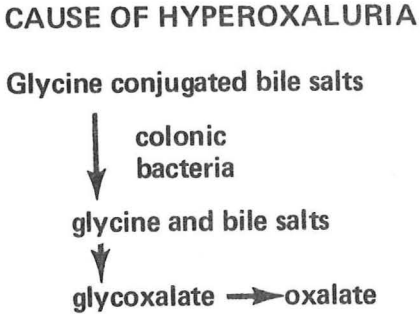

Figure 10. Initially postulated cause of hyperoxaluria

The result of studies by Admirand, et al, and Dowling, et al, indicated that by feeding taurine, bile salts became conjugated largely with taurine instead of glycine, and urine oxalate excretion decreased (26, 88). Subsequent studies in Dowling's laboratory utilizing cholylglycine-1-^{14}C and glyoxylate-1-^{14}C, demonstrated that neither the conjugated bile salt cholylglycine or glyoxylate were important precursors of urinary oxalate in patients with ileal resections (89). If ^{14}C oxalate were fed orally with a diet high in oxalate, ^{14}C oxalate absorption and urine excretion were increased when compared to normals. In additional studies with taurine feeding, no change in oxalate excretion could be demonstrated (85, 90). These studies and those of Stauffer, et al, indicate that increased absorption of dietary oxalate is the cause of hyperoxaluria (87).

Oxalate absorption appears to occur as a passive process in all segments of the bowel when studied in vitro (91). The addition of cholestyramine or calcium chloride binds or precipitates oxalate and reduces absorption, whereas the addition of the fatty acid sodium oleate increases absorption. It has been postulated that normally oxalate absorption is limited by precipitation with intraluminal calcium. When fatty acids are not absorbed they form calcium soaps which permit increased absorption of oxalate. If this postulate is true, increased dietary calcium should decrease oxalate absorption by precipitating it in the bowel. In addition, by decreasing dietary fat, one might expect more intraluminal calcium would be available to precipitate oxalate.

In preliminary studies, Earnest, et al, found that by supplementing diets with calcium, urine oxalate excretion was decreased in patients with ileal resection (92). Pak in preliminary studies has found a similar response to oral calcium in patients with jejunoileal bypasses (93). However, Chadwick and Modha were unable to demonstrate a decrease in urine oxalate excretion in patients with ileal disease with either calcium supplements or with low fat diets (90). The reason for these differences is not clear. The effect of cholestyramine in reducing urine oxalate excretion has been demonstrated by two separate groups (87, 94). In addition to binding oxalate in the intestinal lumen, cholestyramine may also exert its action by binding bile salts. Preliminary data indicate that bile salts in the colon appear to increase the permeability of the mucosa to oxalate (94).

Treatment of hyperoxaluria should therefore consist of decreased dietary oxalate (avoid greens, spinach, asparagus, rhubarb, tea, citrus fruits, cocoa, carrots, and excessive ascorbic acid (86, 96a). Calcium supplements are probably necessary anyway to aid in preventing hypocalcemia and osteomalacia. Low fat diets are often necessary to decrease steatorrhea and diarrhea. The use of cholestyramine may be dangerous in that by binding bile salts, bile salt loss will be greater, and steatorrhea will likely increase.

E. Liver Disorders

The adverse effect of jejunoileal bypass on liver function and morphology is probably the most serious and perplexing complication. Sixty to ninety percent of morbidly obese patients have at least some fatty metamorphosis of the liver prior to jejunoileal bypass (1, 51, 63, 80, 96-101). The relation of fatty liver to obesity per se is not clear since the presence or absence of diabetes or alcoholic consumption (factors also associated with fatty liver) is not taken into consideration. Furthermore, the degree of fatty infiltration does not always correlate with the degree of obesity (51, 59).

After jejunoileal bypass, most studies indicate that fat accumulation in the liver increases during the period of rapid weight loss (first 4 to 12 months), and then appears to decrease as the weight stabilized (96, 98, 100, 101). Holzbach, et al, performed chemical measurements of hepatic lipids from biopsies taken from 23 patients, some before and some 5 to 13 months after jejunoileal bypass (59). A net increase in total hepatic lipids was found during the period of rapid weight loss and was largely triglycerides (Figure 11).

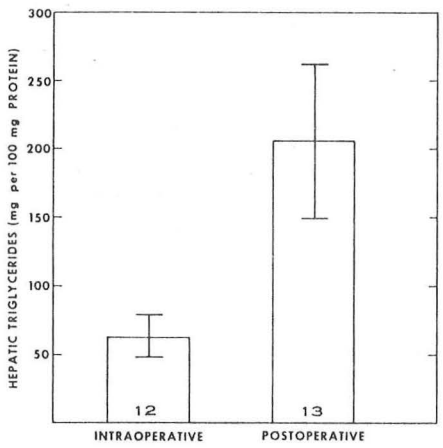

Figure 11

This increase in fatty infiltration is generally associated with slight abnormalities in liver function tests, primarily the SGOT (98). The process is usually benign as the liver function tests, if abnormal, usually return to normal as hepatic fat content decreases. However, it has been emphasized that significant hepatic morphological changes can occur without abnormalities in liver function tests (96, 101).

Of greater concern are the reports of the development of focal necrosis, bile duct proliferation, fibrosis, cirrhosis, and even death in hepatic failure after jejunoileal bypass (76, 96, 98, 100-103). One of the primary reasons the jejunocolic bypass was abandoned was the development of cirrhosis and death. Seven of the first 63 cases reported who had jejunocolic bypass died from liver disease (37, 40, 96, 104-107). Peters, et al, reported the findings in 5 patients who between 2½ and 5 months after jejunoileal bypass developed nausea, vomiting, abdominal pain, and hepatomegaly (108). Some of the patients developed ascites and splenomegaly. Four of the five patients died in hepatic failure in spite of hyperalimentation and/or reestablishment of intestinal continuity. Despite no history of alcoholic intake in two of these patients, hepatic histologic changes in all five were remarkably similar to alcoholic hepatitis with fatty degeneration, neutrophilic infiltrate, Mallory's hyaline, and intrasinusoidal collagenosis. The incidence of the development of progressive fibrosis after jejunoileal bypass is not known, but is probably less than 5% (18, 46, 47, 51, 55-56, 101, 110).

The mechanisms by which increased fat accumulates in the liver and active cirrhosis develops is not clear. When massively obese patients are starved or fed 500 calorie balanced diets, hepatic fat infiltration decreases (96, 111). In severely obese patients after jejunoileal bypasses, Moxley, et al, found at the time of maximum rate of weight loss; increased hepatic fat, elevated transaminase, and a decrease in most serum essential and nonessential amino acids (except glycine and serine which were elevated (98, 112). Amino acid absorption was also impaired. Similar amino acid profiles, fatty livers, and liver function abnormalities are reported in patients with Kwashiorkor and in experimental animals with protein-calorie malnutrition (113-115). It was therefore suggested that these patients with jejunoileal bypass developed a transient protein-calorie malnutrition or Kwashiorkor as a cause of their fatty livers (112). When patients with jejunoileal bypass were studied during periods when weights were stable, the transaminase became normal, hepatic fat diminished, and the concentration of serum amino acids returned toward normal. Improvement in oral amino acid tolerance tests suggested that an adaptive enhancment of amino acid absorption was responsible for improvement (98). It is not clear if the triglyceride which accumulates in the liver is derived from mobilized depot fat or from dietary carbohydrates as previously demonstrated in protein-calorie malnourished animals (116-118). However, the liver fibrosis and cirrhosis which can occur after small bowel bypass is not seen in patients with only protein-calorie malnutrition, and the development of progressive liver disease is most likely due to the superimposition of other factors in patients after jejunoileal bypass.

Drenick, et al, proposed that the accumulation in the liver of the secondary bile salt, lithocholate, could be responsible for the hepatic necrosis and fibrosis (96). Lithocholate can be produced after intestinal bypass when large amounts of bile salts are delivered into the colon by the bacterial 7-dehydroxylation of the primary bile salt chenodeoxycholate (119). Lithocholate when given to experimental animals produces hepatic necrosis, bile duct proliferation, and fibrosis (119, 120). In one patient studied by Moxley, et al, a marked elevation in serum lithocholate was found (98). Sherr, et al, studied five patients, four months after jejunoileal bypass and found in four patients marked elevation in the serum concentration of the primary bile salts, cholate and chenodeoxycholate (103). Serum lithocholate was markedly elevated in the one patient with moderately severe liver disease. Analysis of bile salt concentrations in the patient's liver biopsy revealed no lithocholate but an elevation in chenodeoxycholate. Chenodeoxycholate has also previously been shown to produce liver injury in experimental animals (121). Sherr, et al, suggested that after jejunoileal bypass, the development of protein-malnutrition could lead to decreased hepatic transport of chenodeoxycholate, and the accumulation of toxic quantities of this bile salt could lead to further and progressive liver injury (103). Other possible causes of liver injury include absorption of partially digested peptides which are hepatotoxic, essential fatty acid or vitamin E deficiency, or absorption of bacteria or toxic bacterial products (83, 120).

Popper and Schaffner have taken a rather casual approach to this problem in patients with jejunoileal bypass (120). They suggested that if periodic monitoring of liver function tests show consistently abnormal results, a liver biopsy should be performed. If bridging fibrosis or regenerative nodules are found, normal bowel continuity should be restored. However, because of the lag in the appearance of abnormal hepatic function tests, it would be more prudent to perform serial liver biopsies until the patient's weight has stabilized. If there is evidence of histologic deterioration with significant inflammation, necrosis, bile duct proliferation, or fibrosis, one should consider taking down the shunt (102). Attempts to treat patients with liver failure have not often been successful. Although the feeding of protein digests into the excluded loop of animals with jejunoileal bypass can prevent fatal liver injury, oral supplementation with amino acids in man does not prevent the increased accumulation of fat in the liver (96, 122). Intravenous administration of amino acids has been reported in a few cases to be associated with the reversal of severe fatty infiltration of the liver after jejunoileal bypass, but as noted, once the severe liver failure supervenes, intravenous hyperalimentation and/or reversal of the bypass is usually unsuccessful in preventing death (108, 123).

F. Cholelithiasis

Several studies have reported a positive corrrelation between obesity

and gallstones (124). Most gallstones in obese patients are composed predominantly of cholesterol. Cholesterol precipitation and gallstone formation can occur when the bile contains more cholesterol than can be held in solution by bile salts and phospholipids. This could be due to decreased bile salt excretion and/or increased cholesterol excretion by the liver into bile. Recent studies in obese patients by Bennion and Grundy indicate that supersaturation of bile with cholesterol in obese patients can be attributed to a single defect in biliary lipid excretion, an excessive output of cholesterol (124). In obese patients bile was supersaturated with cholesterol even though bile salt and phospholipid excretion were increased and bile salt pool size was increased. Weight reduction by dietary means resulted in a decrease in biliary cholesterol, bile salt, and phospholipid excretion without decreasing the saturation of bile with cholesterol. Although many of the massively obese patients are found to have gallstones before and at the time of jejunoileal bypass, there are only a few reports of cholelithiasis developing after surgery (52, 56). It would appear that bile salt malabsorption might result in decreased bile salt excretion and decreased cholesterol solubility in bile. Studies have not been reported concerning biliary lipid excretion before and after jejunoileal bypass to resolve this problem.

G. Arthralgias and Arthritis

Articular symptoms resembling rheumatoid arthritis have been described after jejunocolic bypass (107, 125, 126). Symmetrical synovitis or tenosynovitis involving the fingers, hands, wrists, knees and/or ankles has been reported. The rheumatoid factor and antinuclear antibody are absent and serum uric acid, calcium, and alkaline phosphatase are normal. The symptoms are usually transitory, and relieved by salicylates, but can be severe and persistent requiring reconstitution of the bowel for relief. No roentgenological or histopathological changes are present other than soft tissue swelling.

Similar articular symptoms have been described in a small number of patients after jejunoileal bypass (16, 47, 127). Wands, et al, in a preliminary report identified circulating immune complexes in cryoproteins in two of four patients with arthritis after bypass (128). The finding of immunoglobulins, complement components, and antibacterial antibodies suggested the possibility that absorbed intestinal bacteria antigens activated complement and play a role in the pathogenesis of arthritis after jejunoileal bypass.

H. Other Complications

The jejunoileal bypass may cause extensive malabsorption of not only dietary fat and bile salts, but all of the fat and water soluble vitamins, proteins, and minerals. Scott, et al, has clearly demonstrated increased stool nitrogen and malabsorption of vitamins A, E, and K, and d-xylose (129). The number and variety of complications from malabsorption alone

that could develop are potentially limitless.

Anemia developed in 11% of the patients studied by Starkoff, et al (46). The cause in most cases was attributed to "chronic disease" but iron deficiency and folate deficiency were also identified. Baddley and Dano, et al, have noted the development of folate deficiency is 20 to 40% of patients studied after bypass (47, 56). Weismann found an abnormal Schilling test in all patients he studied with a variety of jejunoileal bypass procedures (51). Dano, et al, found vitamin B_{12} absorption was impaired in 36% of patients with only 12 cm of ileum intact (70). However, if 36 cm of terminal ileum were left in continuity, vitamin B_{12} absorption was normal. It is not clear that if with time significant adaptation to B_{12} absorption occurs (130, 131). Study of this problem is complicated by the development of bacteria overgrowth in the remaining small intestine which can prevent B_{12} absorption. Currently, all patients should receive monthly vitamin B_{12} parenteral replacement (132).

As many as 25% of patients develop transient hair loss after jejuno-ileostomy (4, 16, 56, 132). This has been attributed to diffuse protein deficiency because analysis of hair follicles revealed a lack of keratin (16).

Gastric hypersecretion may occur after extensive small bowel resection in man and in animals (133). Seelig and co-workers have demonstrated in rats that proliferation of the epithelium of gastric glands occurs after resection of the small intestine (134). This effect on gastric gland hyperplasia and on acid secretion may be the result of alterations in the hormonal regulation of acid secretion (135). Studies of acid secretion in patients before and after jejunoileal bypass are conflicting (136-138). In general only slight or no increase in basal or stimulated acid secretion has been found after jejunoileal bypass. If gastric acid hypersecretion were to occur, it could be deleterious by producing gastric or intestinal ulcerations or by further interfering with digestion and absorption of foodstuffs.

X1. Summary

The morbidity associated with massive obesity has not been completely delineated, and in view of the "epidemic" of jejunoileal bypasses being performed is not likely to be defined in the near future. However, it is likely that "morbid" obesity is indeed a morbid condition. Furthermore, the creation of a malabsorptive state by means of a jejunoileal bypass in patients with severe obesity will result in most cases in significant reduction in body weight. It is probable that some of the associated disorders of obesity are at least in part alleviated, and many of the patients are able to live more "normal" lives after the surgery. Yet the real and potential risks of the surgery are numerous and the operation is successful over short term follow-up in no more than 80% of the patients if one takes into account mortality, intolerable morbidity, required reestablishment of intestinal continuity, and failure to lose sufficient weight. Medical complications of this surgically created malabsorptive state are well

documented and often difficult to manage.

The procedure, therefore, should be considered an experiment (performed without preclinical trials). If the jejunoileal bypass is to be performed, it is critical that the patients be carefully selected and informed of the known and untoward complications. Arrangements should be made so that the patients are followed and carefully studied for the rest of their lives by physicians who are aware of the real and potential complications. It would be preferable that these experiments be performed only as part of an approved prospective study. It is possible that after sufficient follow-up that dangerous complications will develop in all of these patients receiving a jejunoileal bypass and they will have to be "called-in" for reestablishment of intestinal continuity.

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